A Novel Formulation of Insulin Lispro Containing Citrate and Treprostinil Shows Faster Absorption and Improved Postprandial Glucose Excursions vs. Humalog in Patients with T1DM

Christof Kazda[1], Jennifer Leohr[1], Rong Liu[1], Shobha Reddy[1], Mary Anne Dellva[1], Shufen Th Lim[1], Mei Teng Loh[1], Mary Pat Knadler[1], Thomas Hardy[1], Leona Plum-Moerschel[2]

[1]Eli Lilly and Company, Indianapolis, USA; [2]Profil, Mainz, Germany

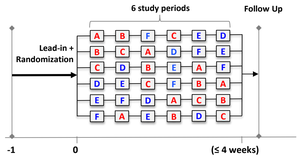
OBJECTIVE

To evaluate the difference in insulin pharmacokinetics (PK) and pharmacodynamics (PD) between

- **Humalog**
- **Ultra rapid insulin lispro (LY900014; LY), a novel insulin formulation using locally acting excipients citrate and treprostinil**

following a mixed meal in patients with T1DM

STUDY DESIGN



Treatments		
Treatment ID	LY or Humalog	Dose Timing relative to Meal
A	LY900014	-15 min
B	LY900014	0 min
C	LY900014	+15 min
D	Humalog	-15 min
E	Humalog	0 min
F	Humalog	+15 min

- Single site, 6-period, patient- and investigator-blind, randomized crossover study in patients with T1DM
- 30 c-peptide negative patients were randomized to 1 of 6 treatment sequences
- Prior to treatment, blood glucose concentrations were stabilized to 126 mg/dL using intravenous Apidra® (insulin glulisine) and glucose infusion
- Patients received the same individualized single subcutaneous doses of LY and Humalog (based on individual insulin to carbohydrate ratios) at -15, 0 and +15 minutes relative to the start of a mixed meal test
  - PK analyses included data from all dose timings
  - PD data only shown for time 0
- Individual basal insulin treatment continued unchanged throughout the course of the study

KEY RESULTS

LY900014 (LY), ultra rapid insulin lispro, showed faster, earlier insulin lispro absorption and greater postprandial glucose reduction when administered immediately before the test meal

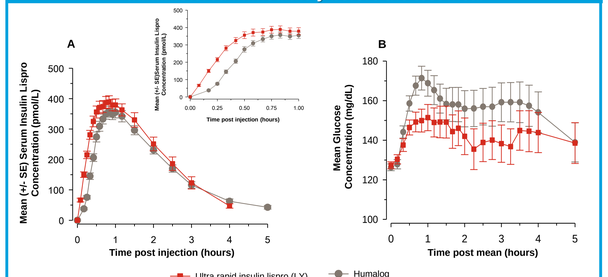


Figure 1. Ultra rapid insulin lispro and Humalog (A) mean serum insulin lispro concentration over time (inset is time 0-1h) and (B) mean postprandial glucose over time
Abbreviation: SE=standard error

CONCLUSIONS

- **Ultra rapid insulin lispro (LY) demonstrated accelerated insulin lispro absorption with a 2.2 fold increase in the insulin exposure within the first 30 min and a 37% reduction of early 50% t_{max} compared with Humalog**
- **LY reduced the total postprandial glucose excursion by 44% relative to Humalog**
- **Treprostinil concentrations were below the quantification limit**
- **No clinically relevant differences in local tolerability or hypoglycemia incidence were observed**
- **These results support further evaluation of LY as an ultra rapid mealtime insulin for the treatment of T1DM**

BACKGROUND

- A prandial insulin with an ultra rapid on/off profile has the potential to reduce glycemic excursions better than current rapid-acting analogs
- Current rapid-acting insulins administered by pumps or syringes are not fast enough to match carbohydrate absorption
- LY is a novel formulation using the locally acting excipients citrate and treprostinil
  - Citrate increases vascular permeability at the injection site
  - Treprostinil accelerates insulin lispro absorption by local vasodilation with no measurable systemic exposure
- LY was developed to more closely mimic physiologic prandial insulin secretion with the goal of improving postprandial glucose control and allowing flexibility in the timing of insulin administration

METHODS

- Statistical Methods
  - Log-transformed PK parameters were analyzed using a linear mixed model with treatment and period as fixed effects and subject as random effect
  - Glucodynamic parameters (without log-transformation) were analyzed using a model with treatment, dose timing, treatment-by-dose timing interaction and period as fixed effects, and subject as random effect
  - Significance claimed if $P < 0.1$
- PK analyses conducted using noncompartmental analysis
- Glucodynamic change from baseline (premeal) glucose area under the concentration curve (AUC) calculated using linear trapezoidal method during the 5-hour test meal
- Assay Methods
  - Insulin lispro: ELISA assay specific to insulin lispro without cross-reactivity to endogenous insulin
  - Treprostinil: Liquid chromatography tandem mass spectrometry, lower limit = 0.010 ng/mL
  - Glucose measured by validated laboratory standard methodology

BASELINE CHARACTERISTICS

Demographics

- 30 patients with T1DM
- Mean age = 42.2 years
- Males = 24; Females = 6
- Mean weight = 79.9 kg

Clinical Characteristics (Mean)

- Body mass index = 25.2 kg/m^2
- HbA1c = 7.1%
- Duration of T1DM = 22 years
- Fasting blood glucose = 171 mg/dL

Patient Disposition

- All 30 randomized patients completed the 6-period crossover

PHARMACOKINETICS

LY Accelerated Early and Late Insulin Exposure

Parameter	LY (N=30)	Humalog (N=30)	Ratio of Geo LSM LY:Humalog (90% CI)	*P* Value[1]
Early Insulin Exposure	**Geo LSM**			
Early 50% t_{max}, min	15.5	24.3	0.635 (0.598-.0675)	<.0001
AUC(0-30min), pmol•h/L	89.1	40.1	2.23 (2.01-2.46)	<.0001
AUC(0-1h), pmol•h/L	262	192	1.37 (1.28-1.46)	<.0001
Late Insulin Exposure				
AUC(3-5h), pmol•h/L	62.1	82.6	0.751 (0.674-0.837)	<.0001
Late 50% t_{max}, min	124	131	0.946 (0.896-0.999)	.0913
Total Insulin Exposure				
t_{max}, h	0.863	0.855	1.01 (0.932-1.09)	.8388
C_{max}, pmol/L	410	362	1.13 (1.07-1.20)	.0008
AUC(0-∞), pmol•h/L	789	745	1.06 (1.00-1.12)	.0848

[1]Predefined significance level of P=0.1
Abbreviations:(0-∞) = from time 0 to infinity; (0-30min) = from 0 to 30 minutes post-dose; (0-1h) = from 0 to 1 hour post-dose; (3-5h) = from 3 to 5 hour post-dose; AUC = area under the concentration vs time curve; CI = confidence interval; C_{max} = maximal concentration; Early 50%t_{max} = time to early half-maximal concentration; Geo = geometric; h = hour; Late 50% t_{max} = time to late half-maximal concentration; LSM = least squares mean; min = minute; t_{max} = time to maximal concentration.

GLUCODYNAMICS

LY Reduced the Postprandial Glucose Excursion

Parameter	LY (N=30) LSM	Humalog (N=30) LSM	Ratio[1] LY:Humalog (90% CI)	*P* Value[2]
ΔAUC(0-2h), mg•h/dL	35.26	58.13	0.61 (0.32, 0.93)	.0315
ΔAUC(0-5h), mg•h/dL	76.37	135.54	0.56 (0.21, 1.04)	.0972

[1] CI calculated using Fieller's Theorem
[2] *P* value is for the test of mean difference, predefined significance level of P=0.1

Abbreviations: Δ=change from baseline (premeal); (0-2h)=from time 0 to 2 hours post-meal; (0-5h)=from time 0 to 5 hours post-meal; AUC=area under the concentration vs. time curve; CI=confidence interval; LSM=least squares mean

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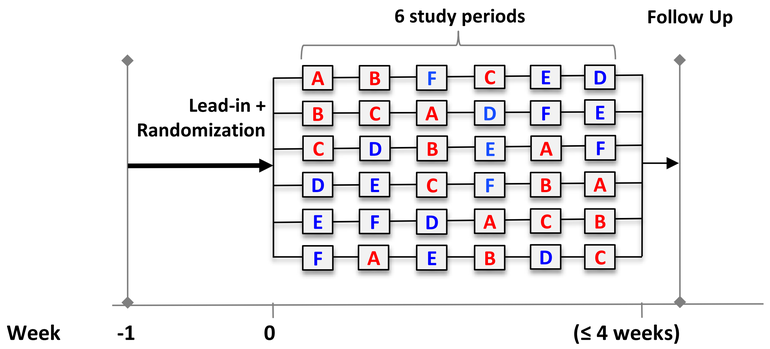

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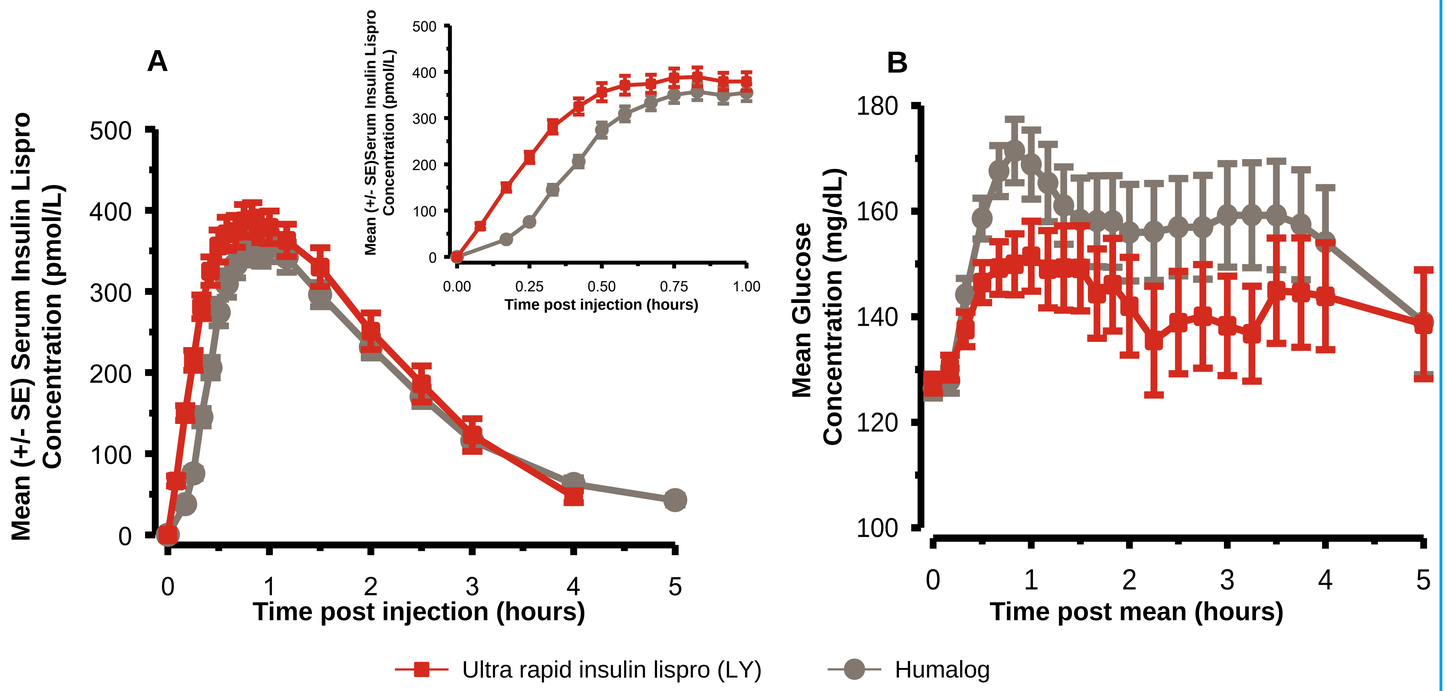

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LY REDUCED THE POSTPRANDIAL GLUCOSE EXCURSION

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SAFETY

- Three patients reported TEAEs, 1 patient while receiving LY (+15 min) and 2 while receiving Humalog (0 min)
- TEAEs were all mild to moderate
- No apparent association between meal-to-dose time and TEAE for either LY or Humalog
- No clinically relevant differences observed in incidence or severity of hypoglycemia
- No injection site reactions or increased injection site pain observed with single doses of up to 40 U.
- All treprostinil concentrations were below the lower limit of quantification (0.010 ng/mL)

CONCLUSIONS

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