# Randomized Double-Blind Clinical Trial Comparing Ultra Rapid Lispro With Lispro in a Basal-Bolus Regimen in Patients With Type 2 Diabetes: PRONTO-T2D

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## OBJECTIVE

**To evaluate the efficacy and safety of ultra rapid lispro (URLi) versus lispro in patients with type 2 diabetes on a basal-bolus insulin regimen.**

## RESEARCH DESIGN AND METHODS

**This was a phase 3, treat-to-target, double-blind 26-week study. After an 8-week lead-in to optimize basal insulin glargine or degludec in combination with prandial lispro treatment, patients were randomized to blinded URLi ($n = 336$) or lispro ($n = 337$) injected 0–2 min prior to meals. Patients could continue metformin and/or a sodium–glucose cotransporter 2 inhibitor. The primary end point was change in $HbA_{1c}$ from baseline to 26 weeks (noninferiority margin 0.4%), with multiplicity-adjusted objectives for postprandial glucose (PPG) excursions during a standardized meal test.**

## RESULTS

**$HbA_{1c}$ improved for both URLi and lispro, and noninferiority was confirmed: estimated treatment difference (ETD) 0.06% (95% CI −0.05; 0.16). Mean change in $HbA_{1c}$ was −0.38% for URLi and −0.43% for lispro, with an end-of-treatment $HbA_{1c}$ of 6.92% and 6.86%, respectively. URLi was superior to lispro in controlling 1- and 2-h PPG excursions: 1-h ETD, −0.66 mmol/L (95% CI −1.01, −0.30); 2-h ETD, −0.96 mmol/L (−1.41, −0.52). Significantly lower PPG excursions were evident from 0.5 to 4.0 h postmeal with URLi treatment. There were no significant treatment differences in rates of severe or documented hypoglycemia (<3.0 mmol/L). Incidence of overall treatment-emergent adverse events was similar between treatments.**

## CONCLUSIONS

**URLi compared with lispro in a basal-bolus regimen was confirmed to be noninferior for $HbA_{1c}$ and superior to lispro for PPG control in patients with type 2 diabetes.**


There have been many advances in the treatment of type 2 diabetes; however, reaching glycemic goals remains a challenge. Only ~30% of patients with type 2 diabetes are able to attain an $HbA_{1c}$ target of <7% even with insulin therapy (1). The overall proportion of patients reaching $HbA_{1c}$ <7% or individualized $HbA_{1c}$ targets has not improved during the past decade (2). $HbA_{1c}$ provides an integrated

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measurement of both fasting and postprandial glycemic control (3,4), and in order to reach target $HbA_{1c}$ goals, both fasting and postprandial hyperglycemia must be well controlled (4). As $HbA_{1c}$ approaches the desirable range, the relative contribution of postprandial hyperglycemia to overall glycemic control increases (5).

Several studies have shown that introducing a prandial insulin as part of a basal-bolus regimen in type 2 diabetes is more effective than a basal-only regimen at improving $HbA_{1c}$, as it provides postprandial insulin coverage (6–9). For optimal postprandial glucose (PPG) control, an ideal prandial insulin should match carbohydrate absorption by demonstrating faster absorption, more rapid onset, and shorter duration of action.

Ultra rapid lispro (URLi) is a novel ultra rapid insulin lispro formulation developed to more closely match physiological insulin secretion, with the goal of improving PPG control. It uses two excipients to accelerate the absorption of insulin lispro at the injection site: a microdose of treprostinil, a prostacyclin analog, which increases local vasodilation, and citrate, which enhances local vascular permeability (10,11). In a phase 1 study comparing the pharmacokinetics and pharmacodynamics of URLi to lispro (Humalog) with a euglycemic clamp in patients with type 2 diabetes, the onset of appearance of insulin lispro in serum was 5 min faster with URLi, resulting in a sixfold higher insulin exposure in the first 15 min after injection (12). In addition, the duration of exposure was reduced by 51 min with URLi treatment. A corresponding shift was observed in the pharmacodynamic profile. A fourfold increase in the amount of glucose infused within the first 30 min and a 19% reduction in insulin action from 4 h to the end of the clamp were observed with URLi compared with lispro.

The aim of this study was to demonstrate that glycemic control with URLi is noninferior to lispro as measured by the change from baseline to week 26 in $HbA_{1c}$ in patients with type 2 diabetes when administered subcutaneously as part of a basal-bolus regimen.

## RESEARCH DESIGN AND METHODS

This phase 3, double-blind, treat-to-target, 26-week, multicenter, multinational, randomized, controlled, parallel-design trial (Supplementary Fig. 1) was approved by local ethics review boards and conducted in accordance with the Good Clinical Practice of the International Conference on Harmonization Guideline (13). All patients provided written informed consent.

### Participants

Adults with type 2 diabetes and an $HbA_{1c}$ between 7.0% (53.0 mmol/mol) and 10.0% (85.8 mmol/mol) inclusive were eligible for inclusion in the trial. Eligible participants had been treated for ≥90 days with basal insulin in combination with one or more prandial injections of bolus insulin per day or premixed insulin at least twice daily. In addition, they may have been treated with up to three oral antihyperglycemic medications (OAMs) with stable dosing for ≥90 days prior to screening. (Additional inclusion/exclusion criteria are listed in Supplementary Table 1). Investigators at 131 study centers and 15 countries participated in the study (Supplementary Table 7).

### Study Design and Treatment

Following a 1-week screening period, patients entered an 8-week lead-in period focusing on basal insulin optimization. Patients were treated with basal insulin glargine U100 once or twice daily or insulin degludec U100 or U200 once daily as determined by the investigator and three prandial injections per day of insulin lispro. Patients could continue metformin and/or a sodium–glucose cotransporter 2 inhibitor during the study but were required to discontinue all other OAMs at the beginning of the lead-in. Basal insulin was titrated to a fasting blood glucose (FBG) target of 4.4–6.1 mmol/L during the lead-in period (Supplementary Table 2).

After the lead-in, patients were randomized 1:1 to either double-blind URLi U100 or lispro U100, administered by blinded prefilled insulin pens 0–2 min prior to the start of each meal. Patients continued treatment with basal insulin glargine or degludec. Assignment to treatment groups was determined by a computer-generated random sequence using an interactive web response system and stratified by country, $HbA_{1c}$ stratum (≤8.0% or >8.0% at 1 week prior to randomization), type of basal insulin, and number of prestudy prandial insulin injections (<3 or ≥3/day).

During the initial 12 weeks after randomization, study prandial insulin doses were adjusted in a treat-to-target manner to self-monitored blood glucose (SMBG) levels of 4.4–6.1 mmol/L fasting or premeal, 5.0–7.2 mmol/L bedtime, and <7.8 mmol/L 1–2 h postmeal. Insulin dosing was assessed at least weekly for 12 weeks and thereafter at each visit or more often as needed. Recommended basal and prandial insulin titration algorithms (Supplementary Table 2) were included in the protocols and could be adjusted by investigators for individual patient considerations. Basal insulin could be titrated as needed to facilitate optimal prandial dosing or for safety reasons. Patients then entered a 14-week maintenance period from weeks 12–26 during which basal and prandial insulin doses could be adjusted to maintain glycemic control or for safety reasons.

A 4-h standardized liquid meal test (Ensure Plus, or a similar country option, with nutrient composition of ~700 calories, 100 g carbohydrate, 22 g fat, and 26 g protein) was performed at baseline (all patients on lispro) and week 26 (patients on blinded study insulin lispro or URLi) to assess PPG levels. Patients were required to have FBG in the range of 3.9–10.0 mmol/L, and the meal was to be consumed within 15 min. Serum glucose measurements were collected at time −15, 0, 15, 30, 60, 120, 180, and 240 min after the start of the meal. The prandial insulin dose administered during the meal test was individualized for each patient based on the carbohydrate content of the test meal and the patient's insulin-to-carbohydrate ratio calculated from the average total daily insulin dose.

Patients performed 10-point SMBG profiles prior to scheduled visits at the following time points: fasting (morning premeal), prior to midday/evening meals, 1- and 2-h post–morning/midday/evening meals, and at bedtime. Patients were also instructed to take a minimum of four SMBG readings daily, with additional SMBG readings as needed for diabetes management and whenever hypoglycemia was suspected.

Documented hypoglycemia was defined as measured SMBG <3.0 mmol/L. Nocturnal hypoglycemia was documented hypoglycemia occurring between bedtime and waking. Severe hypoglycemia was determined by the investigator as an episode requiring assistance of another

person due to neurological impairment and was reported as a serious adverse event per protocol.

### Sample Size and Statistical Analyses

A total of 670 randomized patients would provide 99% statistical power to demonstrate noninferiority of URLi to lispro for change in $HbA_{1c}$ from 0 to 26 weeks with assumptions of no difference between treatment, an SD of 1.1%, at two-sided $\alpha$-level 0.05, and 15% dropout rate in 26 weeks.

The primary efficacy measure was noninferiority of URLi to lispro for $HbA_{1c}$ change from baseline to 26 weeks. URLi was declared noninferior to lispro if the upper limit of the two-sided 95% CI for the least squares mean (LSM) difference (URLi − lispro) for the change from baseline in $HbA_{1c}$ was <0.4% (i.e., noninferiority margin 0.4% [4.4 mmol/mol]). Two primary analysis methods were employed: *1*) the efficacy estimand using the data prior to permanent discontinuation of study insulin and a mixed-effect model for repeated measures (MMRM) analysis; *2*) the intention-to-treat estimand using all data from randomization through week 26 regardless of study insulin use, with multiple imputations for missing end points and an ANCOVA model. The MMRM model included treatment, strata (pooled country, type of basal insulin, and number of prandial doses at study entry), visit, and treatment-by-visit interaction as the fixed effects and baseline $HbA_{1c}$ as a covariate. The ANCOVA model included treatment and strata (pooled country, type of basal insulin, and number of prandial doses at study entry) as fixed effects and baseline $HbA_{1c}$ as a covariate.

A graphical approach (14) was used to strongly control the overall type I error of 0.05 for testing the treatment effect for the primary and the following key multiplicity-adjusted objectives: superiority of URLi compared with lispro for 1- and 2-h PPG excursion from the meal test at week 26 and change from baseline to week 26 in $HbA_{1c}$ (Supplementary Fig. 3).

ANCOVA was used to analyze the 1- and 2-h PPG excursions. The model included terms of strata (pooled country, type of basal insulin, number of prandial doses at study entry, and $HbA_{1c}$ stratum), treatment, and baseline. The superiority testing on change from baseline in $HbA_{1c}$ was assessed by the same analysis used for the primary objective. Additional continuous efficacy variables, as well as the change from baseline for these variables, were analyzed similarly either by the MMRM or ANCOVA models. For repeated binary measurements, a longitudinal logistic regression model was conducted.

Safety analyses were conducted on all randomized patients who received one or more doses of the randomly assigned study insulin. For the binary variables, Fisher exact test or a logistic regression model was used for treatment comparison. The rate of severe hypoglycemia was analyzed using an empirical method, and other hypoglycemia event rates were analyzed by a negative binomial regression model. MMRM or ANCOVA model was used for other continuous variables.

## RESULTS

Overall, 673 patients were randomized to URLi ($n$ = 336) and lispro ($n$ = 337). Patient disposition was similar between groups: 636 patients (95%) ($n$ = 317, URLi; $n$ = 319, lispro) completed 26 weeks of study treatment (Supplementary Fig. 2). Demographic and baseline characteristics were similar between groups (Table 1).

### Efficacy

#### *$HbA_{1c}$*

Mean $HbA_{1c}$ improved during the 8-week lead-in period in both groups from 8.3% (67.2 mmol/mol) to 7.3% (56.3 mmol/mol). After 26 weeks of treatment with URLi or lispro, there was further improvement in mean $HbA_{1c}$ to ~6.9% (51.9 mmol/mol) in both groups (Fig. 1). The mean change from baseline to week 26 was −0.38% (−4.1 mmol/mol) for URLi and −0.43% (−4.7 mmol/mol) for lispro, with an LSM difference (URLi − lispro) of 0.06% (95% CI −0.05 to 0.16) (−0.6 mmol/mol [95% CI −0.6 to 1.8]), confirming noninferiority of URLi to lispro (Fig. 1). Similar results were observed for the intention-to-treat estimand with an LSM difference of 0.03% (95% CI −0.08 to 0.13) (0.3 mmol/mol [95% CI −0.8 to 1.4 mmol/mol]). The multiplicity-adjusted objective for superiority of URLi to lispro in change from baseline to week 26 in $HbA_{1c}$ was not achieved for both analyses. At week 26, 58% of patients in the URLi group and 53% of patients in the lispro group reached target $HbA_{1c}$ <7.0%, and 38% and 35%, respectively, achieved an $HbA_{1c}$ ≤6.5%.

#### *Meal Test at Week 26*

PPG excursions during the standardized meal test at week 26 are shown in Fig. 2 (and Supplementary Table 3). URLi was superior to lispro in controlling 1- and 2-h PPG excursions, meeting the first and second multiplicity-adjusted objectives. Estimated change from baseline in PPG excursions was −0.77 mmol/L with URLi vs. −0.11 mmol/L with lispro at 1 h and −1.06 vs. −0.09 mmol/L, respectively, at 2 h postmeal. Mean PPG excursions were significantly lower in the URLi group compared with the lispro group at all time points from 30 min to 4 h (Supplementary Table 3).

Fasting glucose during the meal test was similar between groups (URLi, 7.17 mmol/L, and lispro, 6.98 mmol/L; $P$ = 0.198), and mean PPG levels were significantly lower with URLi compared with lispro at all time points from 1 to 4 h (Supplementary Table 3). Incremental area under the serum glucose concentration time curve during the meal test was statistically significantly lower in the URLi group versus the lispro group at all time intervals during the 4-h test at week 26 (Supplementary Table 3). In addition, maximum glucose after the meal was significantly lower in the URLi group versus the lispro group (12.98 vs. 13.56 mmol/L, respectively; $P$ = 0.015). Mean insulin dose with the meal test was similar between groups (URLi, 0.19 units/kg, and lispro, 0.18 units/kg).

#### *SMBG Profile*

At week 26, with 10-point SMBG profile testing, fasting glucose was similar between treatment groups with lower values observed with URLi compared with lispro for the morning 1-h postmeal (9.35 vs. 10.02 mmol/L respectively; $P$ < 0.001) and 2-h postmeal (8.54 vs. 9.40 mmol/L respectively; $P$ < 0.001) time points (Fig. 3). There were no statistically significant differences between groups at other time points. Overall daily mean glucose values from 10-point SMBG profiles at week 26 were not significantly different between groups (URLi, 8.84 mmol/L, and lispro, 9.01 mmol/L; $P$ = 0.185) (Supplementary Table 6). However, daily mean PPG values were significantly lower with URLi compared with lispro at 1 h (9.23 vs. 9.60 mmol/L; $P$ = 0.010) and at 2 h postmeal (8.86 vs.

**Table 1—Baseline characteristics**

| | Lispro, $N = 337$ | URLi, $N = 336$ | Overall, $N = 673$ |
|---|---|---|---|
| Age (years), mean ± SD | 61.0 ± 9.2 | 60.2 ± 9.4 | 60.6 ± 9.3 |
| Women/men, % | 48.1/51.9 | 45.2/54.8 | 46.7/53.3 |
| Race, *n* (%) | | | |
| American Indian or Alaska Native | 3 (0.9) | 1 (0.3) | 4 (0.6) |
| Asian | 81 (24.0) | 83 (24.7) | 164 (24.4) |
| Black or African American | 16 (4.7) | 14 (4.2) | 30 (4.5) |
| Multiple | 6 (1.8) | 5 (1.5) | 11 (1.6) |
| Native Hawaiian or other Pacific Islander | 1 (0.3) | 0 (0.0) | 1 (0.1) |
| White | 229 (68.0) | 233 (69.3) | 462 (68.6) |
| Hispanic or Latino, *n* (%) | 78 (23.1) | 79 (23.5) | 157 (23.3) |
| Weight (kg), mean ± SD | 90.0 ± 20.0 | 89.8 ± 20.5 | 89.9 ± 20.2 |
| BMI (kg/m$^2$), mean ± SD | 32.4 ± 5.8 | 32.1 ± 5.7 | 32.3 ± 5.7 |
| Duration of diabetes (years), mean ± SD | 16.6 ± 7.9 | 16.4 ± 7.8 | 16.5 ± 7.8 |
| Number of prestudy bolus injections, *n* (%) | | | |
| <3/day | 85 (25.2) | 83 (24.7) | 168 (25.0) |
| ≥3/day | 252 (74.8) | 253 (75.3) | 505 (75.0) |
| Basal insulin during study, *n* (%) | | | |
| Insulin glargine | 257 (76.3) | 260 (77.4) | 517 (76.8) |
| Insulin degludec | 80 (23.7) | 76 (22.6) | 156 (23.2) |
| OAM use during study, *n* (%) | | | |
| Metformin | 231 (68.5) | 244 (72.6) | 475 (70.6) |
| SGLT2 inhibitor | 54 (16.0) | 65 (19.3) | 119 (17.7) |
| $HbA_{1c}$ at study entry, mean ± SD | | | |
| % | 8.30 ± 0.75 | 8.30 ± 0.79 | 8.30 ± 0.77 |
| mmol/mol | 67.2 ± 8.3 | 67.2 ± 8.6 | 67.2 ± 8.4 |
| $HbA_{1c}$ at randomization, mean ± SD | | | |
| % | 7.31 ± 0.72 | 7.27 ± 0.68 | 7.29 ± 0.70 |
| mmol/mol | 56.4 ± 7.9 | 56.0 ± 7.5 | 56.2 ± 7.7 |

SGLT2, sodium–glucose cotransporter 2.

9.25 mmol/L; $P = 0.013$). Daily mean PPG excursions were also significantly lower with URLi from premeal to 1 and 2 h postmeal with a treatment difference (URLi − lispro) of −0.51 mmol/L at 1 h and −0.54 mmol/L at 2 h (all $P < 0.001$) (Supplementary Table 6).

### *Other Efficacy Measures*

From baseline to week 26, 1,5-anhydroglucitol increased (improved) in both treatment groups (LSM change from baseline to week 26: URLi, increase of 1.99 mg/L; lispro, increase of 2.15 mg/L) with no difference between groups.

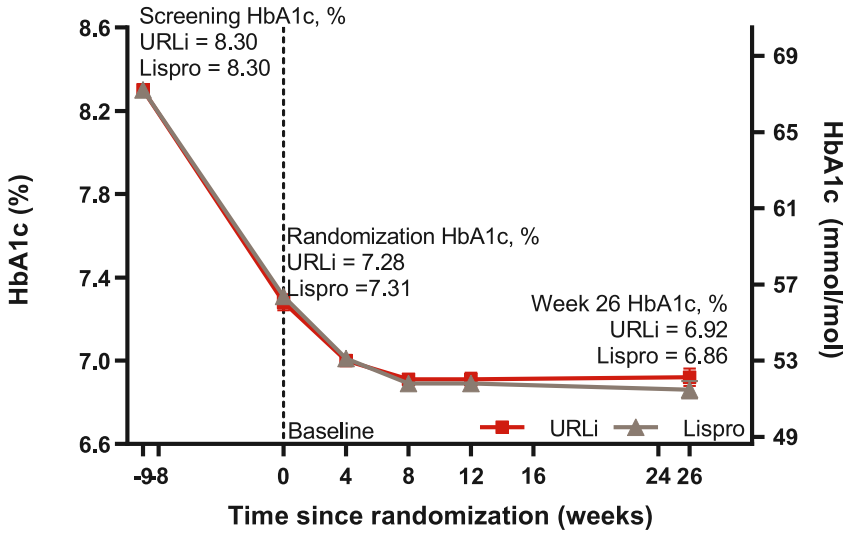


**Figure 1**—Mean $HbA_{1c}$ during study lead-in and 26-week treatment. Data are mean at screening and LSM ± SE for all other time points.

Mean total daily insulin dose increased from 0.99 units/kg at baseline to 1.13 units/kg at week 26 for URLi and from 0.94 to 1.08 units/kg for lispro with no statistically significant difference between groups (Supplementary Table 4). Basal and bolus insulin doses (units/kg) were not statistically significantly different between groups at baseline or at week 26 (Supplementary Table 4). The ratio of prandial to total insulin dose at week 26 was similar between groups (URLi, 49.7%; lispro, 48.5%).

### Safety

The incidence of severe hypoglycemia was low, with six patients (1.8%) reporting seven episodes in the lispro group and three patients (0.9%) reporting four episodes in the URLi group over 26 weeks of treatment ($P = 0.350$). There were no statistically significant differences in the rates of severe hypoglycemia, documented hypoglycemia (SMBG <3.0 mmol/L), or nocturnal hypoglycemia between groups (Table 2). The rate of postmeal hypoglycemia (SMBG <3.0 mmol/L) 0–1, 0–2, and >4 h after the meal was not significantly different between groups (Table 2). There was a statistically significantly higher rate of postmeal hypoglycemia with URLi compared with lispro treatment 0–4 h after the meal (Table 2).

Three deaths occurred during the study: 2 (0.6%) in the URLi group (acute myocardial infarction and septic shock) and 1 (0.3%) in the lispro group (sudden death). The incidence of serious adverse events, discontinuations from the study because of an adverse event, and treatment-emergent adverse events (TEAEs) was similar across treatment groups (Supplementary Table 5). Severe hypoglycemia was the most frequently reported serious adverse event. A small number of injection site reaction TEAEs was reported in this trial. Nine patients (2.7%) in the URLi group experienced a total of 10 injection site reaction TEAEs versus none in the lispro group ($P = 0.002$). The most common event was injection site pain ($n = 5$, 1.5%). All events were reported as of mild ($n = 7$) or moderate ($n = 3$) severity, and one patient discontinued study treatment because of an injection site reaction TEAE (injection site edema).

Weight increased with both treatments during the study with no significant

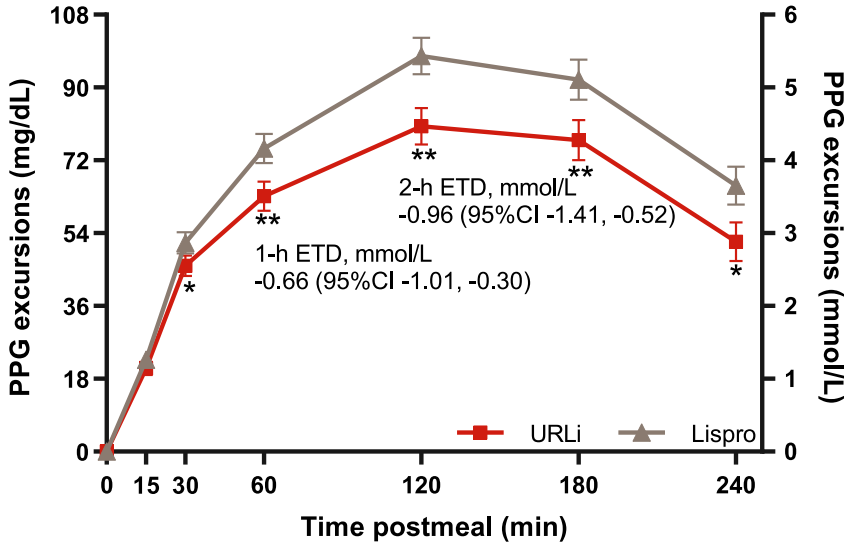


**Figure 2**—PPG excursions at week 26 with meal test. *$P < 0.05$ for between-treatment comparison; **$P < 0.001$ for between-treatment comparison. Data are LSM ± SE.

difference between groups (1.4 kg with URLi vs. 1.6 kg with lispro; $P = 0.350$). There were no clinically meaningful changes in laboratory assessments, blood pressure, or pulse in either treatment group.

## CONCLUSIONS

In this double-blind, treat-to-target study of patients with type 2 diabetes, basal-bolus treatment with URLi compared with lispro met the primary objective of noninferiority of $HbA_{1c}$ change over 26 weeks of treatment. This is consistent with previous treat-to-target trials where noninferiority of $HbA_{1c}$ was demonstrated with novel insulins when they were compared with currently available insulin treatment options including fast-acting insulin aspart versus insulin aspart (15), insulin glargine versus NPH (16,17), insulin degludec versus insulin glargine (18), and in a systematic review of treat-to-target trials in patients with type 2 diabetes (17). Treat-to-target trial designs are commonly used to compare a new insulin with a currently available formulation. In these trials, insulin is titrated in both treatment groups based on the same prespecified glycemic targets. Similar changes in $HbA_{1c}$ between treatment groups allow for comparison of other efficacy and safety end points in order to better establish the risk-benefit profile of the new insulin (17). Treat-to-target trials are further strengthened when treatment groups are blinded, as in the current study.

$HbA_{1c}$ significantly improved in both treatment groups including during the 8-week basal optimization lead-in period from a mean of 8.3% at screening to 7.3% at the end of lead-in with basal-bolus treatment using lispro. With 26 weeks of blinded study treatment with URLi or lispro, glycemic control improved further in both groups, with achievement of overall good glycemic control and mean end point $HbA_{1c}$ of 6.9%.

URLi demonstrated superiority over lispro in controlling both 1- and 2-h PPG excursions during the standardized meal test at week 26, meeting the prespecified objectives. URLi significantly reduced the 1-h PPG excursion by 0.66 mmol/L and the 2-h PPG excursion by 0.96 mmol/L compared with lispro. Additionally, URLi treatment resulted in significantly lower PPG excursions starting at 30 min to over the 4-h duration of the meal test, with similar insulin dosing. The reductions in PPG excursions with URLi approach what were reported in studies of rapid-acting insulin analogs compared with human regular insulin (19,20). Studies of fast-acting insulin aspart in basal-bolus regimens with either insulin glargine or degludec in patients with type 2 diabetes have also demonstrated noninferiority of $HbA_{1c}$ (15,21). These studies resulted in a statistically significant reduction in the 1-h PPG excursion of 0.59 and 0.40 mmol/L with fast-acting insulin aspart versus insulin aspart but no treatment difference at the 2-h time point after a liquid meal test (15,21). In addition, in a clinical pharmacology study in patients with type 1 diabetes, URLi demonstrated statistically significant improvement in PPG excursions compared with insulin lispro and insulin aspart and numerically greater improvement compared

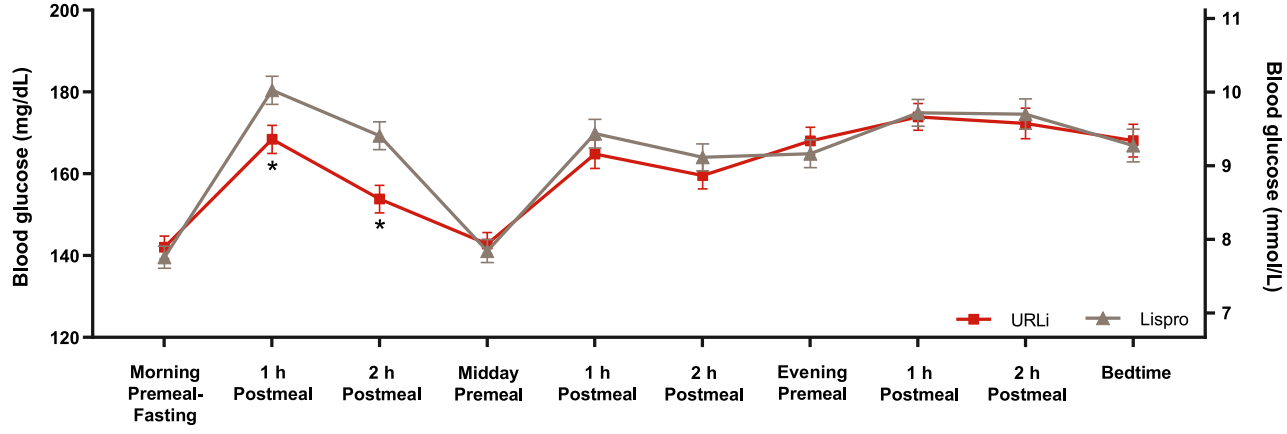


**Figure 3**—Ten-point SMBG profile at week 26. *$P < 0.05$ for between-treatment comparison. Data are LSM ± SE.

**Table 2—Summary of rates of hypoglycemia (baseline to week 26)**

| | Lispro, $N = 337$ Rate (events/patient/year) | URLi, $N = 336$ Rate (events/patient/year) | Relative rate URLi/lispro (95% CI) |
|---|---|---|---|
| Severe hypoglycemia | 0.04 | 0.02 | 0.58 (0.14, 2.50) |
| Documented hypoglycemia | 7.43 | 7.57 | 1.02 (0.81, 1.28) |
| Nocturnal hypoglycemia | 0.53 | 0.68 | 1.29 (0.82, 2.03) |
| Postmeal hypoglycemia (h) | | | |
| 0–1 | 1.54 | 1.76 | 1.14 (0.75, 1.74) |
| 0–2 | 1.86 | 2.47 | 1.33 (0.92, 1.92) |
| 0–4 | 2.58 | 3.51* | 1.36 (1.01, 1.83)* |
| >4 | 1.15 | 1.10 | 0.95 (0.61, 1.48) |

Data are LSM unless otherwise stated. Hypoglycemia was defined as SMBG <3.0 mmol/L (54 mg/dL) for documented, nocturnal, and postmeal hypoglycemia. For postmeal hypoglycemia, patient reported timing in relation to meal. *$P < 0.05$ for between-treatment group comparisons.

with fast-acting insulin aspart in response to a liquid meal test (22).

Supportive of the meal test results, 10-point SMBG testing demonstrated improved PPG control with significantly lower PPG levels after the morning meal and reduced daily mean PPG levels and daily mean PPG excursions with URLi compared with lispro. PPG treatment differences may not have been as evident with other meals, as the morning meal may be the most standardized, particularly in a large global study, and because glucose levels were already under reasonable control in both treatment groups at baseline after the lead-in period, with mean $HbA_{1c}$ of 7.3%. Insulin dose (units/kg) and the ratio of prandial to total insulin were not significantly different between treatment groups at 48–50%. The overall pattern of glucose levels increased after the midday meal and thereafter remained stable until bedtime. It is possible that a higher percentage of bolus compared with basal insulin, with higher prandial insulin dosing with the midday and evening meals, may further improve glycemic control and PPG. One could also speculate that adjustment of basal insulin dosing may be needed to further optimize glycemic control and PPG control throughout the entire day with URLi and other next-generation ultra rapid insulin analogs (23). Despite these considerations, good glycemic control with an end point mean $HbA_{1c}$ of <7% was achieved with URLi and lispro, with similar rates of overall hypoglycemia. Further evaluation and potential optimization of basal/bolus dosing for individual patients with use of URLi in studies as well as in real-life settings and in clinical practice would be of interest.

In patients with longer duration of type 2 diabetes, as in the PRONTO-T2D study, management of postprandial hyperglycemia remains the primary unmet need, with a significant number of patients not meeting glycemic goals despite treatment with multiple agents as well as basal insulin (24). Therapeutic interventions to decrease PPG excursions may be as important as or more important than fasting glucose in reaching overall glycemic goals and in decreasing the risk of diabetes and cardiovascular complications (25,26). Epidemiology studies have shown the increased risk of cardiovascular disease and mortality associated with elevated PPG levels (27–30).

Improved glycemic control was achieved with no statistically or clinically significant differences in the most clinically relevant categories of hypoglycemia, including severe hypoglycemia, documented hypoglycemia <3.0 mmol/L, and nocturnal hypoglycemia. The incidence of severe hypoglycemia was low despite achievement of good glycemic control. Postmeal hypoglycemia rates were statistically significantly higher in URLi-treated patients within 4 h of the meal; however, the absolute rates were very low, corresponding to less than one additional event per patient-year. Postmeal hypoglycemia rates were similar between treatment groups >4 h postmeal. These findings are also overall consistent with the increased postmeal rate of hypoglycemia 0–2 h after meals with fast-acting insulin aspart compared with insulin aspart (15). Consistent with the faster time-action profile of URLi and of ultra rapid bolus insulin formulations in general, these data are suggestive of a trend toward earlier hypoglycemic events (but importantly no difference in overall hypoglycemia) with URLi compared with lispro.

The safety profile and overall frequency of treatment-emergent adverse events between treatments were similar between groups. As with any insulin treatment, injection site reactions (of primarily mild severity) were reported with URLi treatment; however, the incidence was low (~2.7%) and overall similar to that previously reported for other insulins such as fast-acting insulin aspart (1.6%) (31) and insulin glargine (2.7%) (32).

Strengths of this study include the double-blind design, the high completion rate (>94%), and the global nature of the study including North/South America, Asia, Australia, and Europe. Although 10-point SMBG profiles provided data for diabetes management and for assessment of PPG in more of a real-life setting, continuous glucose monitoring (CGM) data were not obtained in the study. Blinded CGM data were obtained in a subset of patients with type 1 diabetes in the phase 3 PRONTO-T1D study and demonstrated improved PPG control and significantly increased time in range during the daytime period with URLi treatment versus lispro (33). For future directions, it would be of interest to obtain CGM data in patients with type 2 diabetes to further assess the effects of URLi treatment on glycemic control and outcomes beyond $HbA_{1c}$ such as time in target glucose range and to further evaluate PPG control and the 24-h ambulatory glucose profile. Study limitations include the use of a liquid meal test, which allowed standardization across multiple countries in a global study but

may not fully represent a typical meal. Of note, URLi has been shown to reduce PPG excursions compared with lispro in clinical pharmacology studies with use of solid mixed-meal tolerance tests in patients with type 1 and type 2 diabetes (34,35). In addition, given the design with the lead-in period, patients overall had reasonably controlled diabetes at baseline prior to starting blinded study treatment. The study enrolled patients already treated with a component of basal-bolus therapy; it would also be of interest to evaluate URLi treatment in patients with type 2 diabetes new to bolus insulin therapy.

In conclusion, this 26-week, double-blind, treat-to-target study in patients with type 2 diabetes previously treated with insulin demonstrated that basal-bolus treatment with URLi compared with lispro provided good glycemic control, with clinically significant reductions in $HbA_{1c}$ and similar overall hypoglycemia. Furthermore, URLi in a basal-bolus regimen provided superior PPG control over lispro treatment in patients with type 2 diabetes.

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**Author Contributions.** T.B., J.P.F., and H.J. participated as trial investigators and reviewed and edited the manuscript. Q.Z contributed to the study design, the statistical analyses, the interpretation of the research, writing the statistical methods, and reviewing and editing the manuscript. A.M.C. was responsible for medical oversight during the trial and contributed to the study design, the data analysis and interpretation of the research, and writing the manuscript. All authors approved the final manuscript to be published. A.M.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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