Clinical trial results:
A Prospective, Randomized, Double Blind Comparison of LY900014 to Humalog in Adults with Type 1 Diabetes Using Continuous Subcutaneous Insulin Infusion

Summary

EudraCT number	2015-005358-36
Trial protocol	HU DE AT FR ES IT
Global end of trial date	06 January 2020

Results information

Result version number	v1 (current)
This version publication date	20 January 2021
First version publication date	20 January 2021

Trial information

Trial identification

Sponsor protocol code	I8B-MC-ITRO

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03830281
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 16315

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	06 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 January 2020
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) when both are used in insulin pump therapy in adults 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	14 February 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	Austria: 18
Country: Number of subjects enrolled	Hungary: 50
Country: Number of subjects enrolled	United States: 198
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Israel: 43
Country: Number of subjects enrolled	Australia: 32
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	Spain: 35
Worldwide total number of subjects	471
EEA total number of subjects	172

Notes:

Subjects enrolled per age group

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	409
From 65 to 84 years	62
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The purpose of the lead-in period was to assess basal rates and bolus calculator settings and adjust if needed prior to randomization. Participants (Pts) were then randomized to insulin lispro (Humalog) or ultra-rapid lispro as both basal and bolus insulin and delivered bolus doses 0 to 2 minutes prior to each meal (pre-meal).

Period 1

Period 1 title	Lead-in Period (2 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Arm title	Insulin Lispro (Humalog)

Arm description:

Participants received individual dose of 100 units per milliliter (U/mL) insulin lispro (Humalog) by continuous subcutaneous insulin infusion (CSII); where mealtime boluses were delivered 0 to 2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.

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

Dosage and administration details:

Participants received individual dose of 100 U/mL insulin lispro (Humalog) by CSII; where mealtime boluses were delivered 0 to 2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.

Number of subjects in period 1	Insulin Lispro (Humalog)
Started	471
Completed	432
Not completed	39
Physician decision	2
Consent withdrawn by subject	29
Adverse event, non-fatal	2
Not Met Eligibility Criteria	6

Period 2

Period 2 title	Treatment Period (16 Weeks)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Insulin Lispro (Humalog)

Arm description:

Participants received individual dose of 100 units per milliliter (U/mL) insulin lispro (Humalog) by continuous subcutaneous insulin infusion (CSII); where mealtime boluses were delivered 0 to 2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.

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

Dosage and administration details:

Participants received individual dose of 100 U/mL insulin lispro (Humalog) by CSII; where mealtime boluses were delivered 0 to 2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.

Arm title	Ultra-Rapid Lispro

Arm description:

Participants received individual dose of 100 U/mL ultra rapid lispro by CSII; where mealtime boluses were delivered 0 to 2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.

Arm type	Active comparator
Investigational medicinal product name	Ultra-Rapid Lispro
Investigational medicinal product code	LY900014
Other name	Insulin lispro
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received individual dose of 100 U/mL ultra rapid lispro by CSII; where mealtime boluses were delivered 0 to 2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.

Notes:

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

Justification: The Lead-in Period (Period 1) was used to assess basal rates and bolus calculator settings and adjust if needed prior to randomization. Baseline analysis population is based on all randomized participants. Participants were randomized to insulin lispro (Humalog) or ultra-rapid lispro in Period 2.

Number of subjects in period 2[2]	Insulin Lispro (Humalog)	Ultra-Rapid Lispro
Started	217	215
Completed	205	198
Not completed	12	17
Physician decision	1	-
Consent withdrawn by subject	5	6
Adverse event, non-fatal	1	7
Sponsor Decision	1	1
Lost to follow-up	4	3

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: Participants who completed lead-in period randomized to either insulin lispro (Humalog) or ultra-rapid lispro in treatment period.

Baseline characteristics

Reporting groups	
Reporting group title	Insulin Lispro (Humalog)
Reporting group description:	
Participants received individual dose of 100 units per milliliter (U/mL) insulin lispro (Humalog) by continuous subcutaneous insulin infusion (CSII); where mealtime boluses were delivered 0 to 2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.	
Reporting group title	Ultra-Rapid Lispro
Reporting group description:	
Participants received individual dose of 100 U/mL ultra rapid lispro by CSII; where mealtime boluses were delivered 0 to 2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.	

Reporting group values	Insulin Lispro (Humalog)	Ultra-Rapid Lispro	Total
Number of subjects	217	215	432
Age categorical			
Units: Subjects			
Age continuous			
All randomized participants.			
Units: years			
arithmetic mean	44.7	48.2	
standard deviation	± 14.9	± 15.4	-
Gender categorical			
All randomized participants.			
Units: Subjects			
Female	119	120	239
Male	98	95	193
Ethnicity (NIH/OMB)			
All randomized participants.			
Units: Subjects			
Hispanic or Latino	17	18	35
Not Hispanic or Latino	180	178	358
Unknown or Not Reported	20	19	39
Race (NIH/OMB)			
All randomized participants.			
Units: Subjects			
American Indian or Alaska Native	0	2	2
Asian	0	2	2
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	6	7	13
White	207	202	409
More than one race	1	0	1
Unknown or Not Reported	2	2	4
Region of Enrollment			
All randomized participants.			
Units: Subjects			

Canada	11	11	22
Puerto Rico	2	3	5
Austria	8	8	16
Hungary	24	24	48
United States	86	84	170
Italy	9	9	18
Israel	22	19	41
Australia	15	15	30
France	7	7	14
Germany	17	19	36
Spain	16	16	32
Hemoglobin A1c			
All randomized participants.			
Units: Percentage of HbA1c			
arithmetic mean	7.54	7.56	
standard deviation	± 0.58	± 0.59	-

End points

End points reporting groups

Reporting group title	Insulin Lispro (Humalog)
Reporting group description:	
Participants received individual dose of 100 units per milliliter (U/mL) insulin lispro (Humalog) by continuous subcutaneous insulin infusion (CSII); where mealtime boluses were delivered 0 to 2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.	

Reporting group title	Insulin Lispro (Humalog)
Reporting group description:	
Participants received individual dose of 100 units per milliliter (U/mL) insulin lispro (Humalog) by continuous subcutaneous insulin infusion (CSII); where mealtime boluses were delivered 0 to 2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.	

Reporting group title	Ultra-Rapid Lispro
Reporting group description:	
Participants received individual dose of 100 U/mL ultra rapid lispro by CSII; where mealtime boluses were delivered 0 to 2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.	

Primary: Change from Baseline in Hemoglobin A1c (HbA1c) Efficacy Estimand at Week 16

End point title	Change from Baseline in Hemoglobin A1c (HbA1c) Efficacy Estimand at Week 16
End point description:	
HbA1c is the glycosylated fraction of hemoglobin A. HbA1c is measured to identify average plasma glucose concentration over prolonged periods of time. Least Squares (LS) mean was determined by mixed-model repeated measures (MMRM) model with covariates: Baseline + Pooled Country + Personal continuous glucose Monitor (CGM) or Flash glucose monitor (FGM) use during study flag + Treatment + Time + Treatment*Time (Type III sum of squares). The efficacy estimand included participant data when baseline and at least one post-baseline measurement were available prior to permanent discontinuation of study drug. Analysis population included all randomized participants with baseline and at least one post-baseline HbA1c data.	
End point type	Primary
End point timeframe:	
Baseline, Week 16	

End point values	Insulin Lispro (Humalog)	Ultra-Rapid Lispro		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	191		
Units: Percentage of HbA1c				
least squares mean (standard error)	-0.09 (± 0.030)	-0.06 (± 0.031)		

Statistical analyses

Statistical analysis title	Statistical Analysis for HbA1c
Comparison groups	Ultra-Rapid Lispro v Insulin Lispro (Humalog)
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.565
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.11

Notes:

[1] - Noninferiority margin = 0.4% for HbA1c.

Secondary: Change From Baseline in 1-hour Postprandial Glucose (PPG) During Mixed-Meal Tolerance Test (MMTT) Efficacy Estimand at Week 16

End point title	Change From Baseline in 1-hour Postprandial Glucose (PPG) During Mixed-Meal Tolerance Test (MMTT) Efficacy Estimand at Week 16

End point description:

A standardized MMTT was used to characterize postprandial glucose control following administration of the study insulin. Serum glucose measured at 1-hour timepoint after the start of meal minus fasting serum glucose. Least Squares (LS) mean was determined by analysis of variance (ANCOVA) model with independent variables: Baseline + Pooled Country + Hemoglobin A1C Stratum + Personal CGM/FGM use during study Flag + Treatment (Type III sum of squares).The efficacy estimand included participant data when baseline and at least one post-baseline measurement were available prior to permanent discontinuation of study drug. Analysis population included all randomized participants with baseline and at least one post-baseline 1-hour PPG data.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Insulin Lispro (Humalog)	Ultra-Rapid Lispro		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	182		
Units: milligrams per deciliter (mg/dL)				
least squares mean (standard error)	-2.2 (± 5.02)	-26.3 (± 5.33)		

Statistical analyses

Statistical analysis title	Statistical Analysis for 1-hour PPG
Comparison groups	Insulin Lispro (Humalog) v Ultra-Rapid Lispro

Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-24.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36
upper limit	-12.2

Secondary: Change From Baseline in 2-hour PPG During MMTT Efficacy Estimand at Week 16

End point title	Change From Baseline in 2-hour PPG During MMTT Efficacy Estimand at Week 16

End point description:

A standardized MMTT was used to characterize postprandial glucose control following administration of the study insulin. Serum glucose measured at 2-hour timepoint after the start of meal minus fasting serum glucose. Least Squares (LS) mean was determined by analysis of variance (ANCOVA) model with independent variables: Baseline + Pooled Country + Hemoglobin A1C Stratum + Personal CGM/FGM use during study Flag + Treatment (Type III sum of squares).The efficacy estimand included participant data when baseline and at least one post-baseline measurement were available prior to permanent discontinuation of study drug. Analysis population included all randomized participants with baseline and at least one post-baseline 2-hour PPG data.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Insulin Lispro (Humalog)	Ultra-Rapid Lispro		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	183		
Units: mg/dL				
least squares mean (standard error)	-4.2 (± 6.27)	-32.0 (± 6.59)		

Statistical analyses

Statistical analysis title	Statistical Analysis for 2-hour PPG
Comparison groups	Insulin Lispro (Humalog) v Ultra-Rapid Lispro

Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-27.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.6
upper limit	-13

Secondary: Percentage of Time with Sensor Glucose Values between 70 and 180 mg/dL Efficacy Estimand at Week 16

End point title	Percentage of Time with Sensor Glucose Values between 70 and 180 mg/dL Efficacy Estimand at Week 16

End point description:

Percentage of time with sensor glucose values between 70 and 180 mg/dL using continuous glucose monitoring (CGM). Least square (LS) mean difference will provided for CGM data normalized to a 24hrs period. Daytime: 0600 hours to midnight (06:00:00-23:59:59 on the 24-hour clock). Least Squares (LS) mean was determined by mixed-model repeated measures (MMRM) model with covariates: Baseline + Pooled Country + Hemoglobin A1C Stratum + Personal continuous glucose Monitor (CGM) or Flash glucose monitor (FGM) use during study flag + Treatment + Time + Treatment*Time (Type III sum of squares). Analysis population included all randomized participants with non-missing baseline value and at least one non-missing post-baseline value.

End point type	Secondary

End point timeframe:

Week 16

End point values	Insulin Lispro (Humalog)	Ultra-Rapid Lispro		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	172[2]		
Units: percentage of time				
least squares mean (standard error)				
Daytime	58.6 (± 0.75)	59.3 (± 0.77)		
24-Hour	57.5 (± 0.76)	57.9 (± 0.79)		

Notes:

[2] - 24-Hour: n = 171

Statistical analyses

Statistical analysis title	Statistical analysis for glucose values: Day time

Statistical analysis description:

Statistical analysis during daytime is reported.

Comparison groups	Insulin Lispro (Humalog) v Ultra-Rapid Lispro

Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.532
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	2.8

Notes:

[3] - Statistical analysis during daytime is reported.

Statistical analysis title	Statistical analysis for glucose values: 24-Hour

Statistical analysis description:

Statistical analysis during 24-hour period is reported.

Comparison groups	Insulin Lispro (Humalog) v Ultra-Rapid Lispro
Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.738
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	2.5

Notes:

[4] - Statistical analysis during 24-hour period is reported.

Secondary: Rate of Severe Hypoglycemia at Week 16

End point title	Rate of Severe Hypoglycemia at Week 16

End point description:

Severe hypoglycemia is defined as an event requiring assistance of another person to administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the participant has an altered mental status and cannot assist in his or her own care, or may be semiconscious or unconscious, or experience coma with or without seizures, and may require parenteral therapy. Rate of severe hypoglycemia events per 100 years during a defined period was calculated by total number of severe hypoglycemia episodes within the period divided by the cumulative days on treatment from all participants within a treatment group *36525. Analysis population included all randomized participants with evaluable hypoglycemic data.

End point type	Secondary

End point timeframe:

Baseline through Week 16

End point values	Insulin Lispro (Humalog)	Ultra-Rapid Lispro		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	214		
Units: Events per 100 participant years				
number (not applicable)	2.95	6.36		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Documented Symptomatic Hypoglycemia at Week 16

End point title	Rate of Documented Symptomatic Hypoglycemia at Week 16

End point description:

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by blood glucose (BG) of <54 mg/dL [3.0 millimole per liter (mmol/L)]. The rate of documented symptomatic hypoglycemia was estimated by negative binomial model: number of episodes = treatment with log (treatment exposure in days/365.25) as an offset variable. Analysis population included all randomized participants with evaluable hypoglycemic data.

End point type	Secondary

End point timeframe:

Baseline through Week 16

End point values	Insulin Lispro (Humalog)	Ultra-Rapid Lispro		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	214		
Units: Events per participant per year				
least squares mean (standard error)	30.7 (± 2.48)	24.6 (± 1.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 1,5-Anhydroglucitol (1,5-AG) at Week 16

End point title	Change From Baseline in 1,5-Anhydroglucitol (1,5-AG) at Week 16

End point description:

1,5-anhydroglucitol (1,5-AG) is a marker of short-term glycemic control especially postprandial hyperglycemia. 1,5-AG accurately predicts rapid changes in glycemia and is tightly associated with glucose fluctuations and postprandial glucose. LS Mean was calculated using mixed model repeated measures (MMRM) including fixed class effects of treatment, strata (Pooled Country + Hemoglobin A1C Stratum + Personal continuous glucose Monitor (CGM) or Flash glucose monitor (FGM) use during study flag), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline value. The analysis included data collected prior to permanent discontinuation of study drug. Analysis population included all randomized participants with baseline and at least one post-baseline 1,5-AG data.

End point type	Secondary

End point timeframe:
Baseline, Week 16

End point values	Insulin Lispro (Humalog)	Ultra-Rapid Lispro		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	185		
Units: milligram per liter (mg/L)				
least squares mean (standard error)	0.16 (± 0.116)	0.11 (± 0.121)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in 10-Point Self-Monitoring Blood Glucose (SMBG) Values at Week 16

End point title	Change from Baseline in 10-Point Self-Monitoring Blood Glucose (SMBG) Values at Week 16

End point description:

SMBG 10-point profiles measured at fasting, 1-hour (h) post morning meal,2 h post morning meal,pre midday meal,1 h post midday meal,2 h post midday meal,pre evening meal, 1 h post evening meal,2 hpost evening meal, and bedtime.LS Mean analyzed by MMRM including fixed class effects of treatment,strata (pooled country, HbA1c stratum : less than or equal to (≤)7.5%, greater than (>)7.5% and participant's personal CGM or FGM use during study),visit,and treatment-by-visit interaction,as well as the continuous,fixed covariates of baseline value. Insulin lispro (Humalog) reporting group - Morning (Mrg),evening (evg) 1-hour (h) Postmeal(poml):n=189;Mrg 2 h Poml: n=192; Midday Premeal(preml):n=195; Midday 1h Poml:n=188; Midday 2 h Poml:n=191; Evg Preml:n=193;Evg 2 h Poml:n=190; Bedtime:n=180 and Ultra-Rapid Lispro reporting group - Mrg 1 h,2 h Poml:n=172; Midday Preml:n=175; Midday 1h Poml:n=166; Midday 2 h Poml and Evg 2 h Poml:n=171; Evg Preml:n=178;Evg 1 h Poml:n=167; Bedtime:n=169

End point type	Secondary

End point timeframe:
Baseline, Week 16

End point values	Insulin Lispro (Humalog)	Ultra-Rapid Lispro		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[5]	178[6]		
Units: mg/dL				
least squares mean (standard error)				
Morning Premeal	0.2 (± 2.76)	0.5 (± 2.89)		
Morning 1-hour Postmeal	-3.1 (± 3.15)	-12.9 (± 3.31)		
Morning 2-hour Postmeal	-2.7 (± 3.04)	-2.9 (± 3.21)		
Midday Premeal	-0.6 (± 2.82)	4.9 (± 2.98)		
Midday 1-hour Postmeal	-4.2 (± 2.85)	-6.3 (± 3.03)		
Midday 2-hour Postmeal	-0.2 (± 3.14)	4.4 (± 3.31)		
Evening Premeal	3.8 (± 3.28)	17.5 (± 3.41)		

Evening 1-hour Postmeal	2.6 (± 3.21)	8.6 (± 3.41)		
Evening 2-hour Postmeal	6.3 (± 3.36)	12.2 (± 3.54)		
Bedtime	8.6 (± 6.37)	19.0 (± 6.58)		

Notes:

[5] - All randomized participants with baseline and at least one post-baseline data.

[6] - All randomized participants with baseline and at least one post-baseline data.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Insulin Dose at Week 16

End point title	Change from Baseline in Insulin Dose at Week 16

End point description:

LS mean was determined by MMRM model with covariates: Baseline + Pooled Country + + Hemoglobin A1C Stratum + Personal CGM or FGM use during study flag + Treatment + Time + Treatment*Time (Type III sum of squares). The analysis included data prior to permanent discontinuation of study drug. Analysis population included all randomized participants with baseline and at least one post-baseline basal insulin dose data.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Insulin Lispro (Humalog)	Ultra-Rapid Lispro		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199[7]	186[8]		
Units: units per day (U/day)				
least squares mean (standard error)				
Daily Basal Insulin Dose	-0.2 (± 0.43)	-0.1 (± 0.44)		
Daily Bolus Insulin Dose	0.8 (± 0.66)	-1.0 (± 0.68)		
Total Daily Insulin Dose	0.6 (± 0.80)	-1.1 (± 0.82)		

Notes:

[7] - Daily Bolus Insulin Dose: n = 197; Total Daily Insulin Dose: n = 195.

[8] - Daily Bolus Insulin Dose and Total Daily Insulin Dose: n = 183

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bolus/Total Insulin Dose Ratio at Week 16

End point title	Change from Baseline in Bolus/Total Insulin Dose Ratio at Week 16

End point description:

The bolus/total ratio was derived as the bolus dose divided by the total insulin dose at each visit. LS mean was determined by MMRM model with covariates: Baseline + Pooled Country + + Hemoglobin A1C Stratum + Personal CGM or FGM use during study flag + Treatment + Time + Treatment*Time (Type III sum of squares). The analysis included data prior to permanent discontinuation of study drug. Analysis population included all randomized participants with non-missing baseline value and at least one non-missing post-baseline value.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Insulin Lispro (Humalog)	Ultra-Rapid Lispro		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	183		
Units: Percentage of bolus/total insulin dose				
least squares mean (standard error)	0.6 (± 0.66)	-1.3 (± 0.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with HbA1c <7%

End point title	Percentage of Participants with HbA1c <7%

End point description:

Hemoglobin A1c (HbA1c) is the glycosylated fraction of hemoglobin A. HbA1c is measured to identify average plasma glucose concentration over prolonged periods of time. Analysis population included all randomized participants with baseline and at least one post-baseline HbA1c <7% data. Missing endpoints were imputed by applying the last observation carried forward (LOCF) method to the post-baseline data.

End point type	Secondary

End point timeframe:

Week 16

End point values	Insulin Lispro (Humalog)	Ultra-Rapid Lispro		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	191		
Units: Percentage of participants				
number (not applicable)	20.77	18.85		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with at Least 1 Pump Occlusion Alarm that Leads to an Unplanned Infusion Set Change

End point title	Percentage of Participants with at Least 1 Pump Occlusion Alarm that Leads to an Unplanned Infusion Set Change

End point description:

Percentage of participants with at least 1 pump occlusion alarm that leads to an unplanned infusion set change was evaluated. Analysis population included all randomized participants with baseline and at least one post-baseline value.

End point type	Secondary

End point timeframe:

Baseline through Week 16

End point values	Insulin Lispro (Humalog)	Ultra-Rapid Lispro		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	210		
Units: Percentage of participants				
number (not applicable)	12.7	14.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with at Least 1 Event of Unexplained Hyperglycemia >300 mg/dL confirmed by SMBG that Leads to an Unplanned Infusion Set Change

End point title	Percentage of Participants with at Least 1 Event of Unexplained Hyperglycemia >300 mg/dL confirmed by SMBG that Leads to an Unplanned Infusion Set Change

End point description:

Percentage of participants with at least 1 event of unexplained hyperglycemia >300 milligrams per deciliter (mg/dL) confirmed by SMBG that leads to an unplanned infusion set change was evaluated. Analysis population included all randomized participants with baseline and at least one post-baseline value.

End point type	Secondary

End point timeframe:

Baseline through Week 16

End point values	Insulin Lispro (Humalog)	Ultra-Rapid Lispro		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	217	215		
Units: Percentage of participants				
number (not applicable)	18.4	16.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 20 Weeks

Adverse event reporting additional description:

All randomized participants. There are gender specific adverse events, only occurring in male or female participants. The number of participants exposed has been adjusted accordingly.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Insulin Lispro (Humalog) Lead-in

Reporting group description:

Participants received individual dose of 100 units per milliliter (U/mL) insulin lispro (Humalog) by continuous subcutaneous insulin infusion (CSII); where mealtime boluses were delivered 0 to 2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.

Reporting group title	Insulin Lispro (Humalog)

Reporting group description:

Participants received individual dose of 100 U/mL insulin lispro (Humalog) by CSII; where mealtime boluses were delivered 0 to 2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.

Reporting group title	Ultra-Rapid Lispro

Reporting group description:

Participants received individual dose of 100 U/mL ultra rapid lispro by CSII; where mealtime boluses were delivered 0 to 2 minutes prior to the start of each meal, with basal infusion rates 24 hours/day, and correction boluses as necessary.

Serious adverse events	Insulin Lispro (Humalog) Lead-in	Insulin Lispro (Humalog)	Ultra-Rapid Lispro
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 471 (0.85%)	10 / 217 (4.61%)	17 / 215 (7.91%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
breast cancer			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
malignant melanoma			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 471 (0.00%)	1 / 217 (0.46%)	0 / 215 (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
Investigations			
intraocular pressure increased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 471 (0.21%)	0 / 217 (0.00%)	0 / 215 (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
Injury, poisoning and procedural complications			
fibula fracture			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
foreign body in respiratory tract			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
humerus fracture			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
maternal exposure during pregnancy			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed[1]	0 / 261 (0.00%)	1 / 119 (0.84%)	0 / 120 (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
patella fracture			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 471 (0.00%)	1 / 217 (0.46%)	0 / 215 (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
tibia fracture			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
acute myocardial infarction			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
myocardial infarction			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	0 / 217 (0.00%)	2 / 215 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
stress cardiomyopathy			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
cerebrovascular accident			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
facial paralysis			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 471 (0.00%)	1 / 217 (0.46%)	0 / 215 (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
General disorders and administration site conditions			
impaired healing			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 471 (0.21%)	0 / 217 (0.00%)	0 / 215 (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
Eye disorders			
vitreous haemorrhage			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 471 (0.21%)	0 / 217 (0.00%)	0 / 215 (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
Gastrointestinal disorders			
hiatus hernia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	1 / 217 (0.46%)	0 / 215 (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
intestinal dilatation			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	1 / 217 (0.46%)	0 / 215 (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
intestinal obstruction			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 471 (0.21%)	0 / 217 (0.00%)	0 / 215 (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
Respiratory, thoracic and mediastinal disorders			
respiratory failure			

alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	1 / 217 (0.46%)	0 / 215 (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
Infections and infestations			
abscess limb			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 471 (0.21%)	0 / 217 (0.00%)	0 / 215 (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
gastroenteritis viral			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	1 / 217 (0.46%)	0 / 215 (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
herpes zoster oticus			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	1 / 217 (0.46%)	0 / 215 (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
pneumonia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 471 (0.21%)	0 / 217 (0.00%)	0 / 215 (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
Metabolism and nutrition disorders			
diabetic ketoacidosis			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 471 (0.00%)	3 / 217 (1.38%)	3 / 215 (1.40%)
occurrences causally related to treatment / all	0 / 0	0 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypoglycaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	2 / 217 (0.92%)	5 / 215 (2.33%)
occurrences causally related to treatment / all	0 / 0	1 / 2	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ketosis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 471 (0.00%)	0 / 217 (0.00%)	1 / 215 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: There are gender specific adverse events, only occurring in male or female participants. The number of participants exposed has been adjusted accordingly.

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Insulin Lispro (Humalog) Lead-in	Insulin Lispro (Humalog)	Ultra-Rapid Lispro
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 471 (3.18%)	31 / 217 (14.29%)	90 / 215 (41.86%)
General disorders and administration site conditions			
infusion site pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 471 (0.64%)	6 / 217 (2.76%)	35 / 215 (16.28%)
occurrences (all)	3	6	41
infusion site reaction			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	6 / 471 (1.27%)	16 / 217 (7.37%)	47 / 215 (21.86%)
occurrences (all)	6	16	60
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed occurrences (all)	6 / 471 (1.27%) 6	13 / 217 (5.99%) 14	13 / 215 (6.05%) 15

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported