



## Clinical trial results:

### A Prospective, Randomized, Double-Blind Comparison of LY900014 to Humalog with an Open-Label Postprandial LY900014 Treatment Group in Children and Adolescents with Type 1 Diabetes PRONTO-PEDS

#### Summary

EudraCT number	2018-002371-18
Trial protocol	DK CZ DE FR GB AT ES PL IT
Global end of trial date	02 July 2021

#### Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

#### Trial information

##### Trial identification

Sponsor protocol code	I8B-MC-ITSB
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03740919
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 16698

Notes:

#### Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559,

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 July 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The reason for this study is to compare the study drug LY900014 to insulin lispro (Humalog) in children and adolescents with type 1 diabetes (T1D).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United States: 138
Country: Number of subjects enrolled	Czechia: 60
Country: Number of subjects enrolled	Japan: 12
Country: Number of subjects enrolled	Ukraine: 138
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Spain: 52
Country: Number of subjects enrolled	Russian Federation: 62
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	China: 23
Country: Number of subjects enrolled	Brazil: 57
Country: Number of subjects enrolled	Poland: 34
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Italy: 39
Country: Number of subjects enrolled	Mexico: 60
Country: Number of subjects enrolled	Israel: 43
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 17
Worldwide total number of subjects	751
EEA total number of subjects	208

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	265
Adolescents (12-17 years)	486
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study included a 4-week lead-in period using open-label insulin-lispro (Humalog) followed by a 26-week double-blind treatment period (LY900014 and insulin lispro) and one open-label treatment arm (LY900014 Postmeal).

### Pre-assignment

Screening details:

The purpose of the lead-in period was to obtain blood glucose (BG) values along with basal and prandial insulin doses to assess basal and mealtime insulin dosing and to determine baseline hypoglycemia rates.

### Period 1

Period 1 title	Lead-in Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Arm title	Insulin Lispro (Humalog) Lead-in
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Arm description:

Participants were switched to open-label insulin lispro (Humalog) administered subcutaneously (SC), using a unit for unit conversion or the dose could have been determined based on investigator's clinical judgement.

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro
Investigational medicinal product code	LY275585
Other name	Humalog
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin lispro (Humalog) administered SC using unit for unit conversion or dose may be determined based on investigator's clinical judgement.

Number of subjects in period 1	Insulin Lispro (Humalog) Lead-in
Started	751
Received at Least One Dose of Study Drug	751
Completed	716
Not completed	35
Physician decision	2
Consent withdrawn by subject	10
Study Task Too Burdensome	1
Withdrew Consent Due to Required Procedures	1
Due to Coronavirus Disease 2019 (COVID-19)	18
Lab Results Did Not Match Inclusion Criteria	1

Lost to follow-up	1
Protocol deviation	1

## Period 2

Period 2 title	Treatment Period
Is this the baseline period?	Yes <sup>[1]</sup>
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Insulin Lispro (Humalog)

### Arm description:

Participants received insulin lispro (Humalog) 100 units per milliliter (U/mL) administered SC 0 to 2 minutes before each meal with once or twice daily basal insulin. Preprandial insulin doses were individualized and titrated according to protocol-defined targets.

Arm type	Active comparator
Investigational medicinal product name	Insulin Lispro
Investigational medicinal product code	LY275585
Other name	Humalog
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

### Dosage and administration details:

100 U/mL administered SC 0 to 2 minutes before each meal.

<b>Arm title</b>	LY900014
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### Arm description:

Participants received 100 U/mL LY900014 administered SC 0 to 2 minutes before start of the meal.

Arm type	Experimental
Investigational medicinal product name	LY900014
Investigational medicinal product code	
Other name	Ultra-Rapid Lispro
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

### Dosage and administration details:

100 U/mL LY900014 administered SC 0 to 2 minutes before start of the meal.

<b>Arm title</b>	LY900014 Postmeal
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### Arm description:

Participants received 100 U/mL LY900014 administered SC up to 20 minutes after the start of the meal.

Arm type	Experimental
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Investigational medicinal product name	LY900014
Investigational medicinal product code	
Other name	Ultra-Rapid Lispro
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

100 U/mL LY900014 administered SC up to 20 minutes after the start of the meal.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The 4-week Lead-in period allowed all enrolled participants to switch to Humalog to determine baseline hypoglycemia rates. Not all participants in the Lead-in period chose to continue into the treatment period and treatment period is considered the baseline period.

<b>Number of subjects in period 2<sup>[2]</sup></b>	Insulin Lispro (Humalog)	LY900014	LY900014 Postmeal
Started	298	280	138
Received at Least One Dose of Study Drug	298	280	138
Completed	288	266	135
Not completed	10	14	3
Terminated by Sponsor	1	-	-
Consent withdrawn by subject	7	6	2
Adverse event, non-fatal	-	2	-
Not Completing Diary	-	1	-
Insulin Painful to Participant	-	1	-
Due to COVID-19 Pandemic	-	3	1
Issue with Insulin Pump	1	-	-
Protocol deviation	1	-	-
Failure of Inclusion Criteria	-	1	-

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Not all participants in the Lead-in period chose to continue into the treatment period and treatment period is considered the baseline period.

## Baseline characteristics

### Reporting groups

Reporting group title	Insulin Lispro (Humalog)
Reporting group description:	
Participants received insulin lispro (Humalog) 100 units per milliliter (U/mL) administered SC 0 to 2 minutes before each meal with once or twice daily basal insulin. Preprandial insulin doses were individualized and titrated according to protocol-defined targets.	
Reporting group title	LY900014
Reporting group description:	
Participants received 100 U/mL LY900014 administered SC 0 to 2 minutes before start of the meal.	
Reporting group title	LY900014 Postmeal
Reporting group description:	
Participants received 100 U/mL LY900014 administered SC up to 20 minutes after the start of the meal.	

Reporting group values	Insulin Lispro (Humalog)	LY900014	LY900014 Postmeal
Number of subjects	298	280	138
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	12.4	12.1	12.3
standard deviation	± 3.2	± 3.4	± 3.8
Gender categorical			
Units: Subjects			
Female	140	144	65
Male	158	136	73
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	6	6	0
Asian	20	13	7
Native Hawaiian or Other Pacific Islander	2	0	0
Black or African American	7	3	1
White	256	256	126
More than one race	4	0	1
Unknown or Not Reported	3	2	3
Region of Enrollment			
Units: Subjects			
United States	51	55	25
Czechia	26	23	11
Japan	7	3	2
Ukraine	57	53	27
United Kingdom	3	5	2
Spain	21	19	8
Russia	23	21	12
Austria	1	0	0
China	11	7	4

Brazil	22	20	13
Poland	14	13	6
Denmark	0	1	0
Italy	15	15	6
Mexico	25	22	11
Israel	15	15	5
France	1	1	2
Germany	6	7	4
HbA1c at Baseline			
Units: percent HbA1c			
arithmetic mean	7.81	7.81	7.77
standard deviation	± 0.91	± 0.87	± 0.85

<b>Reporting group values</b>	Total		
Number of subjects	716		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	349		
Male	367		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	12		
Asian	40		
Native Hawaiian or Other Pacific Islander	2		
Black or African American	11		
White	638		
More than one race	5		
Unknown or Not Reported	8		
Region of Enrollment			
Units: Subjects			
United States	131		
Czechia	60		
Japan	12		
Ukraine	137		
United Kingdom	10		
Spain	48		
Russia	56		
Austria	1		
China	22		
Brazil	55		
Poland	33		
Denmark	1		
Italy	36		
Mexico	58		



Israel	35		
France	4		
Germany	17		
HbA1c at Baseline			
Units: percent HbA1c			
arithmetic mean			
standard deviation	-		

## End points

### End points reporting groups

Reporting group title	Insulin Lispro (Humalog) Lead-in
Reporting group description: Participants were switched to open-label insulin lispro (Humalog) administered subcutaneously (SC), using a unit for unit conversion or the dose could have been determined based on investigator's clinical judgement.	
Reporting group title	Insulin Lispro (Humalog)
Reporting group description: Participants received insulin lispro (Humalog) 100 units per milliliter (U/mL) administered SC 0 to 2 minutes before each meal with once or twice daily basal insulin. Preprandial insulin doses were individualized and titrated according to protocol-defined targets.	
Reporting group title	LY900014
Reporting group description: Participants received 100 U/mL LY900014 administered SC 0 to 2 minutes before start of the meal.	
Reporting group title	LY900014 Postmeal
Reporting group description: Participants received 100 U/mL LY900014 administered SC up to 20 minutes after the start of the meal.	

### Primary: Change from Baseline in Hemoglobin A1c (HbA1c) Efficacy Estimand at Week 26

End point title	Change from Baseline in Hemoglobin A1c (HbA1c) Efficacy Estimand at Week 26 <sup>[1]</sup>
End point description: Change from baseline in HbA1c was analyzed using mixed model repeated measures (MMRM) and includes fixed class effects of treatment, strata (pooled country, type of basal insulin, and age group), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline value. An unstructured covariance structure will be used to model the within-participant errors.  The Efficacy Estimand included data collected prior to permanent discontinuation of study drug through Week 26.  Analysis Population Description (APD): All participants randomly assigned to study drug with baseline and at least one postbaseline measurement available while on study drug, per protocol.	
End point type	Primary
End point timeframe: Baseline, Week 26	

#### Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, only participants who received Humalog and LY900014 administered before meals were included in the analysis.

End point values	Insulin Lispro (Humalog)	LY900014		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280	260		
Units: percentage of HbA1c				
least squares mean (standard error)	0.09 (± 0.052)	0.06 (± 0.054)		

## Statistical analyses

<b>Statistical analysis title</b>	Change from Baseline in HbA1c Efficacy Estimand
Comparison groups	Insulin Lispro (Humalog) v LY900014
Number of subjects included in analysis	540
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[2]</sup>
P-value	= 0.783
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference (LS Mean)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.13

Notes:

[2] - Noninferiority margin [NIM]=0.4% for HbA1c

## Secondary: Change from Baseline in HbA1c (Postprandial) at Week 26

End point title	Change from Baseline in HbA1c (Postprandial) at Week 26 <sup>[3]</sup>
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End point description:

Change from baseline in HbA1c postprandial was analyzed using (MMRM and includes fixed class effects of treatment, strata (pooled country, type of basal insulin, and age group), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline value. An unstructured covariance structure will be used to model the within-participant errors.

The Efficacy Estimand included data collected prior to permanent discontinuation of study drug through Week 26.

APD: All participants randomly assigned to study drug with baseline and at least one postbaseline measurement available while of study drug, per protocol.

End point type	Secondary
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End point timeframe:

Baseline, Week 26

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, only participants who received Humalog administered before meals and LY900014 Postmeal were included in the analysis.

<b>End point values</b>	Insulin Lispro (Humalog)	LY900014 Postmeal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280	131		
Units: percentage of HbA1c				
least squares mean (standard error)	0.09 (± 0.052)	0.07 (± 0.076)		

## Statistical analyses

<b>Statistical analysis title</b>	Change from Baseline in HbA1c (Postprandial)
Comparison groups	Insulin Lispro (Humalog) v LY900014 Postmeal

Number of subjects included in analysis	411
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[4]</sup>
P-value	= 0.867
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.17

Notes:

[4] - NIM of 0.4%

### Secondary: Percentage of Participants With Documented Post-dose Hypoglycemic Events Within 1 and 2 Hours After the Prandial Dose

End point title	Percentage of Participants With Documented Post-dose Hypoglycemic Events Within 1 and 2 Hours After the Prandial Dose
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End point description:

Documented post-dose hypoglycemia <54 milligrams per deciliter (mg/dL) and ≤ 70 mg/dL that occurred 1 and 2 hours after prandial dose.

APD: All randomized participants who received at least one dose of the randomly assigned study drug with non-missing baseline value and at least one non-missing post-baseline value of the response variable.

End point type	Secondary
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End point timeframe:

Baseline through Week 26

End point values	Insulin Lispro (Humalog)	LY900014	LY900014 Postmeal	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	298	280	138	
Units: percentage of participants				
least squares mean (standard error)				
<54 mg/dL 1 Hour Post-dose	26.50 (± 2.563)	36.79 (± 2.891)	29.70 (± 3.897)	
<54 mg/dL 2 Hour Post-dose	54.04 (± 2.896)	63.61 (± 2.883)	57.88 (± 4.216)	
≤70 mg/dL 1 Hour Post-dose	49.67 (± 2.901)	63.92 (± 2.874)	48.51 (± 4.261)	
≤70 mg/dL 2 Hour Post-dose	77.03 (± 2.449)	82.67 (± 2.267)	70.29 (± 3.912)	

### Statistical analyses

<b>Statistical analysis title</b>	Documented Post-dose Hypoglycemic Events 1 hr
Statistical analysis description: < 54 mg/dL 1-hour post-dose	
Comparison groups	Insulin Lispro (Humalog) v LY900014
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.13
upper limit	2.3

<b>Statistical analysis title</b>	Documented Post-dose Hypoglycemic Events 1 hr
Statistical analysis description: < 54 mg/dL 1-hour post-dose	
Comparison groups	LY900014 Postmeal v Insulin Lispro (Humalog)
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.487
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.83

<b>Statistical analysis title</b>	Documented Post-dose Hypoglycemic Events 1 hr
Statistical analysis description: < 54 mg/dL 1-hour post-dose	
Comparison groups	LY900014 v LY900014 Postmeal
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.153
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.13

<b>Statistical analysis title</b>	Documented Post-dose Hypoglycemic Events 2 hr
Statistical analysis description: < 54 mg/dL 2-hour post-dose	
Comparison groups	Insulin Lispro (Humalog) v LY900014
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	2.08

<b>Statistical analysis title</b>	Documented Post-dose Hypoglycemic Events 2 hr
Statistical analysis description: < 54 mg/dL 2-hour post-dose	
Comparison groups	Insulin Lispro (Humalog) v LY900014 Postmeal
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.455
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.76

<b>Statistical analysis title</b>	Documented Post-dose Hypoglycemic Events 2 hr
Statistical analysis description: < 54 mg/dL 2-hour post-dose	
Comparison groups	LY900014 v LY900014 Postmeal

Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.259
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.19

<b>Statistical analysis title</b>	Documented Post-dose Hypoglycemic Events 1 hr
Statistical analysis description: ≤ 70 mg/dL 1-hour post-dose	
Comparison groups	LY900014 v Insulin Lispro (Humalog)
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.29
upper limit	2.51

<b>Statistical analysis title</b>	Documented Post-dose Hypoglycemic Events 1 hr
Statistical analysis description: ≤ 70 mg/dL 1-hour post-dose	
Comparison groups	Insulin Lispro (Humalog) v LY900014 Postmeal
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.822
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.43

<b>Statistical analysis title</b>	Documented Post-dose Hypoglycemic Events 1 hr
Statistical analysis description: ≤ 70 mg/dL 1-hour post-dose	
Comparison groups	LY900014 v LY900014 Postmeal
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.8

<b>Statistical analysis title</b>	Documented Post-dose Hypoglycemic Events 2 hr
Statistical analysis description: ≤ 70 mg/dL 2-hour post-dose	
Comparison groups	Insulin Lispro (Humalog) v LY900014
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.092
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	2.14

<b>Statistical analysis title</b>	Documented Post-dose Hypoglycemic Events 2 hr
Statistical analysis description: ≤ 70 mg/dL 2-hour post-dose	
Comparison groups	LY900014 Postmeal v Insulin Lispro (Humalog)



Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.133
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.11

<b>Statistical analysis title</b>	Documented Post-dose Hypoglycemic Events 2 hr
Statistical analysis description: ≤ 70 mg/dL 2-hour post-dose	
Comparison groups	LY900014 v LY900014 Postmeal
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.8

## Secondary: Rate of Documented Post-dose Hypoglycemic Events Within 1 and 2 Hours After the Prandial Dose

End point title	Rate of Documented Post-dose Hypoglycemic Events Within 1 and 2 Hours After the Prandial Dose
End point description: Documented post-dose hypoglycemia event is an event of blood glucose of < 54 mg/dL and ≤70 mg/dL that occurred within 1 and 2 hours after the prandial dose. The rate of documented hypoglycemia was estimated by a negative binomial regression including treatment and age group as independent variables and number of episodes as dependent variables with log (exposure/365.25 days) as the offset in the model.  APD: All randomized participants who received at least 1 dose of the randomly assigned study drug with non-missing baseline value and at least one non-missing post-baseline value of the response variable.	
End point type	Secondary
End point timeframe: Baseline through Week 26	

<b>End point values</b>	Insulin Lispro (Humalog)	LY900014	LY900014 Postmeal	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	298	280	138	
Units: Events per participant per year				
least squares mean (standard error)				
< 54mg/dL 1 Hour Post-dose	1.59 (± 0.251)	2.04 (± 0.262)	1.38 (± 0.287)	
< 54 mg/dL 2 Hour Post-dose	4.48 (± 0.454)	5.95 (± 0.510)	6.17 (± 0.816)	
≤70 mg/dL 1 Hour Post-dose	6.54 (± 1.036)	8.46 (± 0.992)	5.29 (± 1.145)	
≤70 mg/dL 2 Hour Post-dose	19.0 (± 1.58)	23.7 (± 1.86)	21.1 (± 2.31)	

### Statistical analyses

<b>Statistical analysis title</b>	Rate Documented Post-dose Hypoglycemic Events 1 hr
Statistical analysis description: < 54 mg/dL 1 hour post-dose	
Comparison groups	Insulin Lispro (Humalog) v LY900014
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate Documented Post-dose Hypoglycemic Events 1 hr
Statistical analysis description: < 54 mg/dL 1-hour post-dose	
Comparison groups	Insulin Lispro (Humalog) v LY900014 Postmeal
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.599
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate Documented Post-dose Hypoglycemic Events 1 hr
Statistical analysis description: < 54 mg/dL 1 hour post-dose	
Comparison groups	LY900014 v LY900014 Postmeal

Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.112
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate Documented Post-dose Hypoglycemic Events 2 hr
Statistical analysis description: < 54 mg/dL 2 hour post-dose	
Comparison groups	Insulin Lispro (Humalog) v LY900014
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate Documented Post-dose Hypoglycemic Events 2 hr
Statistical analysis description: < 54 mg/dL 2 hour post-dose	
Comparison groups	Insulin Lispro (Humalog) v LY900014 Postmeal
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.055
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate Documented Post-dose Hypoglycemic Events 2 hr
Statistical analysis description: < 54 mg/dL 2 hour post-dose	
Comparison groups	LY900014 v LY900014 Postmeal
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.814
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate Documented Post-dose Hypoglycemic Events 1 hr
Statistical analysis description: ≤70 mg/dL 1 hour post-dose	
Comparison groups	Insulin Lispro (Humalog) v LY900014

Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.194
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate Documented Post-dose Hypoglycemic Events 1 hr
Statistical analysis description: ≤70 mg/dL 1 hour post-dose	
Comparison groups	LY900014 Postmeal v Insulin Lispro (Humalog)
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.428
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate Documented Post-dose Hypoglycemic Events 1 hr
Statistical analysis description: ≤70 mg/dL 1 hour post-dose	
Comparison groups	LY900014 v LY900014 Postmeal
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.057
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate Documented Post-dose Hypoglycemic Events 2 hr
Statistical analysis description: ≤70 mg/dL 2 hour post-dose	
Comparison groups	Insulin Lispro (Humalog) v LY900014
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.056
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate Documented Post-dose Hypoglycemic Events 2 hr
Statistical analysis description: ≤70 mg/dL 2 hour post-dose	
Comparison groups	Insulin Lispro (Humalog) v LY900014 Postmeal

Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.435
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate Documented Post-dose Hypoglycemic Events 2 hr
Statistical analysis description: ≤70 mg/dL 2 hour post-dose	
Comparison groups	LY900014 Postmeal v LY900014
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.404
Method	Negative binomial regression

## Secondary: Percentage of Participants With Documented Hypoglycemic Events

End point title	Percentage of Participants With Documented Hypoglycemic Events
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End point description:

Documented hypoglycemia is defined as <54 mg/dL and ≤70 mg/dL respectively.

APD: All randomized participants who received at least one dose of the randomly assigned study drug with non-missing baseline value and at least one non-missing post-baseline value of the response variable.

End point type	Secondary
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End point timeframe:

Baseline through Week 26

End point values	Insulin Lispro (Humalog)	LY900014	LY900014 Postmeal	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	298	280	138	
Units: percentage of participants				
least squares mean (standard error)				
<54 mg/dL	80.81 (± 2.283)	81.37 (± 2.329)	74.45 (± 3.718)	
≤70 mg/dL	93.98 (± 1.375)	92.55 (± 1.569)	87.62 (± 2.806)	

## Statistical analyses

<b>Statistical analysis title</b>	Percentage Documented Hypoglycemic Events
Statistical analysis description: <54 mg/dL	
Comparison groups	Insulin Lispro (Humalog) v LY900014
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.864
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.57

<b>Statistical analysis title</b>	Percentage Documented Hypoglycemic Events
Statistical analysis description: <54 mg/dL	
Comparison groups	Insulin Lispro (Humalog) v LY900014 Postmeal
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.132
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.12

<b>Statistical analysis title</b>	Percentage Documented Hypoglycemic Events
Statistical analysis description: <54 mg/dL	
Comparison groups	LY900014 v LY900014 Postmeal
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.104
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.09

<b>Statistical analysis title</b>	Percentage Documented Hypoglycemic Events
Statistical analysis description: ≤70 mg/dL	
Comparison groups	Insulin Lispro (Humalog) v LY900014
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.489
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.52

<b>Statistical analysis title</b>	Percentage Documented Hypoglycemic Events
Statistical analysis description: ≤70 mg/dL	
Comparison groups	Insulin Lispro (Humalog) v LY900014 Postmeal
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.9

<b>Statistical analysis title</b>	Percentage Documented Hypoglycemic Events
Statistical analysis description: ≤70 mg/dL	
Comparison groups	LY900014 v LY900014 Postmeal

Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.099
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.11

## Secondary: Rate of Documented Hypoglycemia Events

End point title	Rate of Documented Hypoglycemia Events
End point description:	
Documented hypoglycemia is defined as a hypoglycemic event of blood glucose of $\leq 70$ mg/dL or $< 54$ mg/dL. The rate of documented hypoglycemia was estimated negative binomial regression including treatment and age group as independent variables and number of episodes as dependent variable with log (exposure/365.25 days) as the offset in the model.	
APD: All randomized participants who received at least 1 dose of the randomly assigned study drug with non-missing baseline value and at least one non-missing post-baseline value of the response variable.	
End point type	Secondary
End point timeframe:	
Week 0 through Week 26	

End point values	Insulin Lispro (Humalog)	LY900014	LY900014 Postmeal	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	298	280	138	
Units: events per participant per year				
least squares mean (standard error)				
< 54 mg/dL	16.6 ( $\pm$ 1.23)	16.1 ( $\pm$ 1.20)	17.7 ( $\pm$ 1.99)	
$\leq 70$ mg/dL	78.0 ( $\pm$ 4.23)	75.1 ( $\pm$ 4.44)	76.1 ( $\pm$ 6.10)	

## Statistical analyses

Statistical analysis title	Rate of Documented Hypoglycemia Events
Statistical analysis description:	
< 54 mg/dL	
Comparison groups	Insulin Lispro (Humalog) v LY900014



Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.732
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate of Documented Hypoglycemia Events
Statistical analysis description: < 54 mg/dL	
Comparison groups	Insulin Lispro (Humalog) v LY900014 Postmeal
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.638
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate of Documented Hypoglycemia Events
Statistical analysis description: <54 mg/dL	
Comparison groups	LY900014 Postmeal v LY900014
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.462
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate of Documented Hypoglycemia Events
Statistical analysis description: $\leq$ 70 mg/dL	
Comparison groups	Insulin Lispro (Humalog) v LY900014
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.632
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate of Documented Hypoglycemia Events
Statistical analysis description: $\leq$ 70 mg/dL	
Comparison groups	LY900014 Postmeal v Insulin Lispro (Humalog)

Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	Negative binomial regression

<b>Statistical analysis title</b>	Rate of Documented Hypoglycemia Events
Statistical analysis description: ≤ 70 mg/dL	
Comparison groups	LY900014 v LY900014 Postmeal
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.889
Method	Negative binomial regression

## Secondary: Rate of Severe Hypoglycemia

End point title	Rate of Severe Hypoglycemia
End point description: Severe hypoglycemia: during these episodes, participants have an altered mental status and cannot assist in their own care, may be semiconscious or unconscious, or experience coma with or without seizures, and require assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.  The rate of severe hypoglycemia per 100 years was calculated as: 100 times the total number of severe hypoglycemia episodes within the period divided by total exposure (in year) for all participants within the treatment group.  All randomized participants who received at least one dose of the randomly assigned study drug with non-missing baseline value and at least one non-missing post-baseline value of the response variable.	
End point type	Secondary
End point timeframe: Week 0 through Week 26	

End point values	Insulin Lispro (Humalog)	LY900014	LY900014 Postmeal	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	298	280	138	
Units: Per participant per 100 years				
number (not applicable)	2.05	2.20	0.00	

## Statistical analyses

**Secondary: Change from Baseline in Insulin Dose at Week 26**

End point title	Change from Baseline in Insulin Dose at Week 26
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End point description:
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Change from baseline in insulin dose was analyzed using mixed model repeated measures (MMRM) and includes fixed class effects of treatment, strata (pooled country, type of basal insulin, age group, and HbA1c stratum ( $\leq 8.0\%$ ,  $>8.0\%$ )), baseline value, visit and treatment-by-visit interaction. An unstructured covariance structure was used to model the within-participant errors.

APD: All participants randomly assigned to study drug with baseline and at least one postbaseline measurement available while on study drug.

End point type	Secondary
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End point timeframe:
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Baseline, Week 26
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End point values	Insulin Lispro (Humalog)	LY900014	LY900014 Postmeal	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	283	264	132	
Units: Unit per day				
least squares mean (standard error)				
Total Daily Basal Insulin Dose	2.3 ( $\pm$ 0.28)	2.9 ( $\pm$ 0.29)	2.7 ( $\pm$ 0.40)	
Total Daily Insulin Dose	5.3 ( $\pm$ 0.66)	5.8 ( $\pm$ 0.69)	5.0 ( $\pm$ 0.96)	

**Statistical analyses**

Statistical analysis title	Change from Baseline in Insulin Dose
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Statistical analysis description:
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Total Daily Basal Insulin
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Comparison groups	Insulin Lispro (Humalog) v LY900014
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Number of subjects included in analysis	547
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.13
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Method	Mixed models analysis
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Parameter estimate	LS Mean Difference
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Point estimate	0.6
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Confidence interval
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level	95 %
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sides	2-sided
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lower limit	-0.2
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upper limit	1.4
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Statistical analysis title	Change from Baseline in Insulin Dose
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Statistical analysis description:	
Total Daily Basal Insulin	
Comparison groups	Insulin Lispro (Humalog) v LY900014 Postmeal
Number of subjects included in analysis	415
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.404
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1.4

<b>Statistical analysis title</b>	Change from Baseline in Insulin Dose
Statistical analysis description:	
Total Daily Basal Insulin	
Comparison groups	LY900014 v LY900014 Postmeal
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.693
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.8

<b>Statistical analysis title</b>	Change from Baseline in Insulin Dose
Statistical analysis description:	
Total Daily Insulin Dose	
Comparison groups	Insulin Lispro (Humalog) v LY900014
Number of subjects included in analysis	547
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.625
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	2.3

<b>Statistical analysis title</b>	Change from Baseline in Insulin Dose
Statistical analysis description:	
Total Daily Insulin Dose	
Comparison groups	Insulin Lispro (Humalog) v LY900014 Postmeal
Number of subjects included in analysis	415
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.758
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	1.9

<b>Statistical analysis title</b>	Change from Baseline in Insulin Dose
Statistical analysis description:	
Total Daily Insulin Dose	
Comparison groups	LY900014 v LY900014 Postmeal
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.485
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	1.5

<b>Secondary: Percentage of Participants with HbA1c &lt; 7.0% and &lt;7.5%</b>	
End point title	Percentage of Participants with HbA1c < 7.0% and <7.5%
End point description:	
Percentage of participants with HbA1c < 7.0% and <7.5% was analyzed using a longitudinal logistic	

regression with repeated measurements conducted by a generalized linear mixed model including independent variables of treatment, baseline HbA1c value, visit, baseline HbA1c-by-visit interaction, and treatment-by-visit interaction. An unstructured covariance structure was used.

APD: All participants who were randomly assigned to study drug and had non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in the analysis.

End point type	Secondary
End point timeframe:	
Week 26	

End point values	Insulin Lispro (Humalog)	LY900014	LY900014 Postmeal	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	298	280	138	
Units: percentage of participants				
number (not applicable)				
HbA1c <7%	20.00	21.92	19.08	
HbA1c < 7.5%	40.00	37.31	32.82	

## Statistical analyses

<b>Statistical analysis title</b>	Percentage HbA1c < 7.0%
Statistical analysis description:	
HbA1c < 7%	
Comparison groups	Insulin Lispro (Humalog) v LY900014
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.396
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	2

<b>Statistical analysis title</b>	Percentage HbA1c < 7.0%
Statistical analysis description:	
HbA1c < 7%	
Comparison groups	Insulin Lispro (Humalog) v LY900014 Postmeal

Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.814
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.75

<b>Statistical analysis title</b>	Percentage HbA1c < 7.0%
Statistical analysis description: HbA1c < 7%	
Comparison groups	LY900014 Postmeal v LY900014
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.384
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.43

<b>Statistical analysis title</b>	Percentage HbA1c < 7.5%
Statistical analysis description: HbA1c < 7.5%	
Comparison groups	Insulin Lispro (Humalog) v LY900014
Number of subjects included in analysis	578
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.27

<b>Statistical analysis title</b>	Percentage HbA1c < 7.5%
Statistical analysis description: HbA1c < 7.5%	
Comparison groups	Insulin Lispro (Humalog) v LY900014 Postmeal
Number of subjects included in analysis	436
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.08

<b>Statistical analysis title</b>	Percentage HbA1c < 7.5%
Statistical analysis description: HbA1c < 7.5%	
Comparison groups	LY900014 v LY900014 Postmeal
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.306
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.31

## Secondary: Change from Baseline in 7-Point Self-Monitored Blood Glucose (SMBG) Values at Week 26

End point title	Change from Baseline in 7-Point Self-Monitored Blood Glucose (SMBG) Values at Week 26
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End point description:

Change from baseline in 7-point SMBG values were analyzed using MMRM and includes fixed class effects of treatment, strata (pooled country, type of basal insulin, and age group, and HbA1c stratum ( $\leq 8.0\%$ ,  $>8.0\%$ )) baseline value, visit, and treatment-by-visit interaction. An unstructured covariance structure was used to model the within-participant errors.

All participants randomly assigned to study drug with baseline and at least one postbaseline



measurement available while on study drug.

End point type	Secondary
End point timeframe:	
Baseline, Week 26	

End point values	Insulin Lispro (Humalog)	LY900014	LY900014 Postmeal	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	298	280	138	
Units: milligram per dL (mg/dL)				
least squares mean (standard error)				
Morning Premeal-Fasting: n= 265, 247, 122	1.0 (± 2.78)	-3.4 (± 2.88)	-5.9 (± 4.11)	
Morning 1 hour Postmeal: n= 263, 239, 117	-3.2 (± 2.92)	-17.9 (± 3.06)	-9.8 (± 4.39)	
Midday Premeal: n= 265, 247,122	-3.1 (± 3.06)	2.5 (± 3.17)	-6.0 (± 4.52)	
Midday 1 hour Postmeal: n= 262, 237, 120	0.9 (± 2.99)	-5.2 (± 3.14)	-1.5 (± 4.43)	
Evening Premeal: n= 264, 247,122	1.0 (± 3.18)	4.6 (± 3.29)	0.3 (± 4.69)	
Evening 1 hour Postmeal: n= 261, 234, 118	6.9 (± 3.22)	-6.2 (± 3.39)	-3.9 (± 4.79)	
Bedtime: n= 257, 240, 116	-1.9 (± 3.03)	-2.3 (± 3.14)	-2.7 (± 4.53)	

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Lead-in to Safety Follow-up (up to 32 Weeks)

Adverse event reporting additional description:

All randomized participants who receive at least 1 dose of study drug.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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### Reporting groups

Reporting group title	Humalog Lead-in
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Reporting group description:

Participants were switched to open-label Insulin lispro (Humalog) administered SC, using a unit for unit conversion or the dose may be determined based on investigator's clinical judgement.

Reporting group title	LY900014
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Reporting group description:

Participants received 100 Units per milliliter (U/mL) LY900014 administered SC 0 to 2 minutes before each meal with either basal insulin glargine given SC once or twice daily or insulin degludec given SC once daily. Preprandial insulin doses were individualized and titrated according to protocol-defined targets.

Reporting group title	LY900014 Postmeal
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Reporting group description:

Participants received 100 U/mL LY900014 administered SC up to 20 minutes after the start of the meal.

Reporting group title	Insulin Lispro (Humalog)
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Reporting group description:

Participants received 100 U/mL Insulin lispro (Humalog) administered subcutaneously (SC) 0 to 2 minutes before each meal with once or twice daily basal insulin. Preprandial insulin doses were individualized and titrated according to protocol-defined targets.

Serious adverse events	Humalog Lead-in	LY900014	LY900014 Postmeal
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 751 (0.27%)	6 / 280 (2.14%)	2 / 138 (1.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
reactive gastropathy			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 751 (0.00%)	0 / 280 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
skin laceration			
alternative dictionary used:			

MedDRA 24.0			
subjects affected / exposed	0 / 751 (0.00%)	0 / 280 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
spinal fracture			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 751 (0.00%)	0 / 280 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
macroglossia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 751 (0.00%)	0 / 280 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 751 (0.00%)	1 / 280 (0.36%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypoglycaemic coma			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 751 (0.00%)	0 / 280 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
anaphylactic reaction			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 751 (0.00%)	0 / 280 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

abdominal pain			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 751 (0.00%)	1 / 280 (0.36%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastritis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 751 (0.00%)	0 / 280 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
mental disorder			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 751 (0.13%)	0 / 280 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
complicated appendicitis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 751 (0.00%)	0 / 280 (0.00%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastroenteritis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 751 (0.00%)	0 / 280 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pilonidal cyst			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 751 (0.00%)	0 / 280 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
upper respiratory tract infection			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	0 / 751 (0.00%)	1 / 280 (0.36%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
diabetic ketoacidosis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 751 (0.00%)	2 / 280 (0.71%)	1 / 138 (0.72%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hyperglycaemia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 751 (0.00%)	0 / 280 (0.00%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypoglycaemia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 751 (0.13%)	3 / 280 (1.07%)	0 / 138 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Insulin Lispro (Humalog)		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 298 (4.03%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
reactive gastropathy			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
skin laceration			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	1 / 298 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
spinal fracture			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
macroglossia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 298 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
hypoglycaemic coma			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
anaphylactic reaction			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	0 / 298 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
gastritis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
mental disorder			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 298 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
complicated appendicitis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 298 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
gastroenteritis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
pilonidal cyst			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
upper respiratory tract infection			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	0 / 298 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
diabetic ketoacidosis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 298 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
hyperglycaemia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 298 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
hypoglycaemia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	2 / 298 (0.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

<b>Non-serious adverse events</b>	Humalog Lead-in	LY900014	LY900014 Postmeal
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 751 (5.19%)	67 / 280 (23.93%)	21 / 138 (15.22%)
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	6 / 751 (0.80%)	13 / 280 (4.64%)	5 / 138 (3.62%)
occurrences (all)	6	22	5
General disorders and administration site conditions			
injection site reaction			
alternative dictionary used: MedDRA 24.0			



subjects affected / exposed occurrences (all)	1 / 751 (0.13%) 1	11 / 280 (3.93%) 14	2 / 138 (1.45%) 2
Gastrointestinal disorders vomiting alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	1 / 751 (0.13%) 1	9 / 280 (3.21%) 10	3 / 138 (2.17%) 3
Infections and infestations nasopharyngitis alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	21 / 751 (2.80%) 21	28 / 280 (10.00%) 37	7 / 138 (5.07%) 9
rhinitis alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	7 / 751 (0.93%) 7	6 / 280 (2.14%) 6	4 / 138 (2.90%) 5
upper respiratory tract infection alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	3 / 751 (0.40%) 3	15 / 280 (5.36%) 17	2 / 138 (1.45%) 3

<b>Non-serious adverse events</b>	Insulin Lispro (Humalog)		
Total subjects affected by non-serious adverse events subjects affected / exposed	60 / 298 (20.13%)		
Nervous system disorders headache alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	13 / 298 (4.36%) 21		
General disorders and administration site conditions injection site reaction alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	0 / 298 (0.00%) 0		
Gastrointestinal disorders			

vomiting alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	9 / 298 (3.02%) 11		
Infections and infestations nasopharyngitis alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)  rhinitis alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)  upper respiratory tract infection alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	23 / 298 (7.72%) 30  10 / 298 (3.36%) 10  16 / 298 (5.37%) 18		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported