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ORIGINAL RESEARCH ARTICLE

Pharmacokinetics and Glucodynamics of Ultra Rapid Lispro (URLi) versus Humalog® (Lispro) in Younger Adults and Elderly Patients with Type 1 Diabetes Mellitus: A Randomised Controlled Trial

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Abstract

Background Ultra rapid lispro (URLi) is a novel insulin lispro formulation developed to more closely match physiological insulin secretion and improve postprandial glucose control. This study compared the pharmacokinetics, glucodynamics, safety, and tolerability of URLi and Humalog® in patients with type 1 diabetes mellitus (T1DM).

Methods This was a phase I, two-period, randomised, double-blind, crossover glucose clamp study in younger adult (aged 18–45 years; $n = 41$) and elderly (aged ≥65 years; $n = 39$) patients with T1DM. At each dosing visit, patients received either URLi or Humalog (15 units subcutaneously) followed by a 10 h automated euglycaemic clamp procedure. Serum insulin lispro and blood glucose were measured.

Results Insulin lispro appeared in serum 6 min faster, and exposure was 7.2-fold greater over the first 15 min postdose with URLi versus Humalog in both age groups. Exposure beyond 3 h postdose was 39–41% lower, and exposure duration was reduced by 72–74 min with URLi versus Humalog in both age groups. Onset of insulin action was 11–12 min faster, and insulin action was 3-fold greater over the first 30 min postdose with URLi versus Humalog in both age groups. Insulin action beyond 4 h postdose was 44–54% lower, and duration of action was reduced by 34–44 min with URLi versus Humalog in both age groups. Overall exposure and total insulin action remained similar for both treatments. URLi and Humalog were well tolerated.

Conclusion In patients with T1DM, URLi showed ultra-rapid pharmacokinetics and glucodynamics, with the differences between URLi and Humalog in elderly patients mirroring those in younger adults.

ClinicalTrials.gov identifier: NCT03166124.

1 Introduction

Type 1 diabetes mellitus (T1DM) is characterised by β-cell destruction resulting in insulin deficiency, and requires intensive insulin replacement therapy to control basal and prandial blood glucose [1]. Compared with rapid physiological secretion of prandial insulin in healthy individuals, regular human insulin administered subcutaneously before a meal has a slower onset of action and longer duration of action, potentially leading to early postprandial hyperglycaemia and late postprandial hypoglycaemia [2–4]. Rapid-acting insulin analogues, such as insulin lispro, aspart, and glulisine, were developed to be absorbed more rapidly and have a faster onset of insulin action compared with regular human insulin [5]. Although rapid-acting insulins have shown superiority over regular insulin at reducing postprandial glycaemic excursions [6], they cannot always match carbohydrate absorption profiles, and there remains a need to develop faster, ultra-rapid-acting insulin that more closely mimics the endogenous insulin response to food intake [2].

Insulin lispro (Humalog®) is a commercially available, rapid-acting human insulin analogue administered subcutaneously within 15 min premeal or immediately after a

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Key Points

After injection with ultra rapid lispro (URLi), insulin appeared in the blood at approximately 1 min. Compared with Humalog®, insulin appearance was five times faster and early insulin exposure was up to seven-fold greater with URLi, resulting in greater early glucose-lowering effect. Insulin also left the blood sooner, reducing the late glucose-lowering effect of URLi compared with Humalog, and potentially reducing the occurrence of late hypoglycaemia seen with rapid-acting insulins.

The pharmacokinetic and glucodynamic differences between URLi and Humalog observed in younger adult patients were maintained in elderly patients with type 1 diabetes.

The ultra-rapid pharmacokinetic and glucodynamic profile of URLi has the potential to improve postmeal glucose control over current rapid-acting insulin analogs.

meal to improve glycaemic control in patients with diabetes mellitus [7]. 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 [8–10]. URLi has shown accelerated insulin lispro absorption, with corresponding faster onset of insulin action and reduced duration of insulin action compared with Humalog in Japanese patients with T1DM [11]. Initial disclosures of phase III results demonstrated superiority of URLi to Humalog in controlling postprandial glucose excursions in patients with type 1 or 2 diabetes [12, 13].

Owing to an ageing population, the number of elderly patients who require insulin therapy to manage their diabetes is increasing [14]. Regulatory guidance recommends that, for drugs likely to be used in the elderly, clinical studies should include elderly as well as non-elderly patients [15, 16]. The aim of this study was to compare the insulin lispro pharmacokinetics, glucodynamic characteristics during a euglycaemic clamp, safety, and tolerability of URLi versus Humalog after a single 15-unit subcutaneous dose in younger adult (18–45 years) and elderly (≥65 years) patients with T1DM.

2 Methods

2.1 Study Design

This was a phase I, two-period, randomised, double-blind, two-centre (Profil, Neuss and Mainz, Germany), crossover glucose clamp study in younger adult patients and elderly patients with T1DM. 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 (NCT03166124).

2.2 Study Population

Eligible patients were male or female, aged 18–45 years (younger adults) or ≥65 years (elderly), with a body mass index of 18.5–30.0 kg/m^2, diagnosed with T1DM for ≥1 year, and receiving insulin as multiple daily injections or a continuous subcutaneous insulin infusion (CSII). Patients were to have had fasting C-peptide ≤0.30 nmol/L, haemoglobin A1c < 9.0%, and no episodes of severe hypoglycaemia within the past 6 months. Patients were excluded if they were receiving daily insulin >1.5 units/kg/body weight or if their insulin regimen had changed in the 3 months before screening. Other main exclusion criteria were significant lipohypertrophy in the target abdominal injection area, proliferative retinopathy or maculopathy, severe neuropathy, or a history of renal impairment demonstrated by a glomerular filtration rate < 60 mL/min/1.73 m^2 (estimated according to the Chronic Kidney Disease Epidemiology Collaboration creatinine equation) or serum creatinine ≥ 126 µmol/L (1.43 mg/dL) for male patients or ≥ 111 µmol/L (1.26 mg/dL) for female patients.

2.3 Treatment Protocol

Patients were randomised to receive a single 15-unit subcutaneous dose of study drug (URLi or Humalog U100 formulations [Eli Lilly, Indianapolis, IN, USA]) in the first dosing period and the alternate study drug in the second dosing period (Fig. 1). Before each dosing period, patients discontinued their basal insulin for a predefined washout period (≥72 h for insulin degludec or insulin glargine U300, ≥ 48 h for insulin detemir or glargine, ≥ 24 h for neutral protamine Hagedorn or other intermediate-acting insulins, and ≥ 6 h for any bolus injection of short-acting insulin via CSII). Patients receiving CSII therapy were to switch to insulin glulisine (Apidra®; Sanofi, Paris, France) ≥ 8 h before dosing and to discontinue basal insulin delivery ≥ 3 h before dosing. An outpatient period of 3–15 days occurred between dosing periods. Follow-up was conducted ≥ 14 days after the second dosing period.

2.4 Euglycaemic Clamp

At each dosing visit, subjects underwent a 10 h automated euglycaemic clamp procedure using the ClampArt® device

(Profil, Neuss, Germany) under fasted conditions. Prior to dosing, a target blood glucose of 100 mg/dL (5.5 mmol/L) ± 10% was achieved using a variable intravenous infusion over 1–6 h of either 20% dextrose solution or insulin glulisine (Apidra; Sanofi). Blood glucose was maintained at 100 mg/dL ± 10% (5.5 ± 0.55 mmol/L) without any glucose infusion for the last 30 min before dosing; insulin glulisine infusion was stopped at least 10 min before dosing. If stable blood glucose was not achieved, the run-in period was prolonged and dosing was postponed. Baseline was the mean of blood glucose concentrations at 6, 4, and 2 min before dosing, and the onset of insulin action was defined as when blood glucose dropped by 5 mg/dL (0.3 mmol/L) from baseline. After the onset of insulin action was reached, a variable intravenous glucose infusion was initiated to keep blood glucose at 100 mg/dL (5.5 mmol/L). The glucose infusion rate (GIR) needed to keep blood glucose at the target level was recorded every minute throughout the glucose clamp. Manual blood samples were collected and measured (SuperGL glucose analyser, Dr. Müller; Hitado, Möhnesee, Germany) for blood glucose at least every 30 min during the clamp procedure to validate clamp glucose sensor measurements. The clamp procedure was continued for 10 h postdose or until blood glucose concentrations increased to >200 mg/dL (11.1 mmol/L) without any glucose being administered for at least 30 min, whichever was earlier.

2.5 Bioanalysis

Blood samples for insulin lispro pharmacokinetic analysis were taken every 5 min during the first hour postdose, at 70, 90, 120, 150, and 180 min, then every hour thereafter up to 10 h. 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%. Quantification of insulin lispro was not affected by the presence of lipaemic serum, haemolysed serum, treprostinil (1 ng/mL), human insulin (10 ng/mL), insulin aspart (600 pmol/L), insulin glargine (150 pmol/L), or insulin glulisine (600 pmol/L).

Treprostinil sampling times were 15, 30, 60, and 120 min postdose. Plasma treprostinil was measured by liquid chromatography-mass spectrometry/mass spectrometry assay. The LLOQ was 0.0100 ng/mL, inter-assay precision and accuracy were ≤10%, 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 pharmacokinetic parameters were calculated by non-compartmental methods using Phoenix® version 7.0 and S-PLUS® version 8.2. Early exposure endpoints included time to early half-maximal drug concentration (early 50% t_{max}); area under the concentration-time curve (AUC) from time 0 to 15 min ($AUC_{0–15min}$), to 30 min ($AUC_{0–30min}$), and to 1 h ($AUC_{0–1h}$); and onset of appearance, defined as the time that serum insulin lispro reached the LLOQ. Determination of onset of appearance used a linear interpolation between the time of dosing (zero serum insulin lispro concentration) and the time of the first quantifiable serum insulin lispro concentration. Late exposure endpoints included time to late half-maximal drug concentration (late 50% t_{max}); AUC from time 2 to 10 h ($AUC_{2–10h}$) and from 3 to 10 h ($AUC_{3–10h}$); and duration of exposure, defined as the time from dosing until serum insulin lispro reached the LLOQ. Overall exposure endpoints were AUC from time 0 to infinity ($AUC_{0–\infty}$) and maximum observed drug concentration (C_{max}).

Glucodynamic assessments were determined from the glucose clamp procedure, where the GIR over time was used as a measure of insulin effect. A locally weighted scatterplot smoothing function with a span of 0.1 was applied to all individual GIR-versus-time profiles in each treatment group and/or period. Fitted data for each patient were used to calculate glucodynamic parameters, except time to onset of insulin action (T_{onset}), which was based on raw GIR data. Glucodynamic analyses were conducted using Phoenix version 6.4 or higher and S-PLUS version 8.2. Early insulin action endpoints were T_{onset}, defined as the time when blood glucose drops by 5 mg/dL (0.3 mmol/L) from baseline; time to half-maximal GIR before time to maximum GIR (early

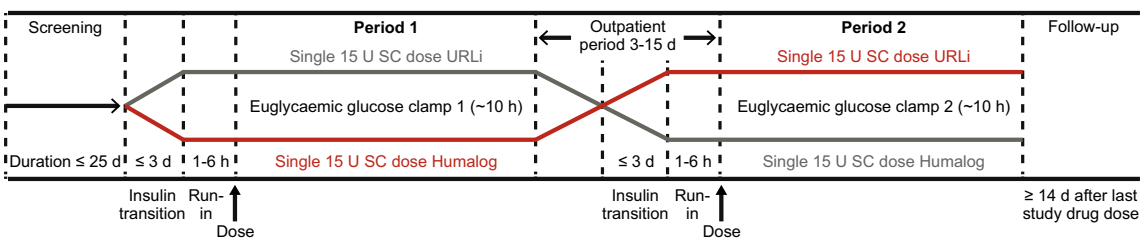

Fig. 1 Trial design. *SC* subcutaneous, *U* units, *URLi* ultra rapid lispro

50% tR_{max}); and total amount of glucose infused over the first 30 min ($G_{tot,0–30min}$), first hour ($G_{tot,0–1h}$), and first 2 h ($G_{tot,0–2h}$). Late insulin action endpoints were time to half-maximal GIR after time to maximum GIR (late 50% tR_{max}); total amount of glucose infused from 3 h to end of the clamp ($G_{tot,3h–End}$) and from 4 h to end of the clamp ($G_{tot,4h–End}$); and duration of insulin action, defined as the time from T_{onset} to end of the clamp. Total insulin action endpoints were maximum GIR (R_{max}) and total amount of glucose infused over the duration of the clamp (G_{tot}).

Safety assessments included adverse events, injection site assessments (immediately postdose, 1 and 4 h postdose, and at end of the clamp), clinical laboratory assessments (predose in period 1 and as deemed necessary), vital signs, and electrocardiograms (predose and at end of the clamp).

2.7 Statistical Analysis

At least 34 completers in each age group provided approximately 95% power to demonstrate a 40% increase in insulin lispro $AUC_{0–30min}$ between URLi and Humalog within each age group. Pharmacokinetic and glucodynamic analyses included all patients who completed at least one euglycaemic clamp procedure. Log-transformed pharmacokinetic and glucodynamic parameters were evaluated using linear mixed models with treatment, sequence, and period as fixed effects and patient as random effect; treatment ratios of geometric least squares (LS) means and corresponding 95% confidence intervals (CIs) were estimated from the model. Pharmacokinetic and glucodynamic time parameters and glucodynamic parameters with at least one patient with a value of 0 were analysed using the same model without log transformation; treatment differences in LS means and 95% CIs were calculated from the model, and treatment ratios of LS means and 95% CIs were estimated using Fieller's theorem [17]. Statistical analyses were conducted using SAS® version 9.4 (SAS Institute, Cary, NC, USA) at a 5% significance level.

Prespecified exploratory analyses comparing the treatment effect (URLi vs. Humalog) between younger adult patients and elderly patients were conducted for pharmacokinetic and glucodynamic endpoints. The model was similar to that for each patient population, with the addition of age group and interaction of age group-by-treatment as fixed effects.

3 Results

3.1 Demographic and Baseline Characteristics

Of 93 patients screened, 80 patients with T1DM were enrolled (electronic supplementary Fig. S1). Of these, 41 were younger adult patients (aged 22–45 years) and 39 were elderly patients (aged 65–77 years). All 41 of the younger adult patients received at least one dose of study drug and 38 completed the study. Three younger adults withdrew after the first dosing visit (URLi: two; Humalog: one), one owing to a serious adverse event (SAE) of hypoglycaemia (occurring 6 days after URLi administration and considered unrelated to study treatment) and two owing to consent withdrawal. Of the 39 elderly patients, 38 received at least one dose of study drug and 37 completed the study. One elderly patient was withdrawn before study treatment, and one was withdrawn after the first dosing visit owing to an adverse event of hypotension following Humalog dosing that was considered by the investigator to be related to study procedure but not study drug. Demographics, baseline characteristics, and previous insulin therapy are shown in Table 1.

3.2 Pharmacokinetics

3.2.1 Insulin Lispro Concentration Profiles

Mean serum insulin lispro concentration-time profiles were shifted to the left following dosing with URLi, compared with Humalog, in younger adult patients (Fig. 2a, c) and elderly patients (Fig. 2b, d), demonstrating accelerated insulin lispro absorption, reduced late exposure, and overall shorter exposure duration with URLi versus Humalog in both age groups.

3.2.2 Early Insulin Lispro Exposure

In younger adult patients, onset of insulin lispro appearance was 5.6 min faster following URLi dosing compared with Humalog (1.26 vs. 6.84 min; $p < 0.0001$), and early 50% t_{max} was 14 min earlier (14.8 vs. 29.0 min; $p < 0.0001$) (Fig. 3a). 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 15 min after URLi dosing, when $AUC_{0–15min}$ was 7.2-fold greater ($p < 0.0001$) with URLi versus Humalog (Fig. 3b). The significant increase in insulin lispro exposure with URLi was maintained over the first hour after dosing ($p < 0.0001$) (Fig. 3b).

The accelerated early insulin lispro exposure in younger adult patients was mirrored in elderly patients (Fig. 3a, b). In elderly patients, onset of insulin lispro appearance was 5.5 min faster with URLi compared with Humalog (1.32 vs. 6.85 min; $p < 0.0001$), and early 50% t_{max} was 12 min earlier (15.6 vs. 27.9 min; $p < 0.0001$). As in the younger adult patients, insulin lispro exposure in elderly patients showed the largest increase during the first 15 min after URLi dosing, with $AUC_{0–15min}$ being 7.2-fold greater ($p < 0.0001$) for URLi versus Humalog (Fig. 3b).

Table 1 Demographics and clinical characteristics

	Younger adults [$n = 41$]	Elderly [$n = 39$]
Age, years [mean (range)]	32.0 (22–45)	68.5 (65–77)
Sex [*n* (%)]		
Male	28 (68.3)	22 (56.4)
Female	13 (31.7)	17 (43.6)
White [*n* (%)]	41 (100.0)	39 (100.0)
Weight, kg [mean (SD)]	78.4 (10.0)	76.7 (12.8)
BMI, kg/m^2 [mean (SD)]	24.8 (2.4)	26.2 (2.6)
HbA1c, % [mean (SD)]	7.2 (0.6)	7.2 (0.7)
Duration of T1DM, years [mean (SD)]	17.7 (9.3)	37.5 (14.7)
Total daily insulin dose, units [mean (SD)]	49.2 (15.3)	44.1 (22.8)
Previous insulin therapy [*n* (%)]		
Basal MDI	24 (58.5)	24 (61.5)
Rapid-acting MDI	23 (56.1)	22 (56.4)
Short-acting MDI	0	2 (5.1)
Mixtard MDI	1 (2.4)	0
Rapid-acting CSII	17 (41.5)	15 (38.5)

BMI body mass index, *CSII* continuous subcutaneous insulin infusion, *HbA1c* haemoglobin A1c, *MDI* multiple daily injections, *SD* standard deviation, *T1DM* type 1 diabetes mellitus

3.2.3 Late Insulin Lispro Exposure

Late insulin lispro exposure, from 2 to 10 h postdose, was significantly reduced for URLi compared with Humalog in both age groups ($p \leq 0.0021$) (Fig. 3d). From 3 to 10 h postdose, exposure was reduced by 41% in younger adult patients and 39% in elderly patients ($p < 0.0001$) (Fig. 3d). Duration of insulin lispro exposure was reduced by 74 min in younger adult patients with URLi versus Humalog (371 vs. 445 min; $p < 0.001$) and by 72 min in elderly patients (404 vs. 475 min; $p < 0.0001$) (Fig. 3c).

3.2.4 Overall Insulin Lispro Exposure

$AUC_{0-\infty}$ and C_{max} did not differ significantly between URLi and Humalog in either age group (Fig. 3e).

3.2.5 Comparison of Pharmacokinetic Treatment Effect Between Ultra Rapid Lispro (URLi) and Humalog by Age Group

There were no significant age group-by-treatment interactions, indicating that the pharmacokinetic differences between URLi and Humalog are similar in both age groups (data not shown).

3.2.6 Treprostinil Exposure

Plasma treprostinil was below the limit of quantification in all except one of 423 samples after URLi injection. In this patient, treprostinil was not detectable in any other post-injection samples, and thus this is likely to be a spurious result.

3.3 Glucodynamics

3.3.1 Glucose Infusion Profiles

Mean GIR profiles with URLi were left-shifted compared with Humalog in younger adult patients (Fig. 4a, c) and elderly patients (Fig. 4b, d), indicating a faster onset of insulin action, reduced late insulin action, and shorter duration of insulin action with URLi versus Humalog in both age groups. The glucose clamp maintained stable mean blood glucose profiles following URLi and Humalog dosing (electronic supplementary Fig. S2). The earlier rise in blood glucose with URLi versus Humalog, starting at approximately 5 h postdose, reflects the shorter duration of insulin action of URLi.

3.3.2 Early Insulin Action

In younger adult patients, onset of insulin action was 10.8 min faster with URLi versus Humalog (20.1 vs. 31.0 min; $p = 0.0007$), and early 50% tR_{max} was 14.1 min earlier (33.2 vs. 47.3 min; $p < 0.0001$) (Fig. 5a). This faster onset of insulin action with URLi significantly increased insulin action over the early part of the euglycaemic clamp, with a 3-fold increase in insulin action during the first 30 min postdose for URLi versus Humalog ($p < 0.0001$) (Fig. 5b). The increase in insulin action was maintained over the first 2 h postdose ($p < 0.0001$) (Fig. 5b).

Elderly patients also showed the faster onset and increase in early insulin action with URLi that was observed in younger adult patients (Fig. 5a, b). In elderly patients, onset of insulin action was 11.8 min faster with URLi versus Humalog (19.0 vs. 30.8 min; $p < 0.0001$), early 50% tR_{max} was 9.9 min earlier (36.8 vs. 46.8 min; $p = 0.012$), and insulin action over the first 30 min increased 3-fold ($p < 0.0001$) (Fig. 5a, b).

3.3.3 Late Insulin Action

Late insulin action, from 3 h postdose to end of the euglycaemic clamp, was significantly reduced with URLi compared with Humalog in both age groups ($p \leq 0.0002$) (Fig. 5d). From 4 h postdose, insulin action was reduced by 54% with URLi versus Humalog in younger adult patients and

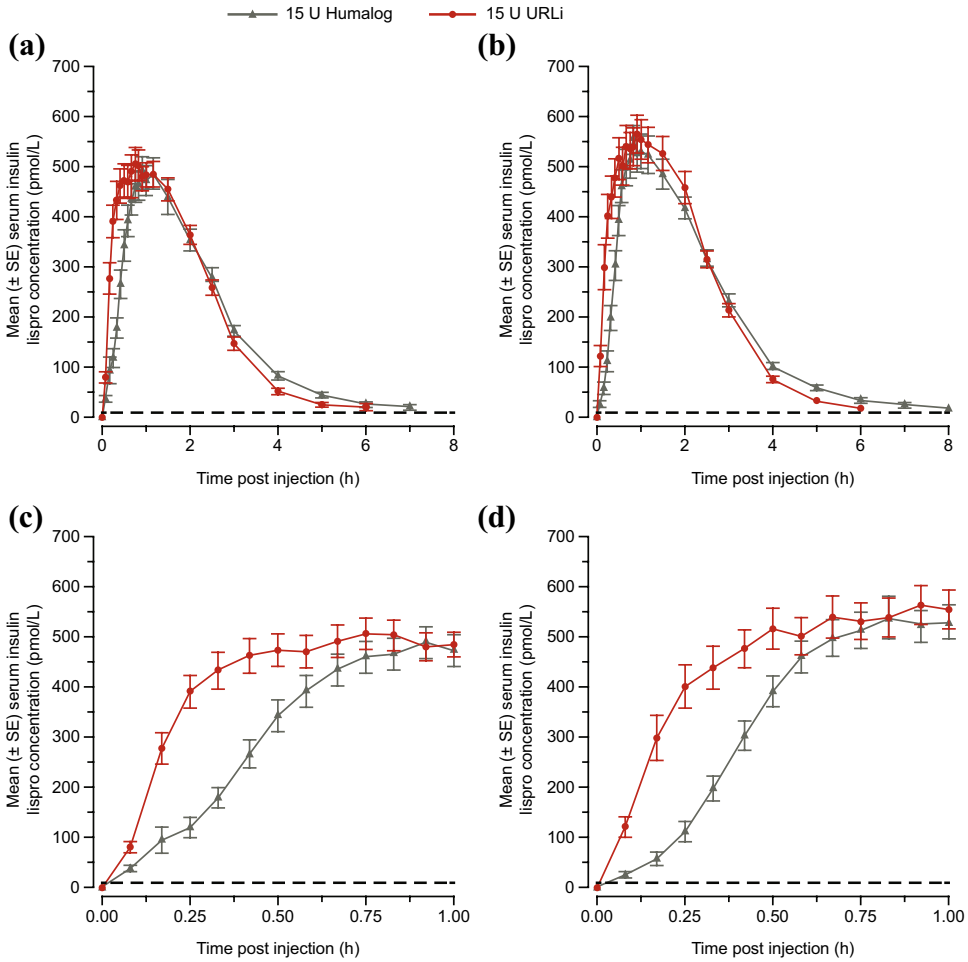

Fig. 2 Mean (±SE) serum insulin lispro concentration-time profile for URLi and Humalog. **a** 0–8 h after injection in younger adult patients; **b** 0–8 h after injection in elderly patients; **c** 0–1 h after injection in younger adult patients; and **d** 0–1 h after injection in elderly patients. Dashed line shows LLOQ for the assay. *LLOQ* lower limit of quantification, *SE* standard error, *U* units, *URLi* ultra rapid lispro

by 44% in elderly patients ($p < 0.0001$) (Fig. 5d). URLi significantly reduced late 50% tR_{max} in both age groups versus Humalog ($p < 0.0001$) and reduced overall duration of insulin action by 44 min in younger adult patients (298 vs. 342 min; $p = 0.0003$) and by 34 min in elderly patients (318 vs. 352 min; $p = 0.0037$) (Fig. 5c).

3.3.4 Total Insulin Action

G_{tot} did not differ significantly between URLi and Humalog in either age group (Fig. 5e). R_{max} was 1.14-fold greater for URLi versus Humalog in both age groups ($p \leq 0.02$) (Fig. 5e).

3.3.5 Comparison of Glucodynamic Treatment Effect between URLi and Humalog by Age Group

No significant age group-by-treatment interactions were identified for glucodynamic endpoints, indicating that the treatment differences in insulin action between URLi and Humalog are similar in both age groups (data not shown).

3.4 Safety and Tolerability

Both URLi and Humalog were well tolerated and no unexpected safety signals were identified. The incidence of treatment-emergent adverse events (TEAEs) was 15% in younger adult patients following each treatment, whereas in elderly patients the incidence of TEAEs was higher following Humalog dosing (31.6%) than URLi dosing (18.9%) (Table 2). Common TEAEs were vomiting, nausea, and headache in both age groups, and nasopharyngitis in elderly patients (Table 2). All TEAEs were mild or moderate in both age groups. One younger adult experienced an SAE of hypoglycaemia 6 days after receiving URLi, which was considered unrelated to study drug and resolved after 5 min with intravenous glucose. Of 154 injections administered, local reactions were identified in two patients after URLi injection (mild erythema and injection site urticaria 4 h postdose, and erythema and oedema at end of the clamp in one younger adult; moderate itching immediately postdose in one elderly patient) and in one patient following Humalog injection (mild pain immediately postdose in an elderly patient). No

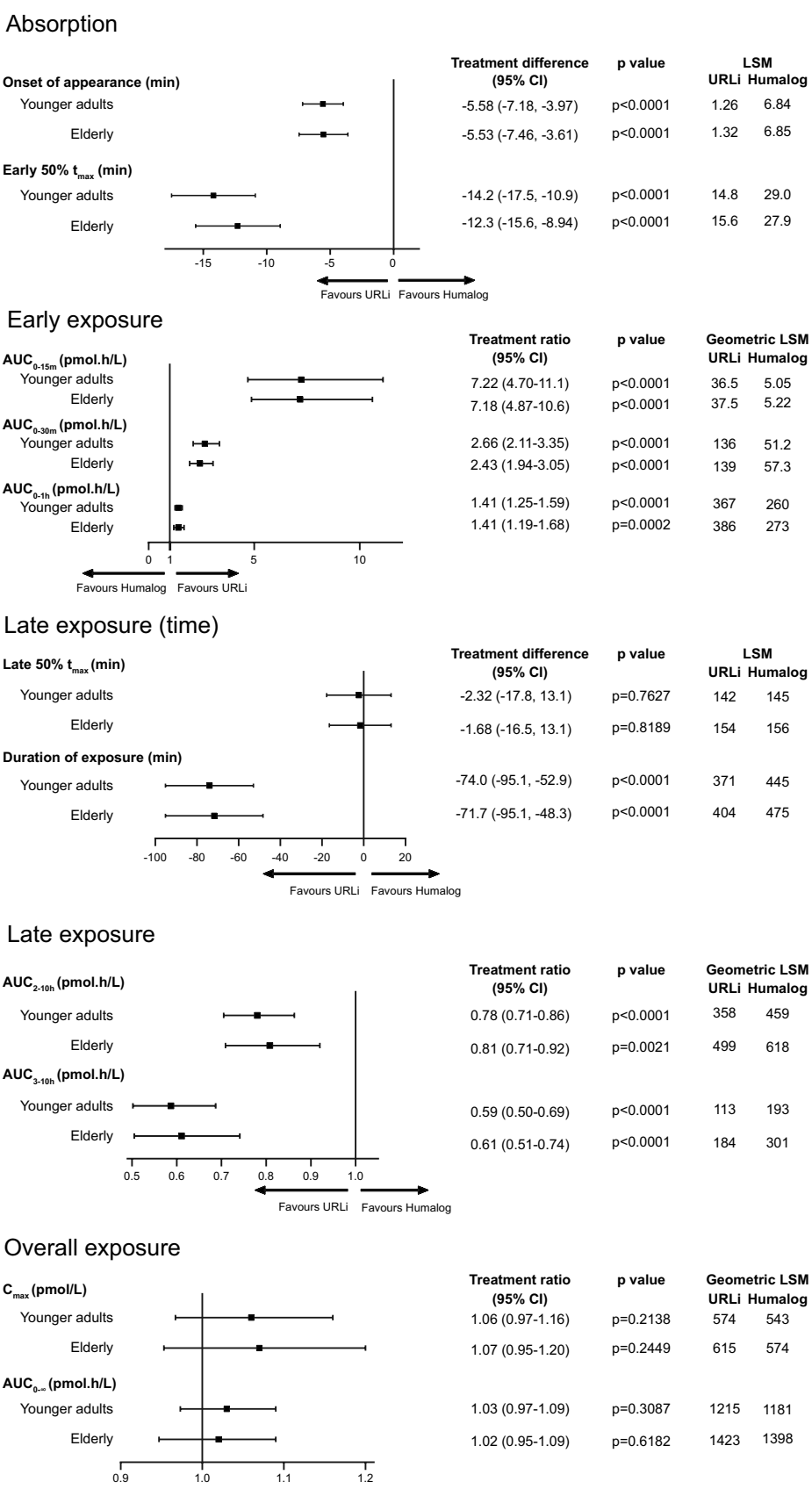

Fig. 3 Forest plots of insulin lispro pharmacokinetic parameters. *AUC* area under the concentration-time curve, $AUC_{0–15min}$ AUC from 0 to 15 min, $AUC_{0–30min}$ AUC from 0 to 30 min, $AUC_{0–1h}$ AUC from 0 to 1 h, $AUC_{2–10h}$ AUC from 2 to 10 h, $AUC_{3–10h}$ AUC from 3 to 10 h, $AUC_{0–\infty}$ AUC from time 0 to infinity, *CI* confidence interval, C_{max} maximum observed drug concentration, *early 50%* t_{max} time to early half-maximal drug concentration, *late 50%* t_{max} time to late half-maximal drug concentration, *LSM* least squares means, *URLi* ultra rapid lispro

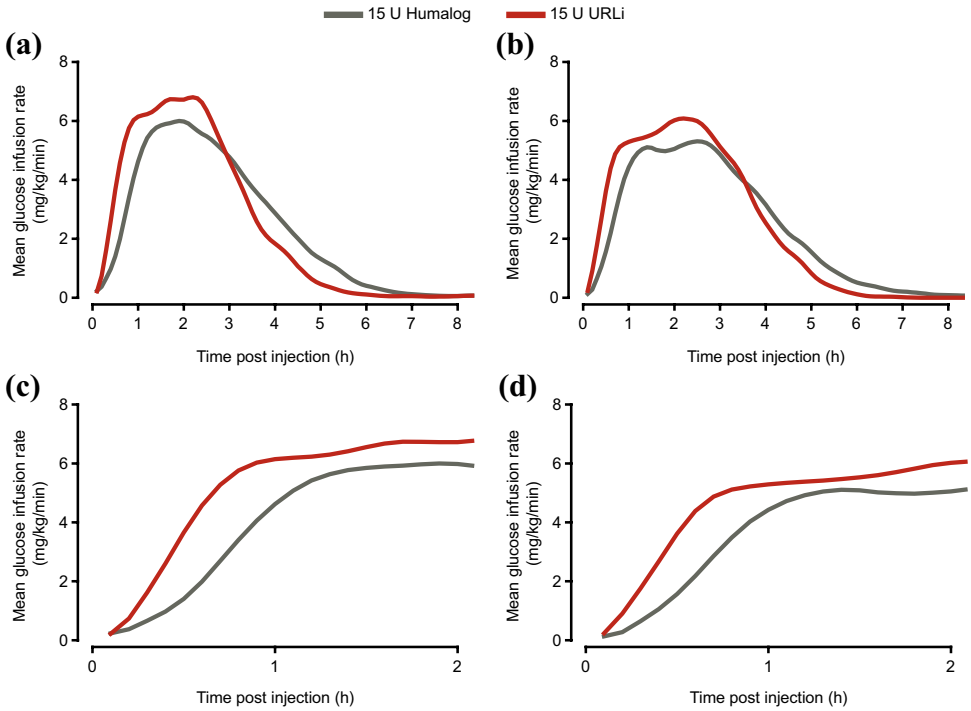

Fig. 4 Mean LOESS fits of glucose infusion rate over time for URLi and Humalog. **a** 0–8 h after injection in younger adult patients; **b** 0–8 h after injection in elderly patients; **c** 0–2 h after injection in younger adult patients; and **d** 0–2 h after injection in elderly patients. *LOESS* locally weighted scatterplot smoothing, *U* units, *URLi* ultra rapid lispro

clinically relevant changes in vital signs, electrocardiograms, or laboratory values were observed.

4 Discussion

URLi demonstrated accelerated insulin lispro absorption, with a reduction in late exposure and an overall shorter pharmacokinetic duration compared with Humalog in both younger adult patients and elderly patients with T1DM. These shifts in pharmacokinetic profile with URLi resulted in a faster onset of insulin action and reduced late insulin action for URLi versus Humalog in both age groups. The pharmacokinetic and glucodynamic differences between URLi and Humalog in elderly patients mirrored those observed in younger adult patients. URLi was well tolerated in patients with T1DM in both age groups.

After URLi injection, insulin lispro was detectable in serum at approximately 1 min, which was 6 min faster than Humalog in both age groups. The accelerated insulin lispro absorption of URLi may more closely match the rapid physiologically induced prandial increase in circulating insulin in healthy individuals [18]. The resulting greater early insulin lispro exposure and early insulin action with URLi may be better able to match prandial carbohydrate absorption profiles, thus providing better blood glucose control. Improvements in postprandial glucose control seen with URLi versus Humalog in the PRONTO-T1D phase III study in patients with T1DM [13] reflect the faster pharmacokinetic and glucodynamic profile of URLi in this study. The accelerated insulin absorption profile of URLi may also allow for improved postprandial glucose control in patients who choose to dose after meals. This could be especially beneficial in elderly patients who may have difficulty adhering to premeal dosing schedules, owing to cognitive impairment or irregular eating patterns [2].

In addition to its accelerated insulin lispro absorption and early insulin action, URLi had reduced late insulin lispro exposure and a consequent reduction in late insulin action compared with Humalog. The earlier rise in blood glucose at the end of the clamp with URLi versus Humalog is also reflective of the shorter duration of exposure and insulin action of URLi. The reduced late insulin action of URLi is anticipated to decrease the risk of late postprandial hypoglycaemia. In the PRONTO-T1D study, URLi had a 37% lower hypoglycaemia rate (glucose concentration <54 mg/dL [3.0 mmol/L]) compared with Humalog in the period >4 h postdose in patients with T1DM [13].

Overall insulin lispro exposure and total glucose infused were similar for URLi and Humalog, which suggests that no dose conversion is required when transitioning patients from Humalog to URLi. In support of this, the phase III study in patients with T1DM (PRONTO-T1D) initiated the dosing of URLi based on a unit-to-unit conversion from Humalog [13]. At the end of the 26-week treatment period, mean daily bolus dose was not statistically significantly different between treatment groups.

Similar results were seen in a euglycaemic clamp crossover study comparing URLi with Humalog in Japanese

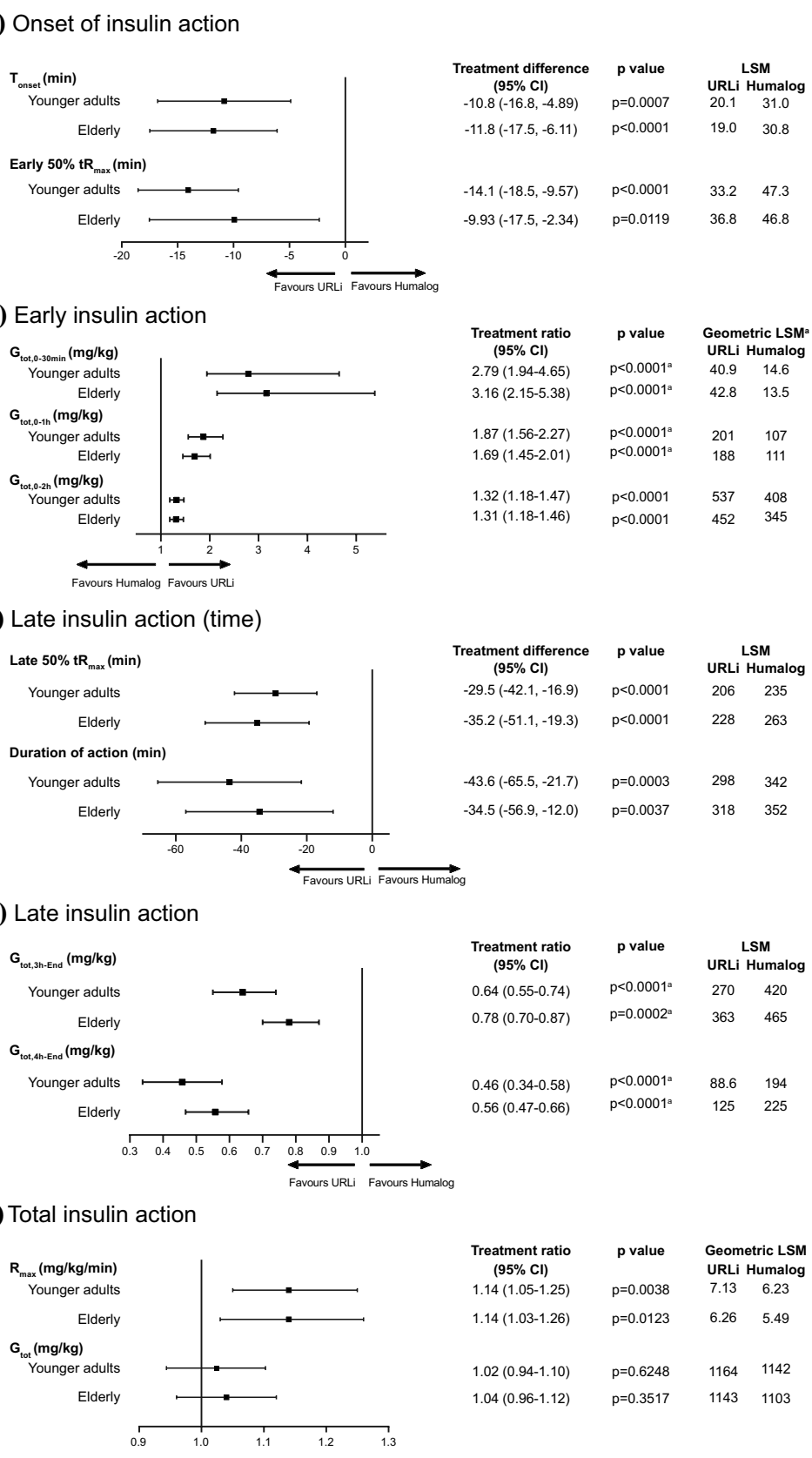

Fig. 5 Forest plots of insulin lispro glucodynamic parameters. [a] For glucodynamic parameters with at least one patient with a value of 0, treatment ratios of LSM and 95% CIs were estimated using Fieller's theorem, and *p*-values were not calculable; presented *p*-values are for treatment difference in LSM. *CI* confidence interval, *early 50% tR_{max}* time to half-maximal glucose infusion rate before maximum glucose infusion rate, G_{tot} total amount of glucose infused over the duration of the clamp, $G_{tot,0–30min}$ total amount of glucose infused over the first 30 min, $G_{tot,0–1h}$ total amount of glucose infused over the first hour, $G_{tot,0–2h}$ total amount of glucose infused over the first 2 h, $G_{tot,3h–End}$ total amount of glucose infused from 3 h to end of the clamp, $G_{tot,4h–End}$ total amount of glucose infused from 4 h to end of the clamp, *late 50% tR_{max}* time to half–maximal glucose infusion rate after maximum glucose infusion rate, *LSM* least squares means, R_{max} maximum glucose infusion rate, T_{onset} time to onset of insulin action, *URLi* ultra rapid lispro

Table 2 Treatment-emergent adverse events

	Younger adults		Elderly	
	URLi [$n = 40$]	Humalog [$n = 39$]	URLi [$n = 37$]	Humalog [$n = 38$]
Any TEAE, *n* (%) [events]	6 (15.0) [13]	6 (15.4) [14]	7 (18.9) [12]	12 (31.6) [23]
TEAEs occurring in more than one patient in any treatment group, *n* [events]				
Vomiting	3 [3]	4 [4]	4 [3]	5 [5]
Headache	2 [2]	3 [3]	1 [1]	4 [4]
Nausea	2 [2]	4 [4]	1 [1]	2 [2]
Nasopharyngitis	1 [1]	1 [1]	2 [2]	0

TEAEs were coded using the Medical Dictionary for Regulatory Activities version 19.1

TEAE treatment-emergent adverse event, *URLi* ultra rapid lispro

adult patients (mean ± standard deviation age, 39.5 ± 11.3 years) with T1DM [11]. URLi showed accelerated absorption, reducing early 50% t_{max} by 56% and increasing AUC $_{0–30min}$ by 2.4-fold versus Humalog, which is similar to the 49% reduction in early 50% t_{max} and 2.7-fold increase in $AUC_{0–30min}$ seen in younger adults in our study. In the Japanese patients, URLi onset of insulin action was 6.4 min faster than with Humalog, and $G_{tot,0–30min}$ increased 2.2-fold, which is also similar to the results of our study. Both studies found a significant reduction in duration of insulin action with URLi versus Humalog, with no significant difference in total glucose infused.

Our study has demonstrated that the accelerated time-action profile of URLi compared with Humalog is preserved in elderly patients with T1DM, despite the known decreases in insulin clearance and sensitivity with age [19–21]. 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 two age groups. In addition, there were no significant differences in overall exposure or total insulin action with URLi between the elderly and younger adult populations.

Similar to previous studies, the treprostinil in the URLi formulation was below the quantification limit, with no evidence of systemic pharmacology [11]. URLi showed an acceptable safety profile in both age groups. URLi was well tolerated in elderly patients, a population in which treatment can be complicated by comorbidities and concomitant medications.

The strengths of this study were the crossover design enabled each patient to act as their own control; the controlled washout period eliminated interference by basal or other prandial insulin; and the inclusion of well-controlled patients with T1DM and no endogenous insulin secretion allowed for accurate assessment of insulin action. Additionally, the stabilisation of blood glucose at the target level before the euglycaemic clamp used dextrose or insulin glulisine, which has a short half-life and does not cross-react with insulin lispro. A limitation of this study was that the euglycaemic clamp procedure does not provide a direct effect of the insulin on postprandial glucose, despite being considered the gold standard methodology for assessing insulin action. In addition, despite there being no upper age limit to recruitment, the study had few patients aged >75 years.

5 Conclusions

URLi showed accelerated insulin lispro absorption, reduced late insulin lispro exposure, and an overall shorter exposure duration in comparison with Humalog in patients with T1DM. URLi also displayed a faster onset of insulin action, reduced late insulin action, and a shorter duration of insulin action compared with Humalog. Overall, there was no difference in the overall insulin lispro exposure or total glucose infused between the two treatments. The accelerated time-action profile of URLi compared with Humalog in elderly patients with T1DM mirrored those in younger adult patients. Furthermore, URLi was well tolerated by both age groups, with no differences in safety and tolerability observed between URLi and Humalog. The ultra-rapid pharmacokinetic and glucodynamic profile of URLi is likely to explain the greater postprandial glucose lowering observed in the phase III study in patients with T1DM [13].

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MAD, UH, LPM, TH, and JL were involved in the study design, and UH, LPM, and TH were investigators in the study. DEC, LPM, and TH were involved in data collection. HL, EL, and JL conducted data analyses, and QZ and MAD conducted the statistical analyses. HL, QZ, MAD, DEC, UH, LPM, TH, and JL were involved in interpretation of the study results.

Compliance with Ethical Standards

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Conflict of Interest Helle Linnebjerg, Qianyi Zhang, Elizabeth LaBell, Mary Anne Dellva, David E. Coutant, and Jennifer Leohr are employees and shareholders of Eli Lilly and Company. Ulrike Hövelmann, Leona Plum-Mörschel, and Theresa Herbrand are employees of Profil.

Data Sharing 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.

Ethical Approval and Informed Consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Medical Council North Rhine, Düsseldorf, Germany, 2017020) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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