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# Ultra rapid lispro showed greater reduction in postprandial glucose versus Humalog in children, adolescents and adults with type 1 diabetes mellitus

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## Abstract

**Aim:** This study compared the pharmacokinetics, glucodynamics and tolerability following single subcutaneous doses of ultra rapid lispro (URLi) versus Humalog in children (6-11 years), adolescents (12-17 years) and adults (18-64 years) with type 1 diabetes mellitus (T1D).

**Materials and Methods:** The study was a randomized, two-period, subject- and investigator-blind, crossover design in participants with T1D. Participants received a 0.2 U/kg bolus dose immediately before a liquid mixed meal tolerance test. Insulin lispro and glucose concentrations were measured.

**Results:** The study included 13 children, 14 adolescents and 15 adults. Consistently across the age groups, onset of appearance was 4-5 min faster, the early 50% $t_{max}$ was reduced by 7-13 min, and exposure in the first 15 min was increased by 3.5-6.5-fold following URLi compared with Humalog (all $p < .01$). Exposure after 3 h was decreased by 37-58% ($p = .02$) and the duration was reduced by 56 min ($p = .006$) in children and 36 min ($p = .022$) in adolescents with URLi compared with Humalog. The maximum and overall exposure were similar between treatments. Postprandial glucose at 1 h was reduced by 42 mg/dl in children ($p = .008$), 19 mg/dl ($p = .195$) in adolescents and 34 mg/dl ($p = .018$) in adults following URLi versus Humalog. The glucose excursion during a 5-h test meal period was reduced by 16% in children and 9% in adolescents compared with Humalog. URLi was well tolerated in all age groups.

**Conclusions:** URLi showed an accelerated insulin lispro absorption and greater postprandial glucose reduction compared with Humalog in children, adolescents and adults with T1D.

ClinicalTrials.gov Identifier: NCT02703350.

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

## 1 | INTRODUCTION

Over 1.2 million children and adolescents have type 1 diabetes (T1D) worldwide. New onset and existing T1D cases are increasing each year globally with approximately 200 000 children and adolescents diagnosed annually.[1] Children with diabetes require different treatment strategies from adults, based on their cognitive, behavioural and social-emotional development, which should be adjusted as they progress through childhood.[2] As with adults, intensive diabetes management through maintenance of tight glycaemic control helps to delay onset and slow the progression of complications of the disease in young people.[2]

The development of rapid-acting insulin analogues (i.e. Humalog, Novolog) has provided better postprandial glucose control as part of a basal/bolus regimen[3]; however, these insulins are unable to match carbohydrate absorption resulting in inadequate postprandial glycaemic control.[4,5] There remains a need to develop more rapid-acting insulin formulations (i.e. ultra-rapid-acting insulins) with a time-action profile to match that of endogenous insulin secretion better, providing effective glycaemic control without increasing the risk of hypoglycaemia and hyperglycaemia. These insulins may be particularly useful for pumps and automated insulin delivery systems.[6]

Ultra rapid lispro (URLi; Lyumjev) is an insulin lispro formulation containing two locally acting excipients, treprostinil and citrate. Treprostinil induces local vasodilation and citrate increases vascular permeability, thereby accelerating insulin lispro absorption and more closely resembling the body's physiological insulin response to a meal.[7,8] URLi previously showed accelerated insulin lispro absorption, with reduced duration of insulin action compared with Humalog in individuals with T1D.[9] Furthermore, the accelerated insulin lispro absorption has resulted in significantly greater decreases of postprandial glucose excursions than Humalog in people with T1D.[10]

In the present study, we evaluated differences in the pharmacokinetic and postprandial glucose response following a mixed meal tolerance test (MMTT) between URLi and Humalog following a single subcutaneous (SC) bolus dose in children, adolescents and adults with T1D. In addition, the safety and tolerability of these SC doses were evaluated. Previously, the clinical efficacy and safety of URLi in a paediatric population on daily insulin therapy in an outpatient setting has been described.[11]

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

This phase 1 study was a two-centre, two-part, two-period crossover, randomized, double-blind design conducted in children (age 6 to <12 years), adolescents (age 12 to <18 years) and adults (age 18 to <65 years) with T1D (Figure S1). Data from the first part of the study are reported here. The study evaluated the pharmacokinetics, glucodynamics, safety and tolerability of URLi in comparison with Humalog following a single SC injection immediately before a liquid MMTT.

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guideline for Good Clinical Practice, and applicable laws and regulations. The protocol was approved by independent ethics committees at Hannover Medical School and Advarra, and all participants or legal guardians provided written informed consent or assent before any study-related activities. The study is registered at www.ClinicalTrials.gov (NCT02703350).

### 2.2 | Study participants

Eligible participants were male or female, diagnosed with T1D for ≥1 year, between ≥6 and <65 years of age, with a haemoglobin A1c level of ≤10.0% (≤86 mmol/mol) using a continuous SC insulin infusion pump or multiple daily injections. Eligible children and adolescents had a body mass index within the 3rd and 95th age-appropriate percentiles,[12] with a minimum weight of 25 kg, and adults had a body mass index of ≤28.0 kg/m$^2$.

### 2.3 | Treatment protocol

Participants who entered the study on multiple daily injection therapy with any basal insulin other than neutral protamine Hagedorn (NPH) twice-daily transitioned to NPH twice-daily therapy approximately 3-7 days before Day 1 of Period 1. This approach standardized the basal insulin therapy across the participants given the different half-lives across the daily basal insulin therapies. Transition guidelines, including dosages and timing, were determined by the investigators based on individual patient needs, with the last injection of glargine administered at least 24 h before the start of the inhouse procedure and degludec at least 48 h before the start of the inhouse procedure. The last injection of NPH was in the morning on Day 1, before the MMTT on Day 1 and resumed only after the completion of the MMTT assessment (~7 h). Patients who entered the study on continuous SC insulin infusion therapy were disconnected from their pump at the start of the run-in. On Day 1, participants were randomized to one of the two treatment sequences (URLi then Humalog, or Humalog then URLi) in a 1:1 ratio. Participants received a single 0.2 U/kg SC bolus injection of either URLi or Humalog (Eli Lilly and Co) immediately before the start of the test meal. A liquid MMTT (Ensure Plus) was given to patients for each period. All adults and children or adolescents with body weight >55 kg received 100 g carbohydrates. For those children and adolescents <55 kg, the amount of carbohydrates was adjusted for weight (Table S2). The test meal for each participant was kept consistent with regards to calorie content across all MMTT assessments in the study. The insulin dose was kept the same for all

MMTTs. Participants were fasted (except for water) for at least 10 h before each test meal. The meal was consumed within 15 min.

The MMTTs were preceded by a 7-h run-in period when blood glucose was carefully monitored at a minimum of 30-min intervals to stabilize blood glucose levels to 135 ± 25 mg/dl (7.5 ± 1.4 mmol/L), using an intravenous insulin (glulisine) and glucose infusion, by a standardized scheme. The run-in period ended once the target blood glucose level was attained and remained stable without intervention for at least 20 min before the scheduled start time of MMTT.

## 2.4 | Safety

Safety assessments included adverse events (AEs), hypoglycaemic events, physical examinations, clinical laboratory tests, vital signs and electrocardiograms. In addition, local tolerability at the injection site was evaluated at 0 (immediately following the injection), 60 and 240 min postdose using the following categories: pain (including burning), itching, erythema, oedema and induration/infiltration.

## 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, 300, 360 and 420 min postdose. A validated enzyme-linked immunosorbent assay was used to quantify free insulin lispro serum concentrations at Charles River Laboratories Montreal in Senneville, Quebec, Canada. 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%. 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).

## 2.6 | Outcome measures

Serum insulin lispro pharmacokinetic parameters were calculated by non-compartmental methods using Phoenix® version 8.0 and S-PLUS® version 8.2. Pharmacokinetic parameters included time to early half-maximal concentration (early 50% $t_{max}$), maximum observed drug concentration ($C_{max}$), time of maximum observed drug concentration ($t_{max}$), AUC from time 0 to 15 min postdose [$AUC_{(0\text{-}15min)}$], AUC from time 0 to 30 min postdose [$AUC_{(0\text{-}30min)}$], AUC from time 0 to 1h postdose [$AUC_{(0\text{-}1h)}$], AUC from time 3 to 7 h postdose [$AUC_{(3\text{-}7h)}$], AUC from time 0 to infinity [$AUC_{(0\text{-}\infty)}$], duration of exposure, defined as time from dosing until serum insulin lispro reached the LLOQ in the terminal phase, and onset of appearance, defined as time that serum insulin lispro first reached the LLOQ. The determination of onset of appearance used a linear interpolation between the time of dosing (0 insulin lispro concentration) and the time of the first quantifiable insulin lispro measurement.

## 2.7 | Glucodynamic analysis

The study site obtained blood samples for the measurement of glucose using a point-of-care glucose meter during the inpatient periods to provide real-time glucose measurement. Glucose concentration values were based on whole blood but calibrated to plasma for reporting. The change from baseline (the average of −30, −15 and 0 min represented the 0-h 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-h test meal. Plasma glucose glucodynamic parameters included change from baseline of glucose at 1-h postmeal, at 2 h postmeal, the AUC from time 0 to 30 min postmeal [$iAUC_{(0\text{-}30min)}$], AUC from time 0 to 1 h postmeal [$iAUC_{(0\text{-}1h)}$], AUC from time 0 to 2 h postmeal [$iAUC_{(0\text{-}2h)}$] and AUC from time 0 to 5 h postmeal [$iAUC_{(0\text{-}5h)}$]. 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). A two-sided confidence interval of 95% 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 pharmacokinetic parameters were analysed using a mixed-effect model that included treatment, sequence, period, age group and treatment by age group interaction as fixed effects and patient within sequence as a random effect. An exploratory analysis on the interaction between treatment and age group was also estimated directly from the model.

The glucodynamic parameters (without log transformation) were analysed using the same model previously described. The least squares mean ratios and their corresponding 95% confidence intervals were calculated using the Fieller's method.[13]

An exploratory analysis on the interaction between treatment and age group was conducted for all glucodynamic parameters using the same statistical model used for treatment comparison.

## 2.9 | Sample size calculations

The sample size determination was based on the recruitment considerations and relevant guidance for paediatric clinical pharmacology studies and is customary for phase 1 studies evaluating safety and pharmacokinetics. The number of participants needed to complete was pre-set to 12 in each age group (6 to <12 years; 12 to <18 years; and 18 to <65 years). Twelve completing participants in each age group would provide at least 85% power to show 30% reduction in time to early half-maximal drug concentration (early 50% $t_{max}$).

## 3 | RESULTS

### 3.1 | Study population

Of the 42 participants (13 children, 14 adolescents and 15 adults) who entered the study, all received at least one dose of study treatment and 41 participants completed the study. Baseline characteristics and demographics are shown in Table 1.

### 3.2 | Pharmacokinetics

Mean serum insulin lispro concentration-time profiles were shifted to the left following a single SC dose of URLi compared with Humalog across all three age groups, showing accelerated insulin lispro absorption and reduced late exposure with URLi (Figure 1). The early 50% $t_{max}$ was reduced by 30-51% with URLi compared with Humalog, a difference of 13 min in children, 7 min in adolescents and 10 min in adults. This accelerated insulin lispro absorption with URLi led to significantly increased early serum insulin lispro exposure. The greatest increase in exposure was observed during the first 15 min after URLi dosing, as the $AUC_{(0\text{-}15min)}$ was increased by 6.5-fold in children, 3.5-fold in adolescents and 5.1-fold in adults ($p \leq .0003$) with URLi versus Humalog (Table 2). The significant increase in insulin lispro exposure with URLi was maintained over the 1 h after dosing ($p \leq .0148$) compared with Humalog across the age groups (Table 2). In addition, the late insulin lispro exposure was reduced with URLi compared with Humalog. From 3- to 7-h postdose, exposure was reduced by 37-58% with URLi versus Humalog across the age groups ($p = .02$). Overall, insulin lispro exposure ($AUC_{(0\text{-}\infty)}$) and $C_{max}$ were comparable between URLi and Humalog (Table 2).

There were no significant age group-by-treatment interactions on the pharmacokinetics, indicating that the treatment effect between URLi and Humalog was similar for all three age groups.

### 3.3 | Glucodynamics following a test meal

Mean glucose concentration-time profiles following single SC doses of URLi and Humalog in children, adolescents and adults are presented in Figure 2. URLi showed an earlier glucose-lowering effect compared with Humalog in all age groups. URLi reduced postprandial

**TABLE 1** Patient demographic

| | Children (6 to <12 years) | Adolescents (12 to <18 years) | Adults (18 to <65 years) |
|---|---|---|---|
| N | 13 | 14 | 15 |
| Age, years; mean (SD) | 9.5 (1.0) | 14.2 (1.4) | 36.0 (15.9) |
| Sex, male; n (%) | 4 (30.8) | 9 (64.3) | 9 (60.0) |
| Race, white; n (%) | 12 (92.3) | 13 (92.9) | 12 (80.0) |
| Body weight kg; mean (SD) | 34.8 (6.1) | 62.6 (11.4) | 75.5 (10.3) |
| BMI $kg/m^2$; mean (SD) | 17.3 (1.3) | 21.2 (2.4) | 24.1 (2.4) |
| Duration of T1D years (SD) | 5.3 (2.6) | 6.9 (4.4) | 17.5 (10.9) |
| Screening HbA1c mmol/mol %; mean (SD) | 61.7 (9.8) | 60.7 (12.0) | 60.7 (10.9) |
| | 7.8 (0.9) | 7.7 (1.1) | 7.7 (1.0) |

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; n, number of subjects in the variable; N, total number of subjects; SD, standard deviation; T1D, type 1 diabetes.

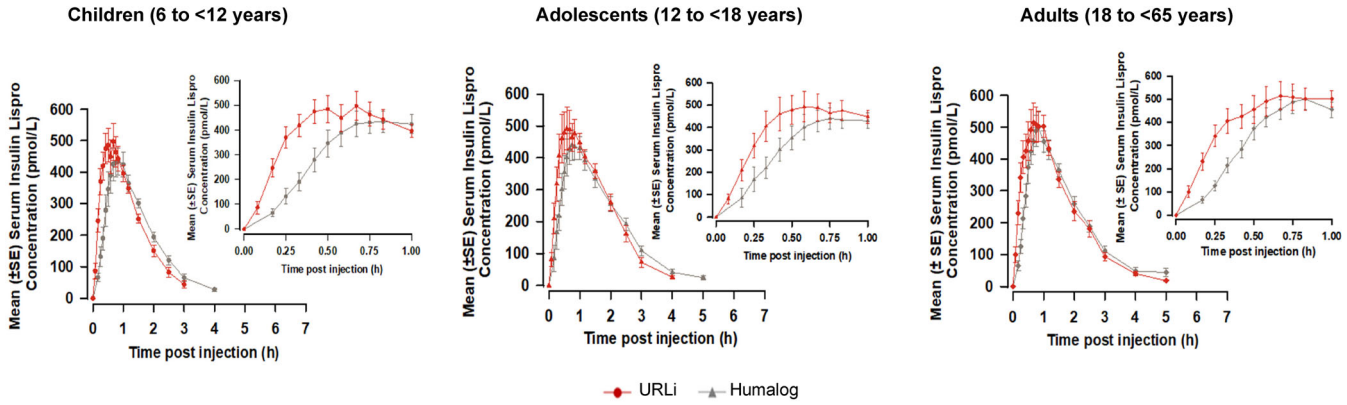


**FIGURE 1** Mean insulin lispro concentration (±SE) versus time after single subcutaneous 0.2 U/kg dose of ultra rapid lispro (URLi) or Humalog® in children (left), adolescents (middle) and adults (right) with type 1 diabetes

**TABLE 2** Statistical analysis of insulin lispro pharmacokinetics parameters for Humalog versus URLi

| Pharmacokinetic parameters | | Treatment | N | Geometric LSM | *p*-Value | Ratio of geometric LSM URLi: Humalog (95% CI) |
|---|---|---|---|---|---|---|
| Early insulin lispro exposure | | | | | | |
| Onset of appearance (min) | Children | Humalog | 13 | 6.5 | .0002* | 0.16 (0.06, 0.32) |
| | | URLi | 13 | 1.1 | | |
| | Adolescents | Humalog | 14 | 6.4 | .0011* | 0.30 (0.01, 0.63) |
| | | URLi | 14 | 1.9 | | |
| | Adults | Humalog | 14 | 4.8 | .0039* | 0.18 (0.06, 0.35) |
| | | URLi | 13 | 0.9 | | |
| Early 50% $t_{max}$ (min) | Children | Humalog | 13 | 25.4 | <.0001* | 0.49 (0.36, 0.65) |
| | | URLi | 13 | 12.4 | | |
| | Adolescents | Humalog | 14 | 23.9 | .0026* | 0.70 (0.48, 0.91) |
| | | URLi | 14 | 16.6 | | |
| | Adults | Humalog | 14 | 24.5 | <.0001* | 0.59 (0.42, 0.75) |
| | | URLi | 14 | 14.4 | | |
| $AUC_{(0\text{-}15min)}$ (pmol·h/L) | Children | Humalog | 12 | 6 | <.0001* | 6.52 (3.35, 12.70) |
| | | URLi | 13 | 39.1 | | |
| | Adolescents | Humalog | 13 | 7.5 | .0003* | 3.51 (1.85, 6.66) |
| | | URLi | 14 | 26.3 | | |
| | Adults | Humalog | 14 | 7.4 | <.0001* | 5.11 (2.74, 9.54) |
| | | URLi | 14 | 37.8 | | |
| $AUC_{(0\text{-}30min)}$ (pmol·h/L) | Children | Humalog | 13 | 52.9 | <.0001* | 2.66 (1.90, 3.73) |
| | | URLi | 13 | 141 | | |
| | Adolescents | Humalog | 14 | 60.4 | .0002* | 1.95 (1.41, 2.71) |
| | | URLi | 14 | 118 | | |
| | Adults | Humalog | 14 | 62.9 | <.0001* | 2.06 (1.49, 2.86) |
| | | URLi | 14 | 130 | | |
| $AUC_{(0\text{-}1h)}$ (pmol·h/L) | Children | Humalog | 13 | 250 | .0009* | 1.42 (1.17, 1.72) |
| | | URLi | 13 | 354 | | |
| | Adolescents | Humalog | 14 | 264 | .0049* | 1.32 (1.09, 1.59) |
| | | URLi | 14 | 348 | | |
| | Adults | Humalog | 14 | 286 | .0148* | 1.27 (1.05, 1.53) |
| | | URLi | 14 | 362 | | |
| Late insulin lispro exposure | | | | | | |
| $AUC_{(3\text{-}7h)}$ (pmol·h/L) | Children | Humalog | 13 | 52.6 | <.0001* | 0.42 (0.28, 0.62) |
| | | URLi | 13 | 21.9 | | |
| | Adolescents | Humalog | 14 | 92.2 | .0126* | 0.60 (0.41, 0.89) |
| | | URLi | 14 | 55.7 | | |
| | Adults | Humalog | 14 | 109 | .0208* | 0.63 (0.43, 0.93) |
| | | URLi | 14 | 68.4 | | |
| Duration (min) | Children | Humalog | 12 | 334 | .0006* | 0.83 (0.73, 0.95) |
| | | URLi | 13 | 278 | | |
| | Adolescents | Humalog | 11 | 349 | .0224* | 0.90 (0.80, 1.00) |
| | | URLi | 12 | 313 | | |
| | Adults | Humalog | 9 | 359 | .3281 | 0.96 (0.85, 1.06) |
| | | URLi | 13 | 343 | | |

**TABLE 2** (Continued)

| Pharmacokinetic parameters | | Treatment | N | Geometric LSM | *p*-Value | Ratio of geometric LSM URLi: Humalog (95% CI) |
|---|---|---|---|---|---|---|
| Overall exposure | | | | | | |
| $C_{max}$ (pmol/L) | Children | Humalog | 13 | 475 | .2704 | 1.09 (0.93, 1.29) |
| | | URLi | 13 | 520 | | |
| | Adolescents | Humalog | 14 | 485 | .1317 | 1.13 (0.96, 1.32) |
| | | URLi | 14 | 546 | | |
| | Adults | Humalog | 14 | 523 | .3688 | 1.07 (0.92, 1.25) |
| | | URLi | 14 | 561 | | |
| $AUC_{(0-\infty)}$ (pmol·h/L) | Children | Humalog | 13 | 759 | .9163 | 1.00 (0.92, 1.08) |
| | | URLi | 13 | 756 | | |
| | Adolescents | Humalog | 14 | 915 | .2228 | 1.05 (0.97, 1.14) |
| | | URLi | 14 | 961 | | |
| | Adults | Humalog | 14 | 987 | .9693 | 1.00 (0.92, 1.09) |
| | | URLi | 14 | 989 | | |

Abbreviations: $AUC_{(0-15min)}$, AUC from time 0 to 15 min; $AUC_{(0-1h)}$, AUC from time 0 to 1 h; $AUC_{(0-30min)}$, AUC from time 0 to 30 min; $AUC_{(0-\infty)}$, AUC from time 0 to infinity; $AUC_{(3-7h)}$, AUC from time 3 h to 7 h; AUC, area under the concentration versus time curve; $C_{max}$, maximum observed insulin lispro concentration; early 50% $t_{max}$, time to early half-maximal observed drug concentration; LSM, least squares mean; N, number of participants; Onset of appearance, time from study drug administration until the first time serum insulin lispro concentrations reached the lower limit of quantification; PK, pharmacokinetics; SC, subcutaneous; $t_{max}$, time to $C_{max}$.

*Note*: *p*-value is for treatment difference in LSM.

*$p < .05$.

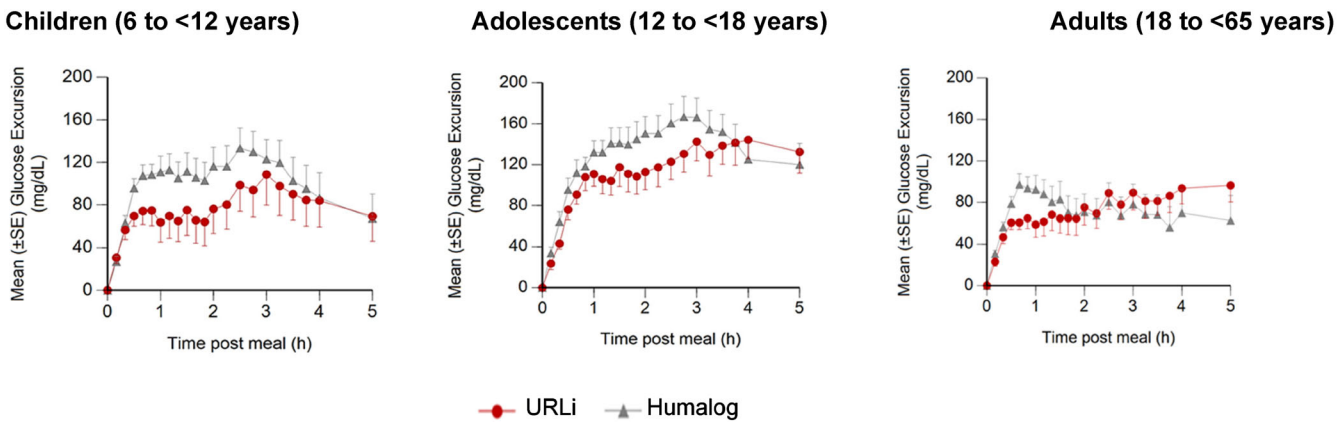


**FIGURE 2** Mean glucose concentration (±SE) versus time after single subcutaneous 0.2 U/kg dose of ultra rapid lispro (URLi) or Humalog® when dosed immediately before the meal in children (left), adolescents (middle) and adults (right) with type 1 diabetes

glucose excursions up to 2-h postmeal in both children and adolescent patients compared with Humalog. In addition, URLi reduced the change from baseline blood glucose at 1 h by 41.7 mg/dl in children, 18.6 mg/dl in adolescents and 33.7 mg/dl in adults (Table 3). Similarly, the change from baseline in blood glucose at 2 h was reduced by 31.7 mg/dl in children and by 38.5 mg/dl in adolescents with URLi compared with Humalog. The glucose excursion during a 5-h test meal period was reduced by 16% in children and 9% in adolescents compared with Humalog (Table 3).

There were no significant age group-by-treatment interactions on the glucodynamics, indicating that the treatment effect between URLi and Humalog was similar for all three age groups.

## 3.4 | Safety and tolerability results

The URLi was well tolerated following a single SC administration in all age groups. The majority of treatment-emergent AEs (TEAEs) were mild in severity and there were no discontinuations because of AEs. One serious AE of an abdominal trauma following a sports injury was reported in a 14-year-old adolescent male. The event occurred 2 days after the last dose of study drug and was deemed unrelated to study treatment.

In children and adolescents, the most frequently reported TEAEs in two or more participants were injection site erythema and nasopharyngitis (Table S1). In adults, none of the TEAEs were reported by more than one patient.

**TABLE 3** Statistical analysis of glucodynamics parameters for Humalog versus URLi

| Glucose parameter | | Treatment | N | LSM | *p*-Value | Ratio of LSM URLi: Humalog (95% CI) |
|---|---|---|---|---|---|---|
| $\Delta BG_{1h}$ (mg/dl) | Children | Humalog | 12 | 108.4 | .0077* | 0.62 (0.28, 1.00) |
| | | URLi | 12 | 66.8 | | |
| | Adolescents | Humalog | 13 | 130.8 | .1950 | 0.86 (0.69, 1.03) |
| | | URLi | 13 | 112.2 | | |
| | Adults | Humalog | 14 | 92.4 | .0180* | 0.64 (0.42, 0.92) |
| | | URLi | 14 | 58.7 | | |
| $\Delta BG_{2h}$ (mg/dl) | Children | Humalog | 12 | 113.4 | .1099 | 0.72 (0.37, 1.09) |
| | | URLi | 12 | 81.7 | | |
| | Adolescents | Humalog | 13 | 149.1 | .0513 | 0.74 (0.55, 0.97) |
| | | URLi | 12 | 110.6 | | |
| | Adults | Humalog | 14 | 70.8 | .8030 | 1.06 (0.61, 2.48) |
| | | URLi | 14 | 75.3 | | |
| $iAUC_{(0\text{-}1h)}$ (mg·h/dl) | Children | Humalog | 12 | 75.2 | .0261* | 0.77 (0.55, 1.02) |
| | | URLi | 12 | 57.6 | | |
| | Adolescents | Humalog | 13 | 81.1 | .0532 | 0.82 (0.67, 0.98) |
| | | URLi | 13 | 66.6 | | |
| | Adults | Humalog | 14 | 67.1 | .0078* | 0.71 (0.53, 0.93) |
| | | URLi | 14 | 47.5 | | |
| $iAUC_{(0\text{-}2h)}$ (mg·h/dl) | Children | Humalog | 12 | 180.7 | .0311* | 0.72 (0.46, 1.00) |
| | | URLi | 12 | 130.7 | | |
| | Adolescents | Humalog | 13 | 219.8 | .0612 | 0.81 (0.63, 0.99) |
| | | URLi | 13 | 178.6 | | |
| | Adults | Humalog | 14 | 145.5 | .1171 | 0.77 (0.54, 1.13) |
| | | URLi | 14 | 112.5 | | |
| $iAUC_{(0\text{-}5h)}$ (mg·h/dl) | Children | Humalog | 12 | 481.4 | .2724 | 0.84 (0.49, 1.21) |
| | | URLi | 12 | 403.0 | | |
| | Adolescents | Humalog | 13 | 646.6 | .3678 | 0.91 (0.76, 1.05) |
| | | URLi | 13 | 585.2 | | |
| | Adults | Humalog | 14 | 350.7 | .7418 | 1.06 (0.72, 1.82) |
| | | URLi | 14 | 372.2 | | |

Abbreviations: iBG1h, change from baseline glucose at 1 h; ΔBG2h, change from baseline glucose at 2 h; AUC, area under the concentration-time curve; BG, blood glucose; CI, confidence interval; LSM, least squares mean; N, total number of subjects; URLi, ultra rapid lispro; $iAUC_{(0\text{-}1h)}$, change from baseline incremental area under the concentration-time curve from time 0 to 1 h postdose; $iAUC_{(0\text{-}2h)}$, change from baseline incremental area under the concentration-time curve from time 0 to 2 h postdose; $iAUC_{(0\text{-}5h)}$, change from baseline incremental area under the concentration-time curve from time 0 to 5 h postdose.
*Note*: *p*-value is for treatment difference in LSM.
*$p < .05$.

In total, 11 participants (four children, four adolescents and three adults) who received URLi reported erythema at the injection site with the majority characterized as very slight or barely perceptible. Three participants (two children and one adult) reported mild injection site pain while one adolescent complained of itching at the injection site. For those participants who received Humalog, three participants (one child, one adolescent and one adult) reported erythema and one reported mild injection site pain. All events were transient and resolved with no clinical sequalae. No hypoglycaemic events of Level 3 (requiring assistance) were observed during the study. During the MMTTs, there were three events of Level 1 hypoglycaemia (plasma glucose ≤70-54 mg/dl) reported in children, no hypoglycaemic events were reported in adult or adolescent participants treated with URLi. Following Humalog administration, six events of Level 1 hypoglycaemia (one child, three adolescents and two adults) and two events of Level 2 hypoglycaemia (plasma glucose <54 mg/dl) were reported by one adolescent and one adult. All events were promptly resolved.

No clinically relevant changes in laboratory tests, vital signs, electrocardiograms or abnormal findings upon physical examinations occurred during the study.

## 4 | DISCUSSION

To our knowledge, this is the first study to evaluate the differences in the pharmacokinetic response and postprandial glucose response under controlled conditions of URLi compared with Humalog following single SC doses in children, adolescents and adults with T1D. This study demostrated that the accelerated time-action profile of URLi compared with Humalog as observed in adults was maintained in children and adolescents with T1D. No significant age group-by-treatment interactions were identified for pharmacokinetic or glucodynamic endpoints, indicating a consistent difference in treatment effect between URLi and Humalog across the age groups.

Consistently across the age groups, URLi showed an accelerated insulin lispro absorption with a reduction in late exposure while maintaining a similar total exposure compared with Humalog. These findings are consistent with the adult pharmacokinetic data from a crossover study comparing URLi with Humalog in younger (18-45 years) and elderly (≥65 years) individuals with T1D.[9] After URLi injection, insulin lispro absorption was accelerated compared with Humalog. This resulted in greater early insulin lispro exposure with URLi that better matched prandial carbohydrate absorption and provided better postprandial glucose control. Reflective of the faster insulin lispro absorption, URLi showed an earlier glucose-lowering effect compared with Humalog in children, adolescents, and adults following a SC injection. URLi reduced 1-h postprandial glucose in children, adolescents and adults compared with Humalog. These findings are consistent with the data reported in adults where URLi showed superiority to Humalog in reducing 1- and 2-h postprandial glucose excursions during the meal test in adults with T1D in both a controlled clinical pharmacology study,[8] as well as in a phase 3 study.[10] These study findings have recently been translated into a larger phase 3 treat-to-target study that evaluated the efficacy and safety of URLi versus Humalog in a paediatric population with T1D.[11] In children and adolescents with T1D, URLi showed a non-inferior glycated haemoglobin change, and a reduction in 1-h postprandial glucose and postprandial glucose excursions versus Humalog.

In addition to the accelerated insulin lispro absorption, URLi had a reduced late insulin lispro exposure compared with Humalog, which is anticipated to decrease the risk of late postprandial hypoglycaemia. Although not observed in this study, a larger trial found a lower hypoglycaemia rate (44.0% vs. 49.3%) for glucose concentration <54 mg/dl (3.0 mmol/L) with URLi compared with Humalog in the period >4 h postdose in paediatric participants with T1D.[11]

Overall, the insulin lispro exposure was similar for URLi and Humalog, which suggests that no dose conversion is required when transitioning participants from Humalog to URLi. Similarly, in support of this conclusion, a recent 26-week trial of URLi used a unit-to-unit conversion from Humalog and found no differences in basal, bolus and total insulin dose between treatment groups.[11]

URLi and Humalog were well tolerated by children and adolescent participants with T1D. The number of TEAEs was similar in children and adults receiving URLi with a slightly higher number seen in adolescents. Few events of Level 1 hypoglycaemia were observed with no Level 2 or 3 hypoglycaemia reported across all age groups while receiving URLi. Injection site reactions of transient erythema and pain were reported, all events were mild and did not result in study discontinuation. In the study by Wadwa et al. conducted in 716 paediatric participants,[11] injection site reactions were reported in 22 participants (7.9%) on mealtime URLi, eight participants (2.7%) on Humalog and four participants (2.9%) on postmeal URLi. Two participants discontinued the study because of injection site reactions: one reported moderate injection site pain and the other reported mild injection site reaction.[11]

The study design was strengthened by the inclusion of adults to support a direct comparison to the paediatric data, the double-blinding of participants and investigators, a crossover design that allowed for intra-patient comparison, the titration of blood glucose to the same starting value before dosing and initiating the MMTTs, and the standardized transition to NPH, which has the shortest half-life of current basal insulins to avoid the carry-over effects of longer-acting basal insulin, such as glargine and degludec. Limitations of the study included the use of a fixed individual dose of insulin, which was not optimized to the test meal, and the use of a liquid test meal, which is not a typical meal for individuals with T1D. The fixed dosing approach and liquid meal is consistent with a previously conducted studies in paediatric patients with another rapid acting analogue.[14,15] The postprandial glucose responses for both URLi and Humalog have been previously assessed in both solid meals and liquid meals and have shown similar responses to those observed in the present study.[8,10,16]

In summary, URLi demostrated an accelerated insulin lispro absorption and a greater postprandial glucose reduction compared with Humalog in children, adolescents and adult participants with T1D. The current findings in children and adolescents suggest the potential for URLi to improve postprandial glucose control. While premeal insulin administration is preferable, postmeal administration of URLi may be an effective alternative that is beneficial for the paediatric population, which often have difficulty adhering to premeal dosing schedules, owing to cognitive development or irregular eating patterns.

### AUTHOR CONTRIBUTIONS

Jennifer Leohr, Helle Linnebjerg, Qianyi Zhang and Thomas Danne were involved in the conception of the study. Jennifer Leohr, Robyn Pollom and Helle Linnebjerg participated in the drafting of the work. All authors participated in the critical revision, and approval of the final version of the manuscript. Torben Biester, Jennifer Leohr, Robyn Pollom, Helle Linnebjerg, Qianyi Zhang and Thomas Danne were involved in the study design. Ronnie Aronson, Torben Biester, Jennifer Leohr, Helle Linnebjerg, David E. Coutant and Thomas Danne were involved in the acquisition of data. Jennifer Leohr, Elizabeth LaBell, and Qianyi Zhang were involved in the statistical analysis of the data. Ronnie Aronson, Jennifer Leohr, Robyn Pollom, Helle Linnebjerg, Qianyi Zhang and Thomas Danne were involved with the interpretation of the study results.

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## CONFLICT OF INTEREST STATEMENT

Jennifer Leohr, Robyn Pollom, Helle Linnebjerg, Elizabeth LaBell, Qianyi Zhang and David E. Coutant, are employees and shareholders of Eli Lilly and Company. Torben Biester has acted as an advisor to Ascensia and Medtronic, is a deputy board leader of the German Paediatric Diabetes Association and has received speaker honoraria from Novo Nordisk, Sanofi and Synlab. Thomas Danne possesses stock/stock options for DreaMed Ltd, and has received speaker honoraria from AstraZeneca, Bayer, Boehringer, Dexcom, Eli Lilly, Lifescan, Medtronic, Novo Nordisk, Roche, Sanofi, Vertex and Ypsomed. Ronnie Aronson has acted as a consultant to Bayer, Boehringer-Ingelheim, Eli Lilly, Novo Nordisk, Viatris, Xeris and Zealand. Ronnie Aronson has received speaker honoraria from Abbott, Astra Zeneca, Boehringer-Ingelheim, Eli Lilly, Gilead, Merck, Novo Nordisk, Pfizer, Sanofi, Xeris and Zealand, has acted as an advisor to Eli Lilly and possesses stock/stock options for LMC Diabetes and Endocrinology.

## PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15063.

## DATA AVAILABILITY STATEMENT

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the 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, 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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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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