Ultra Rapid Lispro Improves Postprandial Glucose Control vs Lispro in Patients With T2D: The PRONTO-T2D Study

Courtesy of Juan Pablo Frias, MD

Background

- Ultra-rapid insulin lispro (URLi) is a novel formulation of insulin lispro using locally acting excipients treprostinil and citrate
  - **Treprostinil** accelerates insulin lispro absorption by local vasodilation with no measurable systemic exposure
  - **Citrate** increases vascular permeability at the injection site
- URLi was developed to more closely match physiological insulin secretion with the goal of improving postprandial glucose (PPG) control

PRONTO-T2D Study Objectives

Primary objective

Non-inferiority of URLi to lispro in change from baseline to Week 26 in HbA1c levels (margin=0.4%)

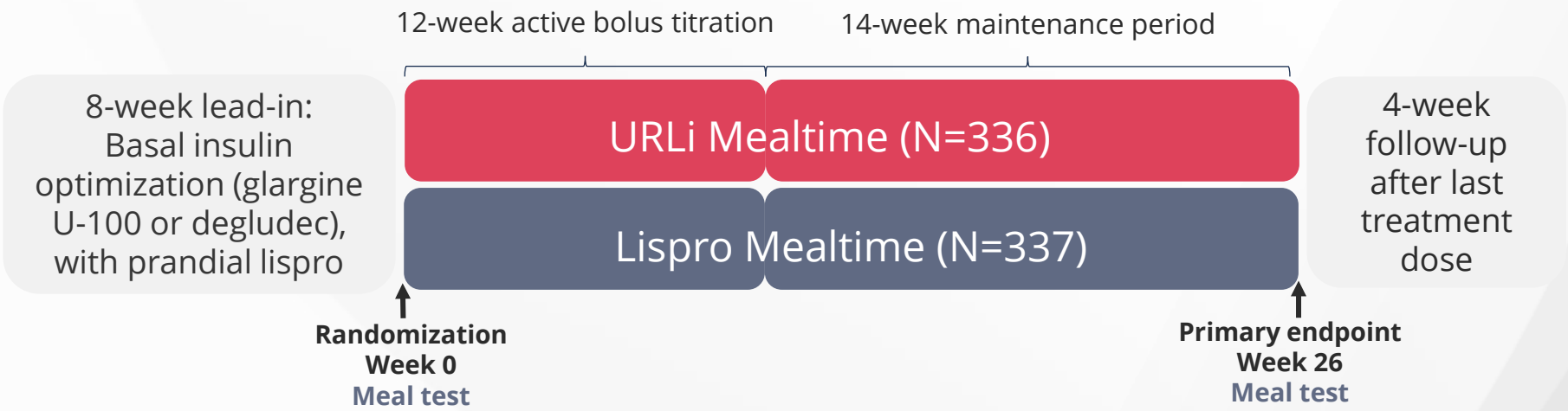
Key secondary objectives

Statistical superiority of URLi to lispro at Week 26 (with multiplicity adjustment)

- 1-hour PPG excursion (meal test)
- 2-hour PPG excursion (meal test)
- Change from baseline in HbA1c

Phase 3, 26-week, Double-blind, Treat-to-target Study in 673 Patients with T2D

Eligibility criteria:
- HbA1c 7%-10%
- Basal + ≥1 bolus or ≥2 pre-mixed insulin injections
- Up to 3 oral agents



- Patients could continue metformin and/or sodium-glucose co-transporter 2 (SGLT2) inhibitor
- Recommended basal/bolus insulin algorithms to achieve protocol self-monitoring of blood glucose (SMBG) targets
- Algorithms were not mandatory, and insulin doses could be individualized
- Completed 26 weeks of study treatment: URLi, N=317 (94.3%); Lispro, N=319 (94.7%)

Blevins T, et al. *Diabetes Care*. 2020;43:2991-2998.

Baseline Characteristics

Characteristic	Lispro (N=337)	URLi (N=336)	Overall (N=673)
Age, years	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 (%)			
Asian	81 (24.0)	83 (24.7)	164 (24.4)
Black or African American	16 (4.7)	14 (4.2)	30 (4.5)
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	90.0 (20.0)	89.8 (20.5)	89.9 (20.2)
Body mass index, kg/m^2	32.4 (5.8)	32.1 (5.7)	32.3 (5.7)
Duration of T2D, years	16.6 (7.9)	16.4 (7.8)	16.5 (7.8)

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Baseline Characteristics (continued)

Characteristic	Lispro (N=337)	URLi (N=336)	Overall (N=673)
Number of pre-study 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)
OAMs during study, n (%)			
Metformin	231 (68.5)	244 (72.6)	475 (70.6)
SGLT2 inhibitor	54 (16.0)	65 (19.3)	119 (17.7)

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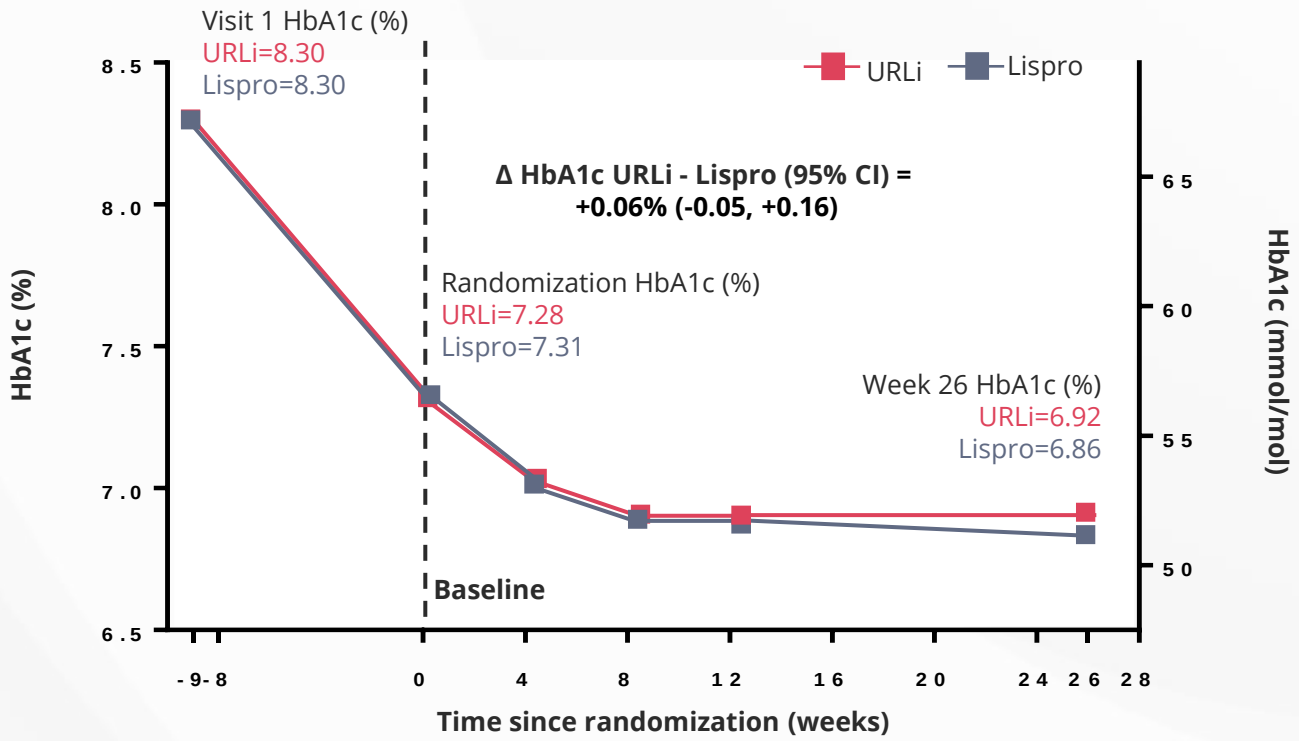
Non-Inferiority of URLi



No statistically significant difference in basal, bolus, and total insulin dose (units/kg) at Week 26

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; LSM, least squares mean; SE, standard error.
Data are mean at Visit 1 and LSM±SE all other time points.

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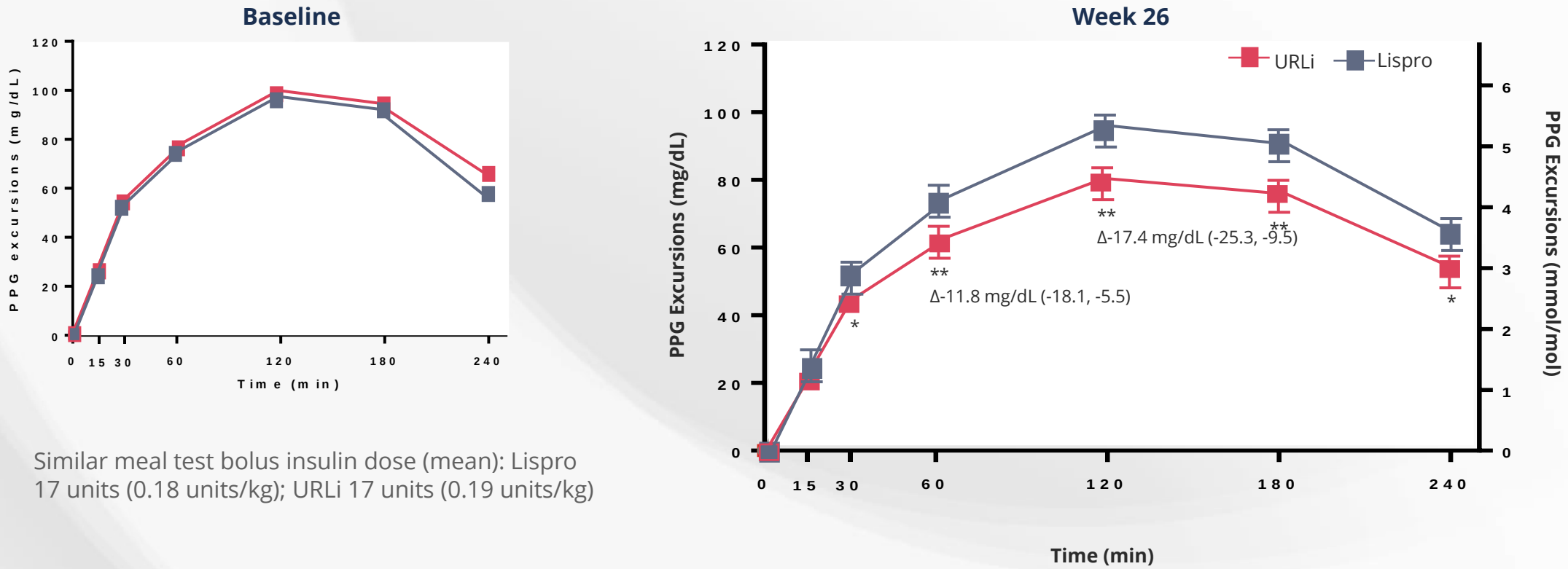
URLi Was Superior to Lispro in Controlling 1- and 2-hr PPG Excursions During Meal Test at Week 26



Similar meal test bolus insulin dose (mean): Lispro 17 units (0.18 units/kg); URLi 17 units (0.19 units/kg)

Abbreviations: LSM, least squares mean; PPG, postprandial glucose; SE, standard error. Data are LSM±SE. * p<0.05; ** p<0.001.

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Severe Hypoglycemia

	Incidence			Rate	
Treatment	# of Patients n (%)	# of Episodes	P-Value	Rate/100 pt yr	P-Value
Lispro (N=337)	6 (1.78)	7	-	4.15	-
URLi (N=336)	3 (0.89)	4	0.350	2.37	0.467

Pt yr, patient-years.

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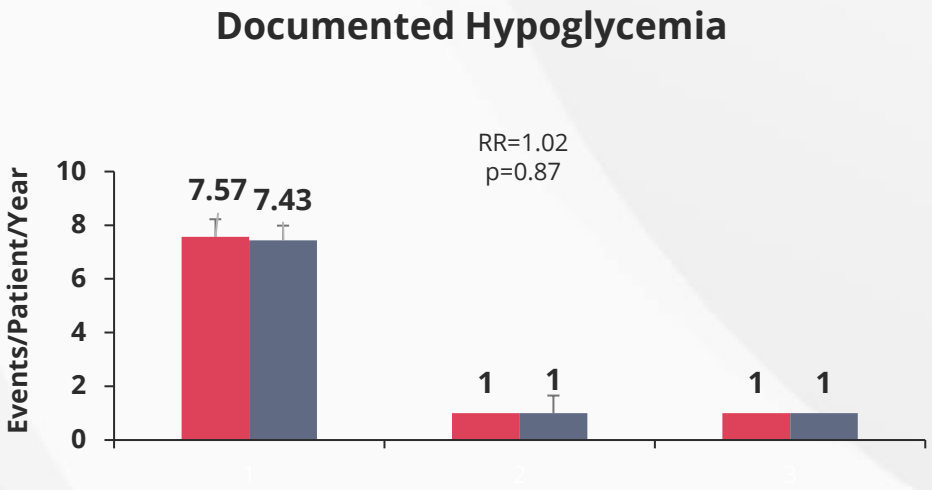
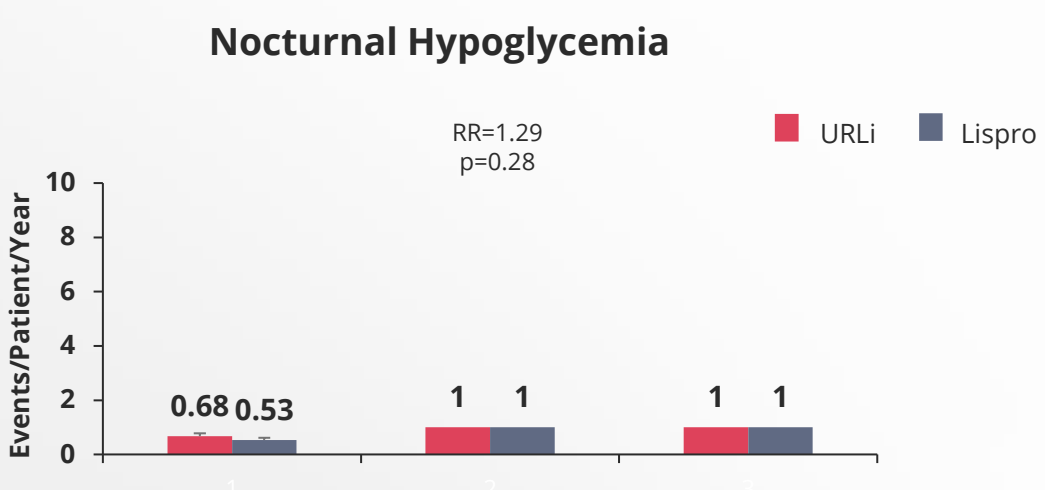
Rate of Hypoglycemia (<54 mg/dL) From Week 0-26





Abbreviations: LSM, least squares mean; RR, relative rate; SE, standard error.
Documented hypoglycemia: BG<54 mg/dL with or without symptoms.
Nocturnal hypoglycemia: documented hypoglycemia from bedtime to waking.
Data are LSM ± SE.

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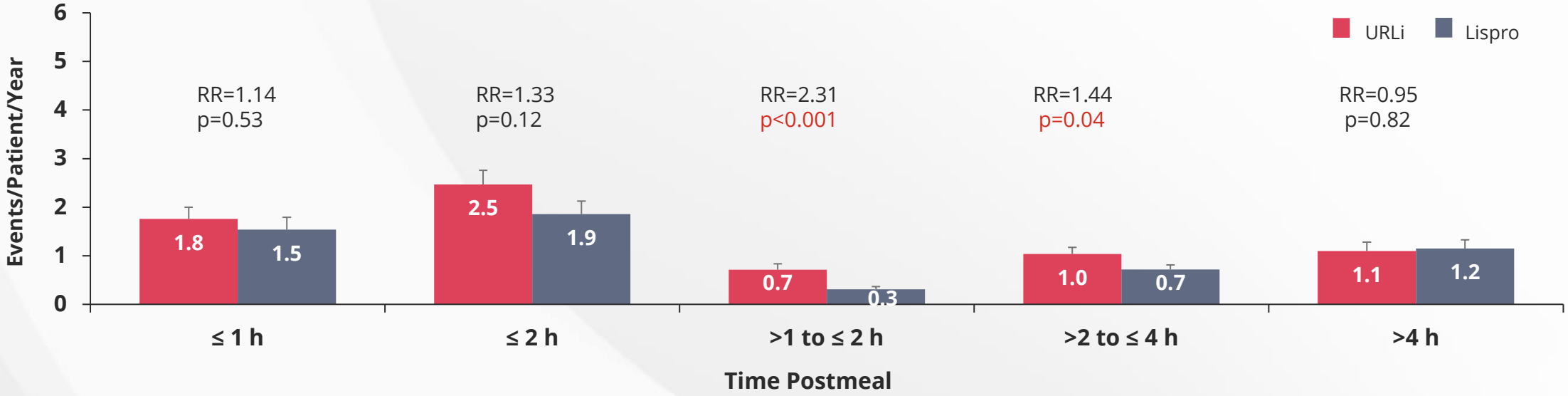
Rate of Postmeal Hypoglycemia (<54 mg/dL) From Week 0-26



Documented hypoglycemia with or without symptoms

- Patient reported symptoms and timing in relation to meal

LSM, least squares mean; RR, relative rate; SE, standard error.
Data are LSM ± SE. Statistically significant p-values highlighted in red text.

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Adverse Events

	Lispro n (%)	URLi n (%)	Total n (%)	P-Value
Deaths	1 (0.3)	2 (0.6)	3 (0.4)	0.624
Serious Adverse Events	25 (7.4)	26 (7.7)	51 (7.6)	0.885
Discontinuation from study because of AE	2 (0.6)	3 (0.9)	5 (0.7)	0.686
Treatment-emergent AE (TEAE)	194 (57.6)	203 (60.4)	397 (59.0)	0.481
Injection site reaction TEAEs*	0 (0.0)	9 (2.7)	9 (1.3)	0.002
Injection site pain	0 (0.0)	5 (1.5)	5 (0.7)	0.031

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
*Collection of pre-specified injection site reaction terms identified through a MedDRA search strategy.

- Reported injection site TEAEs: injection site pain, erythema, induration, edema, reaction
- 1 discontinuation of study treatment because of injection site edema
- Primarily mild severity

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PRONTO-T2D Summary

URLi compared to lispro treatment over 26 weeks in patients with T2D demonstrated:

- Non-inferiority in change from baseline in HbA1c
- Significantly greater reduction in PPG excursions
- No significant differences in severe or documented hypoglycemia
- Similar overall reporting of TEAEs
  - Small number but imbalance in injection site reactions

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PRONTO-T2D Conclusions

- URLi in a basal-bolus regimen was non-inferior to lispro for HbA1c, and both groups achieved good glycemic control in this treat-to-target study
- URLi treatment led to superior PPG control versus lispro in patients with T2D

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