Clinical trial results:
Protocol I8B-MC-ITSI
A Prospective, Randomized, Double-Blind, Crossover Comparison Evaluating Compatibility and Safety of LY900014 and Insulin Lispro with an External Continuous Subcutaneous Insulin Infusion System in Adult Patients with Type 1 Diabetes (PRONTO-Pump)

Summary

EudraCT number	2017-002374-39
Trial protocol	ES
Global end of trial date	04 September 2018

Results information

Result version number	v1 (current)
This version publication date	21 September 2019
First version publication date	21 September 2019

Trial information

Trial identification

Sponsor protocol code	I8B-MC-ITSI

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03433677
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 16908

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	04 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the compatibility and safety of LY900014 and insulin lispro with an external continuous subcutaneous insulin infusion system in adult participants with type 1 diabetes.

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	21 February 2018
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	United States: 28
Country: Number of subjects enrolled	Spain: 21
Worldwide total number of subjects	49
EEA total number of subjects	21

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)	47
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

No Text Available

Pre-assignment

Screening details:

2-period crossover with no washout between periods and a 4 week safety follow-up.

Period 1

Period 1 title	Lead In
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Sequence 1 (LY900014/Insulin Lispro)

Arm description:

All participants received insulin lispro via CSII during lead in.

Arm type	Baseline insulin lispro
Investigational medicinal product name	Baseline insulin lispro
Investigational medicinal product code	
Other name	Humalog®
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

100 U/mL insulin lispro (Humalog®) administered by individualized CSII

Arm title	Sequence 2 (Insulin Lispro/LY900014)

Arm description:

All participants received insulin lispro via CSII during lead in.

Arm type	Baseline insulin lispro
Investigational medicinal product name	Baseline insulin lispro
Investigational medicinal product code	
Other name	Humalog®
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

100 U/mL insulin lispro (Humalog®) administered by individualized CSII

Number of subjects in period 1	Sequence 1 (LY900014/Insulin Lispro)	Sequence 2 (Insulin Lispro/LY900014)
Started	24	25
Completed	24	25

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence 1 (LY900014/Insulin Lispro)

Arm description:

1. 100 U/mL LY900014 administered by continuous subcutaneous insulin infusion (CSII) for six weeks
2. 100 U/mL insulin lispro (Humalog®) administered by CSII for six weeks with no washout between periods

Arm type	Experimental
Investigational medicinal product name	LY900014
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

1. 100 U/mL LY900014 administered by continuous subcutaneous insulin infusion (CSII) for six weeks

Arm title	Sequence 2 (Insulin Lispro/LY900014)

Arm description:

1. 100 U/mL insulin lispro (Humalog®) administered by CSII for 6 weeks
2. 100 U/mL LY900014 administered by continuous subcutaneous insulin infusion (CSII) for six weeks with no washout between periods

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro
Investigational medicinal product code	
Other name	Humalog®
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

100 U/mL insulin lispro (Humalog®) administered by CSII for 6 weeks

Number of subjects in period 2	Sequence 1 (LY900014/Insulin Lispro)	Sequence 2 (Insulin Lispro/LY900014)
Started	24	25
Received at Least 1 Dose of Study Drug	24	25
Completed	23	25
Not completed	1	0
Protocol deviation	1	-

Period 3

Period 3 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence 1 (LY900014/Insulin Lispro)

Arm description:

1. 100 U/mL LY900014 administered by continuous subcutaneous insulin infusion (CSII) for six weeks
2. 100 U/mL insulin lispro (Humalog®) administered by CSII for six weeks with no washout between periods

Arm type	Active comparator
Investigational medicinal product name	Insulin Lispro
Investigational medicinal product code	
Other name	Humalog®
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

100 U/mL insulin lispro (Humalog®) administered by CSII for 6 weeks

Arm title	Sequence 2 (Insulin Lispro/LY900014)

Arm description:

1. 100 U/mL insulin lispro (Humalog®) administered by CSII for 6 weeks
2. 100 U/mL LY900014 administered by continuous subcutaneous insulin infusion (CSII) for six weeks with no washout between periods

Arm type	Experimental
Investigational medicinal product name	LY900014
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

100 U/mL LY900014 administered by continuous subcutaneous insulin infusion (CSII) for six weeks with no washout between periods

Number of subjects in period 3	Sequence 1 (LY900014/Insulin Lispro)	Sequence 2 (Insulin Lispro/LY900014)
Started	23	25
Received at Least 1 Dose of Study Drug	23	25
Completed	22	24
Not completed	1	1
Consent withdrawn by subject	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Sequence 1 (LY900014/Insulin Lispro)
Reporting group description:	
All participants received insulin lispro via CSII during lead in.	
Reporting group title	Sequence 2 (Insulin Lispro/LY900014)
Reporting group description:	
All participants received insulin lispro via CSII during lead in.	

Reporting group values	Sequence 1 (LY900014/Insulin Lispro)	Sequence 2 (Insulin Lispro/LY900014)	Total
Number of subjects	24	25	49
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	22	24	46
From 65-84 years	2	1	3
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	42.50	36.72	
standard deviation	± 12.47	± 10.37	-
Gender categorical Units: Subjects			
Female	12	14	26
Male	12	11	23
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	23	25	48
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	23	25	48
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment			

Units: Subjects			
United States	14	14	28
Spain	10	11	21

End points

End points reporting groups

Reporting group title	Sequence 1 (LY900014/Insulin Lispro)
Reporting group description:	
All participants received insulin lispro via CSII during lead in.	
Reporting group title	Sequence 2 (Insulin Lispro/LY900014)
Reporting group description:	
All participants received insulin lispro via CSII during lead in.	
Reporting group title	Sequence 1 (LY900014/Insulin Lispro)
Reporting group description:	
1. 100 U/mL LY900014 administered by continuous subcutaneous insulin infusion (CSII) for six weeks 2. 100 U/mL insulin lispro (Humalog®) administered by CSII for six weeks with no washout between periods	
Reporting group title	Sequence 2 (Insulin Lispro/LY900014)
Reporting group description:	
1. 100 U/mL insulin lispro (Humalog®) administered by CSII for 6 weeks 2. 100 U/mL LY900014 administered by continuous subcutaneous insulin infusion (CSII) for six weeks with no washout between periods	
Reporting group title	Sequence 1 (LY900014/Insulin Lispro)
Reporting group description:	
1. 100 U/mL LY900014 administered by continuous subcutaneous insulin infusion (CSII) for six weeks 2. 100 U/mL insulin lispro (Humalog®) administered by CSII for six weeks with no washout between periods	
Reporting group title	Sequence 2 (Insulin Lispro/LY900014)
Reporting group description:	
1. 100 U/mL insulin lispro (Humalog®) administered by CSII for 6 weeks 2. 100 U/mL LY900014 administered by continuous subcutaneous insulin infusion (CSII) for six weeks with no washout between periods	
Subject analysis set title	Insulin Lispro (Humalog®)
Subject analysis set type	Per protocol
Subject analysis set description:	
100 U/mL insulin lispro (Humalog®) administered by CSII	
Subject analysis set title	LY900014
Subject analysis set type	Per protocol
Subject analysis set description:	
100 U/mL LY900014 administered by continuous subcutaneous insulin infusion (CSII)	

Primary: Rate of Infusion Set Failures

End point title	Rate of Infusion Set Failures
End point description:	
Infusion set failure events are defined as premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose (SMBG) >250 milligrams per deciliter (mg/dL) (13.9 millimoles per liter [mmol/L]) that does not decrease within 1 hour following a correction bolus delivered via the pump during the 6 week treatment period. Aggregate rate was calculated for each participant as the total number of events while the participant is on study treatment divided by the days of exposure [last dose date and time –first dose date and time –duration of pump or treatment interruption] times 30.	
End point type	Primary
End point timeframe:	
6 Weeks	

End point values	Insulin Lispro (Humalog®)	LY900014		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48[1]	49[2]		
Units: events per 30 participant days				
number (not applicable)	0.05	0.03		

Notes:

[1] - All randomized participants who received at least 1 dose of study drug.

[2] - All randomized participants who received at least 1 dose of study drug.

Statistical analyses

Statistical analysis title	Rate of Infusion Set Failures

Statistical analysis description:

Based on crossover design, 49 participants who received LY900014 and 48 participants who received insulin lispro (Humalog) were included in the analysis.

Comparison groups	Insulin Lispro (Humalog®) v LY900014
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.375
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Percentage of Participants with at Least 1 Event of Infusion Set Failure

End point title	Percentage of Participants with at Least 1 Event of Infusion Set Failure

End point description:

Infusion set failures are defined as premature infusion set changes, due to a pump occlusion alarm OR due to unexplained hyperglycemia with blood glucose (SMBG) >250mg/dL (13.9 mmol/L) that does not decrease within 1 hour following a correction bolus delivered via the pump

End point type	Secondary

End point timeframe:

6 Weeks

End point values	Insulin Lispro (Humalog®)	LY900014		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48[3]	49[4]		
Units: percentage of participants				
number (not applicable)	6.3	4.1		

Notes:

[3] - All randomized participants who received at least 1 dose of study drug.

[4] - All randomized participants who received at least 1 dose of study drug.

Statistical analyses

Statistical analysis title	Percentage of Participants with at Least 1 Event

Statistical analysis description:

Based on crossover design, 49 participants who received LY900014 and 48 participants who received insulin lispro (Humalog) were included in the analysis.

Comparison groups	Insulin Lispro (Humalog®) v LY900014
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.468
Method	Prescott's Exact Test

Secondary: Rate of Premature Infusion Set Changes

End point title	Rate of Premature Infusion Set Changes

End point description:

Rate of premature infusion set changes.

End point type	Secondary

End point timeframe:

6 Weeks

End point values	Insulin Lispro (Humalog®)	LY900014		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48[5]	49[6]		
Units: events per 30 participant days				
number (not applicable)	0.78	1.13		

Notes:

[5] - All randomized participants who received at least 1 dose of study drug.

[6] - All randomized participants who received at least 1 dose of study drug.

Statistical analyses

Statistical analysis title	Rate of Premature Infusion Set Changes

Statistical analysis description:

Based on crossover design, 49 participants who received LY900014 and 48 participants who received insulin lispro (Humalog) were included in the analysis.

Comparison groups	Insulin Lispro (Humalog®) v LY900014

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	Wilcoxon (Mann-Whitney)

Secondary: Time Interval until Infusion Set Change

End point title	Time Interval until Infusion Set Change

End point description:

Time interval until infusion set change reflects the time interval in hours until infusion set change from first to last dose. MMRM model for post-baseline measures: Variable = Baseline + Period + Sequence + Strata(Region + Historical Use of SmartGuard/Threshold Suspend + HbA1c(<=7.3%, >7.3%)) + Treatment (Type III sum of squares). All randomized participants who received at least 1 dose of study drug and non-missing baseline value and at least one non-missing post-baseline value.

End point type	Secondary

End point timeframe:

6 Weeks

End point values	Insulin Lispro (Humalog®)	LY900014		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[7]	47[8]		
Units: hours				
least squares mean (standard error)	76.1 (± 1.52)	74.3 (± 1.51)		

Notes:

[7] - All randomized participants who received at least 1 dose of study drug.

[8] - All randomized participants who received at least 1 dose of study drug.

Statistical analyses

Statistical analysis title	Time Interval until Infusion Set Change

Statistical analysis description:

Based on crossover design, 47 out of 49 participants who received LY900014 and 46 out of 48 participants who received insulin lispro (Humalog) were included in the analysis.

Comparison groups	Insulin Lispro (Humalog®) v LY900014
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.304
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	1.7

Notes:

[9] - Week 0-6

Secondary: Ratio of Bolus/Total Insulin Dose

End point title	Ratio of Bolus/Total Insulin Dose

End point description:

The bolus and total insulin doses for each visit was calculated as the mean of the doses for the last 3 days prior to the visit date that are entered in the eCRF. The bolus/total ratio was derived as the bolus dose divided by the total insulin dose at each visit. All randomized participants who received at least 1 dose of study drug and non-missing baseline value and at least one non-missing post-baseline value.

End point type	Secondary

End point timeframe:

6 Weeks

End point values	Insulin Lispro (Humalog®)	LY900014		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47[10]	46[11]		
Units: percent				
least squares mean (standard error)	46.6 (± 1.17)	44.2 (± 1.17)		

Notes:

[10] - All randomized participants who received at least 1 dose of study drug.

[11] - All randomized participants who received at least 1 dose of study drug.

Statistical analyses

Statistical analysis title	Ratio of Bolus/Total Insulin Dose

Statistical analysis description:

Based on crossover design, 46 out of 49 participants who received LY900014 and 47 out of 48 participants who received insulin lispro (Humalog) were included in the analysis.

Comparison groups	Insulin Lispro (Humalog®) v LY900014
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.057
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	0.1

Secondary: Interstitial Glucose Reduction Rate from Hyperglycemia Following a Non-Meal-Related Correction Bolus Delivered Via the Pump

End point title	Interstitial Glucose Reduction Rate from Hyperglycemia Following a Non-Meal-Related Correction Bolus Delivered Via

	the Pump

End point description:

Interstitial glucose reduction rate milligram per deciliter per minute (glucose reduction [mg/dL] per minute) within 4 hours following a non-meal-related correction bolus via the pump, from hyperglycemia (interstitial glucose >180 mg/dL [10 mmol/L]) to recovery (interstitial glucose ≤180 mg/dL). All randomized participants who received at least 1 dose of study drug and non-missing baseline value and at least one non-missing post-baseline value of the response.

End point type	Secondary

End point timeframe:

6 Weeks

End point values	Insulin Lispro (Humalog®)	LY900014		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33[12]	31[13]		
Units: mg/dL/min				
least squares mean (standard error)	0.71 (± 0.062)	0.82 (± 0.063)		

Notes:

[12] - All randomized participants who received at least 1 dose of study drug.

[13] - All randomized participants who received at least 1 dose of study drug.

Statistical analyses

Statistical analysis title	Interstitial Glucose Reduction Rate from Hypergly

Statistical analysis description:

Based on crossover design, 37 out of 49 participants who received LY900014 and 37 out of 48 participants who received insulin lispro (Humalog) were included in the analysis.

Comparison groups	Insulin Lispro (Humalog®) v LY900014
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.177
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.27

Secondary: Number of Participants with Severe Hypoglycemic Events

End point title	Number of Participants with Severe Hypoglycemic Events

End point description:

Number of participants with severe hypoglycemic events. Severe hypoglycemia was defined as participants with an altered mental status and could not assist in their own care, may have been semiconscious or unconscious, or experienced coma with or without seizures, and the event required assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Blood glucose measurements may not have been available during such an event, but neurological recovery attributable to the restoration of BG concentration to normal was considered

sufficient evidence that the event was induced by a low BG concentration (BG ≤70 mg/dL [3.9 mmol/L]).

End point type	Secondary

End point timeframe:

6 Weeks

End point values	Insulin Lispro (Humalog®)	LY900014		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48[14]	49[15]		
Units: participants				
number (not applicable)	1	1		

Notes:

[14] - All randomized participants who received at least 1 dose of study drug.

[15] - All randomized participants who received at least 1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
up to 12 weeks	
Adverse event reporting additional description:	
I8B-MC-ITSI	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	LY900014
Reporting group description:	
100 LY900014 administered by continuous subcutaneous insulin infusion (CSII)	
Reporting group title	Insulin Lispro (Humalog®)
Reporting group description:	
Insulin lispro (Humalog®) administered by CSII	

Serious adverse events	LY900014	Insulin Lispro (Humalog®)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 49 (2.04%)	1 / 48 (2.08%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Metabolism and nutrition disorders			
hypoglycaemia			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	1 / 49 (2.04%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	LY900014	Insulin Lispro (Humalog®)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 49 (36.73%)	6 / 48 (12.50%)	
General disorders and administration site conditions			

infusion site pain			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	9 / 49 (18.37%)	2 / 48 (4.17%)	
occurrences (all)	11	2	
infusion site reaction			
alternative dictionary used: MedDRA 21.0			
subjects affected / exposed	9 / 49 (18.37%)	4 / 48 (8.33%)	
occurrences (all)	36	5	

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