Clinical trial results:
A double-blinded, randomised, four -period crossover euglycemic clamp trial investigating the dose-response and dose-exposure relationship of Biochaperone insulin lispro in three different doses in subjects with type 1 Diabetes

Summary

EudraCT number	2014-000949-77
Trial protocol	DE
Global end of trial date	28 July 2014

Results information

Result version number	v1 (current)
This version publication date	09 September 2020
First version publication date	09 September 2020

Trial information

Trial identification

Sponsor protocol code	BC3-CT008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02146651
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Adocia
Sponsor organisation address	115 Avenue Lacassagne, LYON, France, 69003
Public contact	Deputy General Manager, Adocia, +33 472610610, o.soula@adocia.com
Scientific contact	Director of Clinical Development, Adocia, +33 472610610, g.meiffren@adocia.com

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	08 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 July 2014
Global end of trial reached?	Yes
Global end of trial date	28 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the dose-response and the dose-exposure relationships of BioChaperone insulin lispro.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use (ICH) Good Clinical Practices.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 May 2014
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	Germany: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	38
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The Clinical Trial was conducted at one site in Germany

Pre-assignment

Screening details:

Subjects with Type 1 Diabetes Mellitus
Aged from 18 to 64 years
With a total daily insulin requirements <1.2 (I)U/kg/day
BMI between 18.5 and 28.0 kg/m²

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

This was a double-blind trial. An authorised person (unblinded person) prepared and administered the trial drug according to the randomisation based assignment to one of the predefined treatment sequences. Except for the unblinded persons involved in the preparation and administration of the trial drug (these persons were not involved in any other clinical trial activities), everyone in the trial, including the PK laboratory, were blinded.

Arms

Arm title	BioChaperone insulin Lispro / Humalog®

Arm description:

Each subject was randomly allocated to a sequence of four treatments, i.e. with one of three single doses of BC lispro (0.1 0.2 or 0.4 U/kg body weight) or one single dose of Humalog®, containing 0.2 U/kg body weight on four separate dosing visits.
Subjects came in a fasted state to the clinical trial center in the morning of each dosing day and stayed at the clinical trial center until the 12-hour clamp procedures have been terminated. The four dosing visits were separated by a wash-out period of 3-15 days.

Arm type	Cross-over (experimental & active comparator)
Investigational medicinal product name	Biochaperone lispro 0.1 U/Kg
Investigational medicinal product code	
Other name	BC lispro 0.1U/kg
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous administration of BC lispro at a dose of 0.1 U/kg body weight during an euglycemic clamp procedure.

Investigational medicinal product name	Biochaperone lispro 0.2 U/kg
Investigational medicinal product code	
Other name	BC lispro 0.2U/kg
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous administration of BC lispro at a dose of 0.2 U/kg body weight during an euglycemic clamp procedure.

Investigational medicinal product name	Biochaperone lispro 0.4 U/kg
Investigational medicinal product code	
Other name	BC lispro 0.4U/kg
Pharmaceutical forms	Solution for injection

Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous administration of BC lispro at a dose of 0.4 U/kg body weight during an euglycemic clamp procedure.

Investigational medicinal product name	Humalog® 0.2U/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous administration of Humalog® at a dose of 0.2 U/kg body weight during an euglycemic clamp procedure.

Number of subjects in period 1	BioChaperone insulin Lispro / Humalog®
Started	38
Completed	37
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)
Reporting group description:	
Overall population as this is a cross-over trial	

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	38	38	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	38	38	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	38	38	

Subject analysis sets	
Subject analysis set title	Safety Analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety analysis set includes all subjects receiving at least one dose of the investigationnal product or its comparator	
Subject analysis set title	BC lispro 0.1U/kg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who received one dose of BC lispro 0.1U/kg body weight in a cross over manner.	
Subject analysis set title	BC Lispro 0.2U/kg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who received one dose of BC lispro 0.2U/kg body weight in a cross over manner.	
Subject analysis set title	BC lispro 0.4U/kg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who received one dose of BC lispro 0.4U/kg body weight in a cross over manner.	
Subject analysis set title	Humalog® 0.2U/kg
Subject analysis set type	Full analysis

Subject analysis set description:
Subjects who received one dose of Humalog® 0.2U/body weight in a cross over manner.

Reporting group values	Safety Analysis set	BC lispro 0.1U/kg	BC Lispro 0.2U/kg
Number of subjects	38	37	38
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)	38	37	38
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	0	0
Male	38	37	38

Reporting group values	BC lispro 0.4U/kg	Humalog® 0.2U/kg	
Number of subjects	38	37	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	38	37	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	38	37	

End points

End points reporting groups

Reporting group title	BioChaperone insulin Lispro / Humalog®

Reporting group description:

Each subject was randomly allocated to a sequence of four treatments, i.e. with one of three single doses of BC lispro (0.1 0.2 or 0.4 U/kg body weight) or one single dose of Humalog®, containing 0.2 U/kg body weight on four separate dosing visits.
Subjects came in a fasted state to the clinical trial center in the morning of each dosing day and stayed at the clinical trial center until the 12-hour clamp procedures have been terminated. The four dosing visits were separated by a wash-out period of 3-15 days.

Subject analysis set title	Safety Analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety analysis set includes all subjects receiving at least one dose of the investigationnal product or its comparator

Subject analysis set title	BC lispro 0.1U/kg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who received one dose of BC lispro 0.1U/kg body weight in a cross over manner.

Subject analysis set title	BC Lispro 0.2U/kg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who received one dose of BC lispro 0.2U/kg body weight in a cross over manner.

Subject analysis set title	BC lispro 0.4U/kg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who received one dose of BC lispro 0.4U/kg body weight in a cross over manner.

Subject analysis set title	Humalog® 0.2U/kg
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who received one dose of Humalog® 0.2U/body weight in a cross over manner.

Primary: AUCGIR(0-last)

End point title	AUCGIR(0-last)

End point description:

Area under the glucose infusion rate time curve from t=0 hours to the end of Clamp

End point type	Primary

End point timeframe:

Form t=0 up to 12hour after dosing

End point values	BC lispro 0.1U/kg	BC Lispro 0.2U/kg	BC lispro 0.4U/kg	Humalog® 0.2U/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	38	38	37
Units: mg/kg				
arithmetic mean (standard deviation)	733.83 (± 230.67)	1353.5 (± 442.96)	2424.2 (± 521.28)	1306.4 (± 374.12)

Statistical analyses

Statistical analysis title	BC lispro 0.1U/kg vs 0.2U/kg

Statistical analysis description:

ANOVA With Untransformed AUC-GIR 0-last (mg/kg) as Response, Treatment, Period and Sequence as Fixed Effect and Subject Within Sequence as Random Effect

Comparison groups	BC lispro 0.1U/kg v BC Lispro 0.2U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS Mean difference
Point estimate	-630.957
Confidence interval	
level	95 %
sides	2-sided
lower limit	-768.3273
upper limit	-493.5859

Notes:

[1] - Dose response difference

Statistical analysis title	BC lispro 0.1U/kg vs 0.4U/kg

Statistical analysis description:

ANOVA With Untransformed AUC-GIR 0-last (mg/kg) as Response, Treatment, Period and Sequence as Fixed Effect and Subject Within Sequence as Random Effect

Comparison groups	BC lispro 0.1U/kg v BC lispro 0.4U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS Mean difference
Point estimate	-1696.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1833.7132
upper limit	-1559.3256

Notes:

[2] - Dose response difference

Statistical analysis title	BC lispro 0.2U/kg vs 0.4U/kg

Statistical analysis description:

ANOVA With Untransformed AUC-GIR 0-last (mg/kg) as Response, Treatment, Period and Sequence as Fixed Effect and Subject Within Sequence as Random Effect

Comparison groups	BC Lispro 0.2U/kg v BC lispro 0.4U/kg
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS Mean difference
Point estimate	-1065.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1201.4413
upper limit	-929.6842

Notes:

[3] - Dose response difference

Statistical analysis title	BC lispro 0.2U/kg vs Humalog 0.2U/kg

Statistical analysis description:

ANOVA with untransformed AUC-GIR 0-last (mg/kg) as Response, Treatment, Period and Sequence as Fixed Effect and Subject within Sequence as Random Effect

Comparison groups	Humalog® 0.2U/kg v BC Lispro 0.2U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.4464
Method	ANOVA
Parameter estimate	LS Mean difference
Point estimate	53.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-88.1325
upper limit	195.6135

Notes:

[4] - Difference

Primary: GIRmax

End point title	GIRmax

End point description:

Maximum glucose infusion rate

End point type	Primary

End point timeframe:

From t=0 to t=12 hours

End point values	BC lispro 0.1U/kg	BC Lispro 0.2U/kg	BC lispro 0.4U/kg	Humalog® 0.2U/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	38	38	37
Units: mg/kg/min				
arithmetic mean (standard deviation)	4.806 (± 1.8491)	7.363 (± 2.7416)	10.164 (± 2.5151)	6.631 (± 2.2980)

Statistical analyses

Statistical analysis title	Bc lispro 0.1U/kg vs 0.2U/kg

Statistical analysis description:

ANOVA With Untransformed GIRmax (mg/kg/min) as Response, Treatment, Period and Sequence as Fixed Effect and Subject Within Sequence as Random Effect

Comparison groups	BC lispro 0.1U/kg v BC Lispro 0.2U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS Mean difference
Point estimate	-2.612
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3262
upper limit	-1.8984

Notes:

[5] - Dose response difference

Statistical analysis title	BC lispro 0.1U/kg vs 0.4U/kg

Statistical analysis description:

ANOVA With Untransformed GIRmax (mg/kg/min) as Response, Treatment, Period and Sequence as Fixed Effect and Subject Within Sequence as Random Effect

Comparison groups	BC lispro 0.1U/kg v BC lispro 0.4U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS Mean difference
Point estimate	-5.393
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1056
upper limit	-4.6797

Notes:

[6] - Dose response difference

Statistical analysis title	BC lispro 0.2U/kg vs 0.4U/kg

Statistical analysis description:

ANOVA With Untransformed GIRmax (mg/kg/min) as Response, Treatment, Period and Sequence as Fixed Effect and Subject Within Sequence as Random Effect

Comparison groups	BC Lispro 0.2U/kg v BC lispro 0.4U/kg
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS Mean difference
Point estimate	-2.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4863
upper limit	-2.0744

Notes:

[7] - Dose response difference

Statistical analysis title	BC lispro 0.2U/kg vs Humalog 0.2U/kg

Statistical analysis description:

ANOVA with untransformed GIRmax (mg/kg/min) as Response, Treatment, Period and Sequence as Fixed Effect and Subject within Sequence as Random Effect

Comparison groups	BC Lispro 0.2U/kg v Humalog® 0.2U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.0661
Method	ANOVA
Parameter estimate	LS Mean difference
Point estimate	0.806
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0567
upper limit	1.669

Notes:

[8] - Difference

Primary: AUCLisp(0-Last)

End point title	AUCLisp(0-Last)

End point description:

Area under the glucose infusion rate time curve from t=0 hours to the end of clamp

End point type	Primary

End point timeframe: From t=0 to t=12 hours

End point values	BC lispro 0.1U/kg	BC Lispro 0.2U/kg	BC lispro 0.4U/kg	Humalog® 0.2U/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	38	38	37
Units: h.mU/L				
arithmetic mean (standard deviation)	98.341 (± 30.016)	202.24 (± 64.794)	441.51 (± 100.34)	209.22 (± 64.10)

Statistical analyses

Statistical analysis title	0.1U vs 0.2U
Statistical analysis description: Treatment Difference was Analyzed Using Wilcoxon's Signed Rank Test	
Comparison groups	BC Lispro 0.2U/kg v BC lispro 0.1U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-96.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-110.022
upper limit	-81.1004

Notes:
[9] - Dose response difference

Statistical analysis title	0.1U vs 0.4U
Statistical analysis description: Treatment Difference was Analyzed Using Wilcoxon's Signed Rank Test	
Comparison groups	BC lispro 0.1U/kg v BC lispro 0.4U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-328.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-350.7408
upper limit	-307.2081

Notes:

[10] - Dose response difference

Statistical analysis title	0.2U vs 0.4U
Comparison groups	BC Lispro 0.2U/kg v BC lispro 0.4U/kg
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-233.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-256.723
upper limit	-207.4862

Notes:

[11] - Dose response difference

Statistical analysis title	BC lispro 0.2U vs Humalog 0.2U

Statistical analysis description:

Treatment Difference was Analyzed Using Wilcoxon's Signed Rank Test

Comparison groups	BC Lispro 0.2U/kg v Humalog® 0.2U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.4184
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-5.591
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.714
upper limit	10.6985

Notes:

[12] - Treatment difference

Primary: Cmax(Lisp)	
End point title	Cmax(Lisp)

End point description:

Maximum observed serum insulin lispro concentration

End point type	Primary

End point timeframe:

From t=0 up to t=12 hours

End point values	BC lispro 0.1U/kg	BC Lispro 0.2U/kg	BC lispro 0.4U/kg	Humalog® 0.2U/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	38	38	37
Units: mU/L				
arithmetic mean (standard deviation)	52.220 (± 15.662)	99.014 (± 34.872)	190.19 (± 52.490)	90.202 (± 28.196)

Statistical analyses

Statistical analysis title	Bc lispro 0.1U/kg vs 0.2U/kg

Statistical analysis description:

ANOVA With Log-transformed Cmax-Lisp (mU/L) as Response, Treatment, Period and Sequence as Fixed Effect and Subject Within Sequence as Random Effect

Comparison groups	BC lispro 0.1U/kg v BC Lispro 0.2U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS Mean Ratio
Point estimate	0.532
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4897
upper limit	0.5788

Notes:

[13] - Dose response difference

Statistical analysis title	BC lispro 0.1U/kg vs 0.4U/kg

Statistical analysis description:

ANOVA With Log-transformed Cmax-Lisp (mU/L) as Response, Treatment, Period and Sequence as Fixed Effect and Subject Within Sequence as Random Effect

Comparison groups	BC lispro 0.1U/kg v BC lispro 0.4U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Ratio
Point estimate	0.271

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2495
upper limit	0.2948

Notes:

[14] - Dose response difference

Statistical analysis title	BC lispro 0.2U/kg vs 0.4U/kg

Statistical analysis description:

ANOVA With Log-transformed Cmax-Lisp (mU/L) as Response, Treatment, Period and Sequence as Fixed Effect and Subject Within Sequence as Random Effect

Comparison groups	BC Lispro 0.2U/kg v BC lispro 0.4U/kg
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS Mean Ratio
Point estimate	0.509
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.469
upper limit	0.5532

Notes:

[15] - Dose response difference

Statistical analysis title	BC lispro 0.2U/kg vs Humalog 0.2U/kg

Statistical analysis description:

ANOVA with log transformed Cmax-Lisp (mU/L) as Response, Treatment, Period and Sequence as Fixed Effect and Subject within Sequence as Random Effect

Comparison groups	BC Lispro 0.2U/kg v Humalog® 0.2U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.0404
Method	ANOVA
Parameter estimate	LS Mean Ratio
Point estimate	1.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.0046
upper limit	1.2104

Notes:

[16] - Treatment difference

Secondary: Early t0.5(GIRmax)

End point title	Early t0.5(GIRmax)
End point description: Time to first observed half maximum glucose infusion rate	
End point type	Secondary
End point timeframe: From t=0 up to T=12hours	

End point values	BC lispro 0.1U/kg	BC Lispro 0.2U/kg	BC lispro 0.4U/kg	Humalog® 0.2U/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	38	38	37
Units: Hours				
arithmetic mean (standard deviation)	0.517 (± 0.1376)	0.559 (± 0.1695)	0.533 (± 0.0967)	0.754 (± 0.2043)

Statistical analyses

Statistical analysis title	Bc lispro 0.1U/kg vs 0.2U/kg
Statistical analysis description: Treatment Difference was Analyzed Using Wilcoxon's Signed Rank Test	
Comparison groups	BC Lispro 0.2U/kg v BC lispro 0.1U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.5521
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.05

Notes:
[17] - Dose response difference

Statistical analysis title	BC lispro 0.1U/kg vs 0.4U/kg
Statistical analysis description: Treatment Difference was Analyzed Using Wilcoxon's Signed Rank Test	
Comparison groups	BC lispro 0.1U/kg v BC lispro 0.4U/kg

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.9733
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0667
upper limit	0.05

Notes:

[18] - Dose response difference

Statistical analysis title	BC lispro 0.2U/kg vs 0.4U/kg
Statistical analysis description:	
Treatment Difference was Analyzed Using Wilcoxon's Signed Rank Test	
Comparison groups	BC Lispro 0.2U/kg v BC lispro 0.4U/kg
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.641
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.0667

Notes:

[19] - Dose response difference

Statistical analysis title	BC lispro 0.2U/kg vs Humalog 0.2U/kg
Statistical analysis description:	
Treatment Difference was Analyzed Using Wilcoxon's Signed Rank Test	
Comparison groups	BC Lispro 0.2U/kg v Humalog® 0.2U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-0.183
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2667
upper limit	-0.1167

Notes:
[20] - Treatment difference

Secondary: Early t0.5max(Lisp)

End point title	Early t0.5max(Lisp)

End point description:
Time to first observed half maximum observed serum insulin lispro concentration

End point type	Secondary

End point timeframe:
From t=0 up to t=12 hours

End point values	BC lispro 0.1U/kg	BC Lispro 0.2U/kg	BC lispro 0.4U/kg	Humalog® 0.2U/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	38	38	37
Units: hours				
arithmetic mean (standard deviation)	0.256 (± 0.0852)	0.262 (± 0.0857)	0.260 (± 0.0870)	0.440 (± 0.1165)

Statistical analyses

Statistical analysis title	Bc lispro 0.1U/kg vs 0.2U/kg

Statistical analysis description:
Treatment Difference was Analyzed Using Wilcoxon's Signed Rank Test

Comparison groups	BC lispro 0.1U/kg v BC Lispro 0.2U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.623
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.0333

Notes:
[21] - Dose response difference

Statistical analysis title	BC lispro 0.1U/kg vs 0.4U/kg

Statistical analysis description:
Treatment Difference was Analyzed Using Wilcoxon's Signed Rank Test

Comparison groups	BC lispro 0.1U/kg v BC lispro 0.4U/kg

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	= 0.5217
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.0333

Notes:

[22] - Dose response difference

Statistical analysis title	BC lispro 0.2U/kg vs 0.4U/kg
Statistical analysis description:	
Treatment Difference was Analyzed Using Wilcoxon's Signed Rank Test	
Comparison groups	BC Lispro 0.2U/kg v BC lispro 0.4U/kg
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.706
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0333
upper limit	0.05

Notes:

[23] - Dose response difference

Statistical analysis title	BC lispro 0.2U/kg vs Humalog 0.2U/kg
Statistical analysis description:	
Treatment Difference was Analyzed Using Wilcoxon's Signed Rank Test	
Comparison groups	BC Lispro 0.2U/kg v Humalog® 0.2U/kg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann estimate
Point estimate	-0.183
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2333
upper limit	-0.1333

Notes:
[24] - Treatment difference

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first study intervention until the safety follow-up visit	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1
Reporting groups	
Reporting group title	BC Lispro 0.1U/kg
Reporting group description: -	
Reporting group title	BC Lispro 0.2U/kg
Reporting group description: -	
Reporting group title	BC Lispro 0.4U/Kg
Reporting group description: -	
Reporting group title	Humalog® 0.2U/kg
Reporting group description: -	
Reporting group title	Before first dosing
Reporting group description: -	

Serious adverse events	BC Lispro 0.1U/kg	BC Lispro 0.2U/kg	BC Lispro 0.4U/Kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	0 / 38 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Humalog® 0.2U/kg	Before first dosing	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	BC Lispro 0.1U/kg	BC Lispro 0.2U/kg	BC Lispro 0.4U/Kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 37 (18.92%)	8 / 38 (21.05%)	7 / 38 (18.42%)

Vascular disorders Circulatory collapse subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	1 / 38 (2.63%) 1	1 / 38 (2.63%) 1
Cardiac disorders Presyncope subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	2 / 38 (5.26%) 2	2 / 38 (5.26%) 2
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0
Injection site erythema subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 38 (0.00%) 0	0 / 38 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 38 (0.00%) 0	1 / 38 (2.63%) 1
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	1 / 38 (2.63%) 1	1 / 38 (2.63%) 1
Vomiting subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	2 / 38 (5.26%) 2	1 / 38 (2.63%) 1
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 4	4 / 38 (10.53%) 9	3 / 38 (7.89%) 4

	Humalog® 0.2U/kg	Before first dosing	

Non-serious adverse events			
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 37 (13.51%)	3 / 38 (7.89%)	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Presyncope			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Injection site erythema			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 37 (0.00%)	0 / 38 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			

Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	3 / 38 (7.89%) 4	

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