Clinical trial results:
An Open-Label, Randomized, Crossover Trial of CSII Reservoir In-use Comparing Insulin Lispro Formulation to Insulin Aspart in Patients with Type 1 Diabetes Mellitus

Summary

EudraCT number	2017-001162-21
Trial protocol	Outside EU/EEA
Global end of trial date	10 August 2011

Results information

Result version number	v1
This version publication date	23 February 2019
First version publication date	23 February 2019

Trial information

Trial identification

Sponsor protocol code	F3Z-MC-IOPV

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01109316
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 12174

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 August 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 August 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a 6-sequence, 3-period (8 weeks each), 3-arm, 24-week crossover study. The purpose of this study is to provide information on the use of insulin lispro in insulin pumps (Continuous Subcutaneous Insulin Infusion [CSII]) compared to insulin aspart over 6 days of pump reservoir in-use. The study will also compare the in-use characteristics of insulin lispro infused at 6 days with insulin lispro infused at 2 days.

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 April 2010
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: 132
Worldwide total number of subjects	132
EEA total number of subjects	0

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)	15
Adults (18-64 years)	105
From 65 to 84 years	12

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Not applicable

Period 1

Period 1 title	Study Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence A

Arm description:

Participants received Insulin Lispro 2D (2 Days), Insulin Lispro 6D and Insulin Aspart 6D as per below dosing schedule Period 1: Lispro 2D, Period 2: Lispro 6D and Period 3: Insulin Aspart 6D.

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Investigational medicinal product name	Insulin Lispro 6 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin lispro 6 Day (L6D) administered by infusion pump for 8 week treatment period.

Investigational medicinal product name	Insulin Aspart 6 Day
Investigational medicinal product code	
Other name	Novorapid
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin aspart 6 Day (A6D) administered by infusion pump for 8 week treatment period.

Arm title	Sequence B

Arm description:

Participants received Insulin Lispro 2D, Insulin Lispro 6D and Insulin Aspart 6D as per below dosing schedule Period 1: Insulin Lispro 2D, Period 2: Insulin Aspart 6D and Period 3: Insulin Lispro 6D.

Arm type	Experimental

Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Investigational medicinal product name	Insulin Lispro 6 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin lispro 6 Day (L6D) administered by infusion pump for 8 week treatment period.

Investigational medicinal product name	Insulin Aspart 6 Day
Investigational medicinal product code	
Other name	Novorapid
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin aspart 6 Day (A6D) administered by infusion pump for 8 week treatment period.

Arm title	Sequence C

Arm description:

Participants received Insulin Lispro 2D, Insulin Lispro 6D and Insulin Aspart 6D as per below dosing schedule Period 1: Insulin Lispro 6D, Period 2: Insulin Lispro 2D and Period 3: Insulin Aspart 6D.

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Investigational medicinal product name	Insulin Lispro 6 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin lispro 6 Day (L6D) administered by infusion pump for 8 week treatment period.

Investigational medicinal product name	Insulin Aspart 6 Day
Investigational medicinal product code	
Other name	Novorapid
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin aspart 6 Day (A6D) administered by infusion pump for 8 week treatment period.

Arm title	Sequence D

Arm description:

Participants received Insulin Lispro 2D, Insulin Lispro 6D and Insulin Aspart 6D as per below dosing schedule Period 1: Insulin Lispro 6D, Period 2: Insulin Aspart 6D and Period 3: Insulin Lispro 2D.

Arm type	Experimental

Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Investigational medicinal product name	Insulin Lispro 6 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin lispro 6 Day (L6D) administered by infusion pump for 8 week treatment period.

Investigational medicinal product name	Insulin Aspart 6 Day
Investigational medicinal product code	
Other name	Novorapid
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin aspart 6 Day (A6D) administered by infusion pump for 8 week treatment period.

Arm title	Sequence E

Arm description:

Participants received Insulin Lispro 2D, Insulin Lispro 6D and Insulin Aspart 6D as per below dosing schedule Period 1: Insulin Aspart 6D, Period 2: Insulin Lispro 2D and Period 3: Insulin Lispro 6D.

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Investigational medicinal product name	Insulin Lispro 6 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin lispro 6 Day (L6D) administered by infusion pump for 8 week treatment period.

Investigational medicinal product name	Insulin Aspart 6 Day
Investigational medicinal product code	
Other name	Novorapid
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin aspart 6 Day (A6D) administered by infusion pump for 8 week treatment period.

Arm title	Sequence F

Arm description:

Participants received Insulin Lispro 2D, Insulin Lispro 6D and Insulin Aspart 6D as per below dosing schedule Period 1: Insulin Aspart 6D, Period 2: Insulin Lispro 6D and Period 3: Insulin Lispro 2D.

Arm type	Experimental

Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Investigational medicinal product name	Insulin Lispro 6 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin lispro 6 Day (L6D) administered by infusion pump for 8 week treatment period.

Investigational medicinal product name	Insulin Aspart 6 Day
Investigational medicinal product code	
Other name	Novorapid
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin aspart 6 Day (A6D) administered by infusion pump for 8 week treatment period.

Number of subjects in period 1	Sequence A	Sequence B	Sequence C
Started	22	22	22
Received at Least One Dose of Study Drug	22	22	22
Completed	22	22	19
Not completed	0	0	3
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	-	1
Sponsor Decision	-	-	-
Lost to follow-up	-	-	1

Number of subjects in period 1	Sequence D	Sequence E	Sequence F
Started	22	22	22
Received at Least One Dose of Study Drug	22	22	22
Completed	21	20	20
Not completed	1	2	2
Consent withdrawn by subject	-	2	-
Adverse event, non-fatal	-	-	-
Sponsor Decision	-	-	2
Lost to follow-up	1	-	-

Period 2

Period 2 title	Study Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence A

Arm description:

Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 2D, Period 2: Humalog 6D and Period 3: Aspart 6D.

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Arm title	Sequence B

Arm description:

Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 2D, Period 2: Aspart 6D and Period 3: Humalog 6D.

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Arm title	Sequence C

Arm description:

Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 6D, Period 2: Humalog 2D and Period 3: Aspart 6D.

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Arm title	Sequence D

Arm description:

Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 6D, Period 2: Aspart 6D and Period 3: Humalog 2D.

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Arm title	Sequence E

Arm description:

Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Aspart 6D, Period 2: Humalog 2D and Period 3: Humalog 6D.

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Arm title	Sequence F

Arm description:

Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Aspart 6D, Period 2: Humalog 6D and Period 3: Humalog 2D.

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Number of subjects in period 2	Sequence A	Sequence B	Sequence C
Started	22	22	19
Completed	21	21	18
Not completed	1	1	1
Entry Criteria not met	-	1	-
Consent withdrawn by subject	-	-	1
Physician decision	-	-	-
Protocol deviation	1	-	-

Number of subjects in period 2	Sequence D	Sequence E	Sequence F
Started	21	20	20
Completed	20	20	19
Not completed	1	0	1

Entry Criteria not met	-	-	-
Consent withdrawn by subject	-	-	1
Physician decision	1	-	-
Protocol deviation	-	-	-

Period 3

Period 3 title	Study Period 3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence A

Arm description:

Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 2D, Period 2: Humalog 6D and Period 3: Aspart 6D.

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Arm title	Sequence B

Arm description:

Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 2D, Period 2: Aspart 6D and Period 3: Humalog 6D.

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Arm title	Sequence C

Arm description:

Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 6D, Period 2: Humalog 2D and Period 3: Aspart 6D.

Arm type	Experimental

Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Arm title	Sequence D

Arm description:

Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 6D, Period 2: Aspart 6D and Period 3: Humalog 2D.

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Arm title	Sequence E

Arm description:

Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Aspart 6D, Period 2: Humalog 2D and Period 3: Humalog 6D.

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Arm title	Sequence F

Arm description:

Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Aspart 6D, Period 2: Humalog 6D and Period 3: Humalog 2D.

Arm type	Experimental
Investigational medicinal product name	Insulin Lispro 2 Day
Investigational medicinal product code	
Other name	Humalog, LY275585
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.

Number of subjects in period 3	Sequence A	Sequence B	Sequence C
Started	21	21	18
Completed	20	21	18
Not completed	1	0	0
Consent withdrawn by subject	1	-	-
Lost to follow-up	-	-	-

Number of subjects in period 3	Sequence D	Sequence E	Sequence F
Started	20	20	19
Completed	20	18	19
Not completed	0	2	0
Consent withdrawn by subject	-	1	-
Lost to follow-up	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Study Period 1

Reporting group description: -

Reporting group values	Study Period 1	Total	
Number of subjects	132	132	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age Continuous Units: years			
arithmetic mean	41.4		
standard deviation	± 16.7	-	
Gender, Male/Female Units:			
Female	96	96	
Male	36	36	
Region of Enrollment Units: Subjects			
United States	132	132	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	12	12	
Not Hispanic or Latino	120	120	
Unknown or Not Reported	0	0	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
More than one race	2	2	
Unknown or Not Reported	0	0	
White	129	129	

End points

End points reporting groups

Reporting group title	Sequence A
Reporting group description:	
Participants received Insulin Lispro 2D (2 Days), Insulin Lispro 6D and Insulin Aspart 6D as per below dosing schedule Period 1: Lispro 2D, Period 2: Lispro 6D and Period 3: Insulin Aspart 6D.	
Reporting group title	Sequence B
Reporting group description:	
Participants received Insulin Lispro 2D, Insulin Lispro 6D and Insulin Aspart 6D as per below dosing schedule Period 1: Insulin Lispro 2D, Period 2: Insulin Aspart 6D and Period 3: Insulin Lispro 6D.	
Reporting group title	Sequence C
Reporting group description:	
Participants received Insulin Lispro 2D, Insulin Lispro 6D and Insulin Aspart 6D as per below dosing schedule Period 1: Insulin Lispro 6D, Period 2: Insulin Lispro 2D and Period 3: Insulin Aspart 6D.	
Reporting group title	Sequence D
Reporting group description:	
Participants received Insulin Lispro 2D, Insulin Lispro 6D and Insulin Aspart 6D as per below dosing schedule Period 1: Insulin Lispro 6D, Period 2: Insulin Aspart 6D and Period 3: Insulin Lispro 2D.	
Reporting group title	Sequence E
Reporting group description:	
Participants received Insulin Lispro 2D, Insulin Lispro 6D and Insulin Aspart 6D as per below dosing schedule Period 1: Insulin Aspart 6D, Period 2: Insulin Lispro 2D and Period 3: Insulin Lispro 6D.	
Reporting group title	Sequence F
Reporting group description:	
Participants received Insulin Lispro 2D, Insulin Lispro 6D and Insulin Aspart 6D as per below dosing schedule Period 1: Insulin Aspart 6D, Period 2: Insulin Lispro 6D and Period 3: Insulin Lispro 2D.	
Reporting group title	Sequence A
Reporting group description:	
Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 2D, Period 2: Humalog 6D and Period 3: Aspart 6D.	
Reporting group title	Sequence B
Reporting group description:	
Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 2D, Period 2: Aspart 6D and Period 3: Humalog 6D.	
Reporting group title	Sequence C
Reporting group description:	
Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 6D, Period 2: Humalog 2D and Period 3: Aspart 6D.	
Reporting group title	Sequence D
Reporting group description:	
Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 6D, Period 2: Aspart 6D and Period 3: Humalog 2D.	
Reporting group title	Sequence E
Reporting group description:	
Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Aspart 6D, Period 2: Humalog 2D and Period 3: Humalog 6D.	
Reporting group title	Sequence F
Reporting group description:	
Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Aspart 6D, Period 2: Humalog 6D and Period 3: Humalog 2D.	
Reporting group title	Sequence A
Reporting group description:	
Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 2D, Period 2: Humalog 6D and Period 3: Aspart 6D.	

Reporting group title	Sequence B
Reporting group description:	
Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 2D, Period 2: Aspart 6D and Period 3: Humalog 6D.	
Reporting group title	Sequence C
Reporting group description:	
Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 6D, Period 2: Humalog 2D and Period 3: Aspart 6D.	
Reporting group title	Sequence D
Reporting group description:	
Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Humalog 6D, Period 2: Aspart 6D and Period 3: Humalog 2D.	
Reporting group title	Sequence E
Reporting group description:	
Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Aspart 6D, Period 2: Humalog 2D and Period 3: Humalog 6D.	
Reporting group title	Sequence F
Reporting group description:	
Participants received Humalog 2D, Humalog 6D and Aspart 6D as per below dosing schedule Period 1: Aspart 6D, Period 2: Humalog 6D and Period 3: Humalog 2D.	
Subject analysis set title	Insulin Lispro 2 Day
Subject analysis set type	Full analysis
Subject analysis set description:	
Insulin Lispro 2 Day (L2D) administered by infusion pump for 8 week treatment period.	
Subject analysis set title	Insulin Lispro 6 Day
Subject analysis set type	Full analysis
Subject analysis set description:	
Insulin Lispro 6 Day (L6D) administered by infusion pump for 8 weeks.	
Subject analysis set title	Insulin Aspart 6 Day
Subject analysis set type	Full analysis
Subject analysis set description:	
Insulin Aspart 6 Day (A6D) administered by infusion pump for 8 weeks.	

Primary: Mean of last five 7-point Self Monitored Blood Glucose (SMBG) taken on day 6 for Insulin Lispro 6D and day 2 for Insulin Lispro 2D and day 6 for Insulin Aspart 6D pump reservoir in-use

End point title	Mean of last five 7-point Self Monitored Blood Glucose (SMBG) taken on day 6 for Insulin Lispro 6D and day 2 for Insulin Lispro 2D and day 6 for Insulin Aspart 6D pump reservoir in-use
End point description:	
Analysis Population Description: All randomized participants who completed at least one post-randomization visit. Those included in the Primary analysis had to have at least one reservoir in-use cycle with an SMBG measurement on Day 6 during the pre-specified collection period.	
End point type	Primary
End point timeframe:	
8 weeks of each treatment	

End point values	Insulin Lispro 2 Day	Insulin Lispro 6 Day	Insulin Aspart 6 Day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	119	116	117	
Units: millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	9.03 (± 2.17)	9.33 (± 2.31)	8.72 (± 1.82)	

Statistical analyses

Statistical analysis title	SMBG
Statistical analysis description:	
This was the primary gated analysis.	
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Least Squares Mean Difference
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.76

Notes:

[1] - Non-inferiority margin of 0.6 mmol/L was used.

Secondary: Mean SMBG

End point title	Mean SMBG
End point description:	
Mean SMBG for combined periods; all reported SMBG values on days 1-6 for Insulin Lispro 6 Day and Insulin Aspart 6 Day, and days 1-2 for Insulin Lispro 2 Day. Analysis Population Description (APD): All randomized participants who completed at least one post-randomization visit and one SMBG measurement on Day 2 for insulin lispro 2 day or Day 6 for the respective treatment arm: insulin lispro 6 day and insulin aspart 6 day.	
End point type	Secondary
End point timeframe:	
8 weeks for each treatment	

End point values	Insulin Lispro 2 Day	Insulin Lispro 6 Day	Insulin Aspart 6 Day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	122	122	122	
Units: mmol/L				
arithmetic mean (standard deviation)	8.79 (± 2.73)	9.01 (± 2.87)	8.83 (± 2.71)	

Statistical analyses

Statistical analysis title	SMBG
Comparison groups	Insulin Aspart 6 Day v Insulin Lispro 6 Day
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Least Squares Mean Difference
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.52

Notes:

[2] - Non-inferiority margin of 0.6 mmol/L was used.

Statistical analysis title	SMBG
Comparison groups	Insulin Lispro 6 Day v Insulin Lispro 2 Day
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Least Squares Mean Difference
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.56

Notes:

[3] - Non-inferiority margin of 0.6 mmol/L was used.

Secondary: Mean daily insulin dose (total, basal, and bolus)

End point title	Mean daily insulin dose (total, basal, and bolus)

End point description:

APD: All randomized participants who completed at least one post-randomization visit. Participants included in insulin analyses are only those for whom data existed regarding insulin dose.

End point type	Secondary

End point timeframe:

8 weeks for each treatment

End point values	Insulin Lispro 2 Day	Insulin Lispro 6 Day	Insulin Aspart 6 Day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	117	117	117	
Units: Units (U) of insulin				
arithmetic mean (standard deviation)	14.33 (± 5.88)	14.51 (± 6.33)	14.44 (± 6.11)	

Statistical analyses

Statistical analysis title	Mean Daily Insulin Dose (Daily Bolus Insulin)
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.51

Statistical analysis title	Mean Daily Insulin Dose (Daily Bolus Insulin)
Comparison groups	Insulin Lispro 2 Day v Insulin Lispro 6 Day
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.73

Statistical analysis title	Mean Daily Insulin Dose (Daily Basal Insulin)
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.24

Statistical analysis title	Mean Daily Insulin Dose (Daily Basal Insulin)
Comparison groups	Insulin Lispro 2 Day v Insulin Lispro 6 Day
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	0.27

Statistical analysis title	Mean Daily Insulin Dose (Daily Total Insulin)
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	0.6

Statistical analysis title	Mean Daily Insulin Dose (Daily Total Insulin)
Comparison groups	Insulin Lispro 2 Day v Insulin Lispro 6 Day
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	0.65

Secondary: Change from baseline to 8 weeks endpoint for each treatment in

Hemoglobin A1c (HbA1c) values	
End point title	Change from baseline to 8 weeks endpoint for each treatment in Hemoglobin A1c (HbA1c) values

End point description:

APD: All randomized participants who completed at least one post-randomization visit, and had a baseline and a post-randomization HbA1c measurement for the respective treatment period. Last Observation Carried Forward (LOCF) method was utilized in this analysis.

End point type	Secondary

End point timeframe:

Baseline, 8 weeks for each treatment

End point values	Insulin Lispro 2 Day	Insulin Lispro 6 Day	Insulin Aspart 6 Day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	121	120	121	
Units: percentage of glycosylated hemoglobin				
arithmetic mean (standard deviation)	-0.04 (± 0.59)	0.06 (± 0.56)	0.00 (± 0.53)	

Statistical analyses

Statistical analysis title	Hemoglobin A1c (HbA1c) Values
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.14

Statistical analysis title	Hemoglobin A1c (HbA1c) Values
Comparison groups	Insulin Lispro 2 Day v Insulin Lispro 6 Day
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Least Squares Mean Difference
Point estimate	0.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.18

Secondary: Number of Participants who achieve or maintain an HbA1c less than or equal to 6.5% and less than 7%

End point title	Number of Participants who achieve or maintain an HbA1c less than or equal to 6.5% and less than 7%

End point description:

APD: All randomized participants who completed a post-randomization visit and had an HbA1c measurement for the respective treatment period.

End point type	Secondary

End point timeframe:

8 weeks for each treatment

End point values	Insulin Lispro 2 Day	Insulin Lispro 6 Day	Insulin Aspart 6 Day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	121	120	121	
Units: participants				
number (not applicable)				
HbA1c ≤6.5%	21	16	18	
HbA1c <7%	40	38	44	

Statistical analyses

Statistical analysis title	HbA1c ≤6.5%
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.75

Statistical analysis title	HbA1c ≤6.5%

Comparison groups	Insulin Lispro 2 Day v Insulin Lispro 6 Day
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.67

Statistical analysis title	HbA1c <7%
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.41

Statistical analysis title	HbA1c <7%
Comparison groups	Insulin Lispro 2 Day v Insulin Lispro 6 Day
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.64

Secondary: Percentage of Participants with Hyperglycemia	
End point title	Percentage of Participants with Hyperglycemia

End point description:

Hyperglycemia was defined as an event with (1) a measured blood glucose concentration >250 milligrams per deciliter (mg/dL) (13.9 mmol/L) and ≥3 hours after eating, or (2) a measured blood glucose concentration >300 mg/dL (16.7 mmol/L) and <3 hours after eating.

APD: All randomized participants who received at least one dose of study drug. Participants included in hyperglycemia analyses are only those for whom data existed regarding hyperglycemia.

End point type	Secondary

End point timeframe:

8 weeks for each treatment

End point values	Insulin Lispro 2 Day	Insulin Lispro 6 Day	Insulin Aspart 6 Day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	122	127	124	
Units: percentage of participants				
number (not applicable)	99.2	98.4	98.4	

Statistical analyses

Statistical analysis title	Percentage of Participants With Hyperglycemia
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [4]
Method	Gart's Test
Confidence interval	
level	95 %

Notes:

[4] - P-value computed using Treatment comparison Gart's Test. Participants represented in both treatment groups and with non-missing incidence value in each treatment period are used for p-value calculation.

Secondary: Hyperglycemic Episode Rate per 30 Days

End point title	Hyperglycemic Episode Rate per 30 Days

End point description:

Hyperglycemia was defined as an episode with (1) a measured blood glucose concentration >250 milligrams per deciliter (mg/dL) (13.9 mmol/L) and ≥3 hours after eating, or (2) a measured blood glucose concentration >300 mg/dL (16.7 mmol/L) and <3 hours after eating. Rate is presented as the number of hyperglycemic episodes adjusted for 30 days.
APD: All randomized participants who received at least one dose of study drug. Participants included in hyperglycemia analyses are only those for whom data existed regarding hyperglycemia.

End point type	Secondary

End point timeframe:

8 weeks for each treatment

End point values	Insulin Lispro 2 Day	Insulin Lispro 6 Day	Insulin Aspart 6 Day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	122	127	124	
Units: hyperglycemic episodes per 30 days				
arithmetic mean (standard deviation)	15.91 (± 12.78)	16.91 (± 13.98)	15.76 (± 12.04)	

Statistical analyses

Statistical analysis title	Hyperglycemic Episode Rate Per 30 Days
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.164 [5]
Method	Negative Binomial Test
Confidence interval	
level	95 %

Notes:

[5] - P-value computed using a negative binomial test including factors for treatment, period, and sequence.

Statistical analysis title	Hyperglycemic Episode Rate Per 30 Days
Comparison groups	Insulin Lispro 6 Day v Insulin Lispro 2 Day
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.185 [6]
Method	Negative Binomial Test
Confidence interval	
level	95 %

Notes:

[6] - P-value computed using a negative binomial test including factors for treatment, period, and sequence.

Secondary: Percentage of Participants with Pump Complications

End point title	Percentage of Participants with Pump Complications

End point description:

Overall Pump Complications were any combination of: tubing clogged, kinked, disconnected, pulled out, blood in tubing; too much heat, too much cold, empty reservoir, low battery, occlusion alarm, no delivery alarm; at site - skin abscess, excessive redness, swelling (not nodule), bleeding, bruising; reservoir change (infusion set change reason only); and other. When either a reservoir change or an infusion set change was reported, participants were questioned whether change was early (prior to 6 days for L6D or A6D, or prior to 2 days for L2D). If 'yes', then recorded as premature change.
APD: All randomized participants who completed at least one post-randomization visit. Participants included in pump complication analyses are only those for whom data existed regarding pump complications.

End point type	Secondary

End point timeframe:

8 weeks for each treatment

End point values	Insulin Lispro 2 Day	Insulin Lispro 6 Day	Insulin Aspart 6 Day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	122	127	124	
Units: percentage of participants				
number (not applicable)	23.8	38.6	36.3	

Statistical analyses

Statistical analysis title	Pump Complication: Premature Reservoir Change
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.736 [7]
Method	Gart's Test
Confidence interval	
level	95 %

Notes:

[7] - P-value for Premature Reservoir Change. P-value computed using Treatment comparison Gart's Test. Participants represented in both treatment groups and with non-missing incidence value in each treatment period are used for p-value calculation.

Statistical analysis title	Pump Complication: Premature Reservoir Change
Comparison groups	Insulin Lispro 6 Day v Insulin Lispro 2 Day
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [8]
Method	Gart's Test
Confidence interval	
level	95 %

Notes:

[8] - P-value for Premature Reservoir Change. P-value computed using Treatment comparison Gart's Test. Participants represented in both treatment groups and with non-missing incidence value in each treatment period are used for p-value calculation.

Statistical analysis title	Pump Complication: Premature Infusion Set Change
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [9]
Method	Gart's Test

Confidence interval	
level	95 %

Notes:

[9] - P-value for Premature Infusion Set Change. P-value computed using Treatment comparison Gart's Test. Participants represented in both treatment groups and with non-missing incidence value in each treatment period are used for p-value calculation.

Statistical analysis title	Pump Complication: Premature Infusion Set Change
Comparison groups	Insulin Lispro 2 Day v Insulin Lispro 6 Day
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017 [10]
Method	Gart's Test
Confidence interval	
level	95 %

Notes:

[10] - P-value for Premature Infusion Set Change. P-value computed using Treatment comparison Gart's Test. Participants represented in both treatment groups and with non-missing incidence value in each treatment period are used for p-value calculation.

Secondary: Pump Complication Rate per 30 Days

End point title	Pump Complication Rate per 30 Days

End point description:

Overall Pump Complications were any combination of: tubing clogged, kinked, disconnected, pulled out, blood in tubing; too much heat, too much cold, empty reservoir, low battery, occlusion alarm, no delivery alarm; at site - skin abscess, excessive redness, swelling (not nodule), bleeding, bruising; reservoir change (infusion set change reason only); and other. When either a reservoir change or an infusion set change was reported, participants were questioned whether change was early (prior to 6 days for L6D or A6D, or prior to 2 days for L2D). If 'yes', then recorded as premature change.
APD: All randomized participants who completed at least one post-randomization visit. Participants included in pump complication analyses are only those for whom data existed regarding pump complications.

End point type	Secondary

End point timeframe:

8 weeks for each treatment

End point values	Insulin Lispro 2 Day	Insulin Lispro 6 Day	Insulin Aspart 6 Day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	122	127	124	
Units: pump complications per 30 days				
arithmetic mean (standard deviation)				
Pump Complication: Premature Reservoir Change	0.16 (± 0.34)	0.40 (± 0.76)	0.51 (± 1.05)	
Pump Complication: Premature Infusion Set Change	0.44 (± 0.65)	0.84 (± 1.18)	0.94 (± 1.35)	

Statistical analyses

Statistical analysis title	Pump Complication: Premature Reservoir Change
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.471 [11]
Method	Negative Binomial Test
Confidence interval	
level	95 %

Notes:

[11] - P-value for Premature Reservoir Change. P-value is computed using negative binomial test including factors for treatment, period and sequence.

Statistical analysis title	Pump Complication: Premature Infusion Set Change
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [12]
Method	Negative Binomial Test
Confidence interval	
level	95 %

Notes:

[12] - P-value for Premature Infusion Set Change. P-value is computed using negative binomial test including factors for treatment, period and sequence.

Statistical analysis title	Pump Complication: Premature Infusion Set Change
Comparison groups	Insulin Lispro 2 Day v Insulin Lispro 6 Day
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [13]
Method	Negative Binomial Test
Confidence interval	
level	95 %

Notes:

[13] - P-value for Premature Reservoir Change. P-value is computed using negative binomial test including factors for treatment, period and sequence.

Statistical analysis title	Pump Complication: Premature Reservoir Change
Comparison groups	Insulin Lispro 2 Day v Insulin Lispro 6 Day
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.737 [14]
Method	Negative Binomial Test
Confidence interval	
level	95 %

Notes:

[14] - P-value for Premature Infusion Set Change. P-value is computed using negative binomial test including factors for treatment, period and sequence.

Secondary: Percentage of Participants With Hypoglycemia

End point title	Percentage of Participants With Hypoglycemia

End point description:

Hypoglycemia was defined as an event which was associated with
(1) reported signs and symptoms of hypoglycemia, and/or
(2) a documented blood glucose (BG) concentration of ≤ 70 mg/dL (3.9 mmol/L).
APD: All randomized participants who received at least one dose of study drug. Participants included in hypoglycemia analyses are only those for whom data existed regarding hypoglycemia.

End point type	Secondary

End point timeframe:

8 weeks for each treatment

End point values	Insulin Lispro 2 Day	Insulin Lispro 6 Day	Insulin Aspart 6 Day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	122	127	124	
Units: percentage of participants				
number (not applicable)	100.0	100.0	99.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Hypoglycemia Episode Rate per 30 Days

End point title	Hypoglycemia Episode Rate per 30 Days

End point description:

Hypoglycemia was defined as an event which was associated with
(1) reported signs and symptoms of hypoglycemia, and/or
(2) a documented blood glucose (BG) concentration of ≤ 70 mg/dL (3.9 mmol/L).
Rate is presented as the number of hypoglycemic episodes adjusted for 30 days.
APD: All randomized participants who received at least one dose of study drug. Participants included in hypoglycemia analyses are only those for whom data existed regarding hypoglycemia.

End point type	Secondary

End point timeframe:

8 weeks for each treatment

End point values	Insulin Lispro 2 Day	Insulin Lispro 6 Day	Insulin Aspart 6 Day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	122	127	124	
Units: hypoglycemic episodes per 30 days				
arithmetic mean (standard deviation)	17.90 (± 11.13)	15.66 (± 12.29)	17.52 (± 11.76)	

Statistical analyses

Statistical analysis title	Hypoglycemia Episode Rate Per 30 Days
Comparison groups	Insulin Lispro 2 Day v Insulin Lispro 6 Day
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [15]
Method	Negative Binomial Test
Confidence interval	
level	95 %

Notes:

[15] - P-value is computed using negative binomial test including factors for treatment, period and sequence.

Statistical analysis title	Hypoglycemia Episode Rate Per 30 Days
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [16]
Method	Negative Binomial Test
Confidence interval	
level	95 %

Notes:

[16] - P-value is computed using negative binomial test including factors for treatment, period and sequence.

Secondary: Change from baseline to 8 weeks endpoint for each treatment in weight

End point title	Change from baseline to 8 weeks endpoint for each treatment in weight

End point description:

APD: All randomized participants who received at least one dose of study drug and had both baseline and post-baseline weight measurements for the respective treatment period.

End point type	Secondary

End point timeframe:

Baseline, 8 weeks for each treatment

End point values	Insulin Lispro 2 Day	Insulin Lispro 6 Day	Insulin Aspart 6 Day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	121	122	122	
Units: kilograms (kg)				
arithmetic mean (standard deviation)	0.44 (± 2.13)	0.34 (± 2.04)	0.65 (± 2.13)	

Statistical analyses

Statistical analysis title	Change from Baseline in Weight
Comparison groups	Insulin Lispro 2 Day v Insulin Lispro 6 Day
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06 [17]
Method	Crossover Model
Confidence interval	
level	95 %

Notes:

[17] - P-value computed using crossover model. Response = Treatment + Sequence + Period + Age stratum + Baseline Body Weight.

Statistical analysis title	Change from Baseline in Weight
Comparison groups	Insulin Aspart 6 Day v Insulin Lispro 6 Day
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.486 [18]
Method	Crossover Model
Confidence interval	
level	95 %

Notes:

[18] - P-value computed using crossover model. Response = Treatment + Sequence + Period + Age stratum + Baseline Body Weight.

Secondary: Change from baseline to 8 weeks endpoint for each treatment in blood pressure

End point title	Change from baseline to 8 weeks endpoint for each treatment in blood pressure

End point description:

APD: All randomized participants who received at least one dose of study drug and had both baseline and post-baseline blood pressure measurements for the respective treatment period.

End point type	Secondary

End point timeframe:

Baseline, 8 weeks for each treatment

End point values	Insulin Lispro 2 Day	Insulin Lispro 6 Day	Insulin Aspart 6 Day	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	121	122	123	
Units: mmHg				
arithmetic mean (standard deviation)				
Systolic Blood Pressure (SBP)	0.80 (± 12.82)	0.80 (± 12.52)	-1.07 (± 12.06)	
Diastolic Blood Pressure (DBP)	-0.14 (± 8.24)	1.37 (± 7.62)	-0.33 (± 7.88)	

Statistical analyses

Statistical analysis title	Systolic Blood Pressure
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.056 [19]
Method	Crossover Model
Confidence interval	
level	95 %

Notes:

[19] - P-value is for Systolic Blood Pressure. P-value computed using crossover model. Response = Treatment + Sequence + Period + Age stratum + Baseline Systolic Blood Pressure.

Statistical analysis title	Systolic Blood Pressure
Comparison groups	Insulin Lispro 2 Day v Insulin Lispro 6 Day
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.805 [20]
Method	Crossover Model
Confidence interval	
level	95 %

Notes:

[20] - P-value is for Systolic Blood Pressure. P-value computed using crossover model. Response = Treatment + Sequence + Period + Age stratum + Baseline Systolic Blood Pressure.

Statistical analysis title	Diastolic Blood Pressure
Comparison groups	Insulin Lispro 6 Day v Insulin Aspart 6 Day
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [21]
Method	Crossover Model
Confidence interval	
level	95 %

Notes:

[21] - P-value is for Diastolic Blood Pressure. P-value computed using crossover model. Response = Treatment + Sequence + Period + Age stratum + Baseline Diastolic Blood Pressure.

Statistical analysis title	Diastolic Blood Pressure
Comparison groups	Insulin Lispro 2 Day v Insulin Lispro 6 Day
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.051 [22]
Method	Crossover Model
Confidence interval	
level	95 %

Notes:

[22] - P-value is for Diastolic Blood Pressure. P-value computed using crossover model. Response = Treatment + Sequence + Period + Age stratum + Baseline Diastolic Blood Pressure.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Entire Study	
Adverse event reporting additional description:	
F3Z-MC-IOPV	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups	
Reporting group title	Humalog 2D
Reporting group description: -	
Reporting group title	Aspart 6D
Reporting group description: -	
Reporting group title	Humalog 6D
Reporting group description: -	

Serious adverse events	Humalog 2D	Aspart 6D	Humalog 6D
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 122 (2.46%)	10 / 124 (8.06%)	8 / 127 (6.30%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
sternal fracture			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	0 / 122 (0.00%)	0 / 124 (0.00%)	1 / 127 (0.79%)
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			
cervical myelopathy			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	1 / 122 (0.82%)	0 / 124 (0.00%)	0 / 127 (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
hydrocephalus			
alternative dictionary used: MedDRA 14.0			

subjects affected / exposed	0 / 122 (0.00%)	0 / 124 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
oesophagitis			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	0 / 122 (0.00%)	0 / 124 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
ovarian cyst			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed[1]	0 / 122 (0.00%)	1 / 90 (1.11%)	0 / 127 (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 14.0			
subjects affected / exposed	0 / 122 (0.00%)	0 / 124 (0.00%)	3 / 127 (2.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypoglycaemia			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	2 / 122 (1.64%)	9 / 124 (7.26%)	4 / 127 (3.15%)
occurrences causally related to treatment / all	2 / 2	7 / 11	2 / 5
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: This event is gender specific, only occurring in male or female participants. The number of participants exposed has been adjusted accordingly.

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Humalog 2D	Aspart 6D	Humalog 6D
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 122 (58.20%)	71 / 124 (57.26%)	68 / 127 (53.54%)

Investigations			
smear cervix abnormal			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed[2]	0 / 122 (0.00%)	0 / 124 (0.00%)	1 / 93 (1.08%)
occurrences (all)	0	0	1
urine ketone body present			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	0 / 122 (0.00%)	2 / 124 (1.61%)	1 / 127 (0.79%)
occurrences (all)	0	3	1
Injury, poisoning and procedural complications			
contusion			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	2 / 122 (1.64%)	1 / 124 (0.81%)	1 / 127 (0.79%)
occurrences (all)	2	1	1
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	1 / 122 (0.82%)	3 / 124 (2.42%)	1 / 127 (0.79%)
occurrences (all)	1	3	1
headache			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	6 / 122 (4.92%)	3 / 124 (2.42%)	3 / 127 (2.36%)
occurrences (all)	7	3	3
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	0 / 122 (0.00%)	1 / 124 (0.81%)	2 / 127 (1.57%)
occurrences (all)	0	1	2
chills			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	2 / 122 (1.64%)	1 / 124 (0.81%)	0 / 127 (0.00%)
occurrences (all)	2	1	0
infusion site erythema			
alternative dictionary used: MedDRA 14.0			

subjects affected / exposed	1 / 122 (0.82%)	2 / 124 (1.61%)	1 / 127 (0.79%)
occurrences (all)	1	2	1
infusion site haemorrhage			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	1 / 122 (0.82%)	2 / 124 (1.61%)	1 / 127 (0.79%)
occurrences (all)	1	3	1
infusion site mass			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	1 / 122 (0.82%)	2 / 124 (1.61%)	1 / 127 (0.79%)
occurrences (all)	1	2	1
pyrexia			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	2 / 122 (1.64%)	2 / 124 (1.61%)	5 / 127 (3.94%)
occurrences (all)	2	2	5
Gastrointestinal disorders			
diarrhoea			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	1 / 122 (0.82%)	2 / 124 (1.61%)	0 / 127 (0.00%)
occurrences (all)	1	2	0
nausea			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	4 / 122 (3.28%)	4 / 124 (3.23%)	3 / 127 (2.36%)
occurrences (all)	4	4	3
toothache			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	0 / 122 (0.00%)	2 / 124 (1.61%)	0 / 127 (0.00%)
occurrences (all)	0	2	0
vomiting			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	5 / 122 (4.10%)	4 / 124 (3.23%)	2 / 127 (1.57%)
occurrences (all)	5	4	2
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 14.0			

subjects affected / exposed	5 / 122 (4.10%)	1 / 124 (0.81%)	3 / 127 (2.36%)
occurrences (all)	5	1	3
dyspnoea			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	3 / 122 (2.46%)	0 / 124 (0.00%)	0 / 127 (0.00%)
occurrences (all)	3	0	0
nasal congestion			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	1 / 122 (0.82%)	1 / 124 (0.81%)	3 / 127 (2.36%)
occurrences (all)	1	1	3
oropharyngeal pain			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	5 / 122 (4.10%)	5 / 124 (4.03%)	4 / 127 (3.15%)
occurrences (all)	5	5	4
paranasal sinus hypersecretion			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	2 / 122 (1.64%)	1 / 124 (0.81%)	0 / 127 (0.00%)
occurrences (all)	2	1	0
rhinitis seasonal			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	2 / 122 (1.64%)	2 / 124 (1.61%)	2 / 127 (1.57%)
occurrences (all)	2	2	2
sinus congestion			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	3 / 122 (2.46%)	3 / 124 (2.42%)	4 / 127 (3.15%)
occurrences (all)	3	3	4
throat irritation			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	2 / 122 (1.64%)	0 / 124 (0.00%)	0 / 127 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
subcutaneous nodule			
alternative dictionary used: MedDRA 14.0			

subjects affected / exposed	1 / 122 (0.82%)	2 / 124 (1.61%)	1 / 127 (0.79%)
occurrences (all)	1	2	1
Psychiatric disorders			
depression			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	2 / 122 (1.64%)	2 / 124 (1.61%)	2 / 127 (1.57%)
occurrences (all)	2	2	2
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	2 / 122 (1.64%)	3 / 124 (2.42%)	4 / 127 (3.15%)
occurrences (all)	2	3	4
back pain			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	2 / 122 (1.64%)	2 / 124 (1.61%)	2 / 127 (1.57%)
occurrences (all)	2	2	2
muscle spasms			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	3 / 122 (2.46%)	0 / 124 (0.00%)	0 / 127 (0.00%)
occurrences (all)	3	0	0
musculoskeletal pain			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	0 / 122 (0.00%)	0 / 124 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	0	3
myalgia			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	0 / 122 (0.00%)	0 / 124 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	0	2
neck pain			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	1 / 122 (0.82%)	1 / 124 (0.81%)	2 / 127 (1.57%)
occurrences (all)	1	1	2
rotator cuff syndrome			
alternative dictionary used: MedDRA 14.0			

subjects affected / exposed	1 / 122 (0.82%)	2 / 124 (1.61%)	2 / 127 (1.57%)
occurrences (all)	1	2	2
tendonitis			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	2 / 122 (1.64%)	1 / 124 (0.81%)	2 / 127 (1.57%)
occurrences (all)	2	1	2
Infections and infestations			
ear infection			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	1 / 122 (0.82%)	1 / 124 (0.81%)	3 / 127 (2.36%)
occurrences (all)	1	1	3
fungal infection			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	2 / 122 (1.64%)	0 / 124 (0.00%)	2 / 127 (1.57%)
occurrences (all)	3	0	2
gastroenteritis viral			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	5 / 122 (4.10%)	3 / 124 (2.42%)	2 / 127 (1.57%)
occurrences (all)	5	3	2
influenza			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	1 / 122 (0.82%)	2 / 124 (1.61%)	1 / 127 (0.79%)
occurrences (all)	1	2	1
nasopharyngitis			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	10 / 122 (8.20%)	13 / 124 (10.48%)	11 / 127 (8.66%)
occurrences (all)	11	14	12
pharyngitis			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	0 / 122 (0.00%)	0 / 124 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	0	2
pharyngitis streptococcal			
alternative dictionary used: MedDRA 14.0			

subjects affected / exposed	0 / 122 (0.00%)	0 / 124 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	0	2
sinusitis			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	4 / 122 (3.28%)	3 / 124 (2.42%)	1 / 127 (0.79%)
occurrences (all)	4	3	1
upper respiratory tract infection			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	10 / 122 (8.20%)	9 / 124 (7.26%)	6 / 127 (4.72%)
occurrences (all)	10	10	6
urinary tract infection			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	1 / 122 (0.82%)	3 / 124 (2.42%)	2 / 127 (1.57%)
occurrences (all)	1	4	2
viral infection			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	1 / 122 (0.82%)	1 / 124 (0.81%)	2 / 127 (1.57%)
occurrences (all)	1	1	2
vulvovaginal mycotic infection			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed[3]	0 / 122 (0.00%)	1 / 90 (1.11%)	0 / 127 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
hyperlipidaemia			
alternative dictionary used: MedDRA 14.0			
subjects affected / exposed	2 / 122 (1.64%)	1 / 124 (0.81%)	1 / 127 (0.79%)
occurrences (all)	2	1	1

Notes:

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

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Input to primary endpoint measurements (SMBG) contained approximately 40% missing data. Several analyses to account for missing data have been conducted and results from these additional analyses were consistent with results of original analysis.

Notes: