Clinical trial results:
A double-blinded, randomised, three-period crossover euglycaemic clamp trial investigating the pharmacokinetics, glucodynamics and safety of BioChaperone human insulin, human insulin (Huminsulin® Normal) and insulin lispro (Humalog®) in subjects with type 1 diabetes

Summary

EudraCT number	2014-001432-11
Trial protocol	DE
Global end of trial date	10 November 2014

Results information

Result version number	v1 (current)
This version publication date	16 September 2020
First version publication date	16 September 2020

Trial information

Trial identification

Sponsor protocol code	BC3-CT010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02213146
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	11 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare, in type 1 diabetes patients, the early insulin exposure after administration of a 0.2 U·kg BW-1 single dose of BioChaperone human insulin (BC Human insulin) and Huminsulin® Normal during euglycaemic clamps.

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	12 August 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 trial was conducted at one site in Germany.

Pre-assignment

Screening details:

Subjects with Type v1 Diabetes Mellitus for 12 months or more
Treated with Multiple daily Insulin Injection for 12 months or more
BMI between 18.5 and 28.0 Kg/m²
HbA1C% equal or less than 9.0%

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	Investigator, Monitor, Subject

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	BC Human insulin / Human insulin / Insulin lispro

Arm description:

Each subject were randomly allocated to a sequence of three treatments, i.e. with one single dose of BC human insulin containing 0.2 U·kg BW, and one single dose of Human insulin (Huminsulin Normal®), containing 0.2 U·kg BW human insulin, and one single dose of insulin lispro (Humalog®), containing 0.2 U·kg BW insulin lispro on three separate dosing visits and during euglycemic clamp procedures. The three dosing visits were separated by a wash-out period of 3 to 15 days.

Arm type	Cross-over (experimental & active comparator)
Investigational medicinal product name	BioChaperone Human Insulin
Investigational medicinal product code	
Other name	BC Human insulin
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Single injection of 0.2 U/Kg Body weight.

Investigational medicinal product name	Human insulin
Investigational medicinal product code	
Other name	Huminsulin® Normal
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Single dose of 0.2 U/kg body weight.

Investigational medicinal product name	Insulin lispro
Investigational medicinal product code	
Other name	Humalog®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:
Single dose of 0.2 U/kg body weight

Number of subjects in period 1	BC Human insulin / Human insulin / Insulin lispro
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 it 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:	
Subjects who received at least one dose of one of the IMP	
Subject analysis set title	BC Human insulin
Subject analysis set type	Full analysis
Subject analysis set description:	
Subject who received at least one dose of BC Human insulin	
Subject analysis set title	Human insulin
Subject analysis set type	Full analysis
Subject analysis set description:	
subject who received at least one dose of Human insulin	
Subject analysis set title	Insulin lispro
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who received at least one dose of insulin lispro	

Reporting group values	Safety Analysis set	BC Human insulin	Human insulin
Number of subjects	37	37	37
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)	37	37	37
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	0	0
Male	37	37	37

Reporting group values	Insulin lispro		
Number of subjects	37		
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)	37		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	0		
Male	37		

End points

End points reporting groups

Reporting group title	BC Human insulin / Human insulin / Insulin lispro
Reporting group description:	
Each subject were randomly allocated to a sequence of three treatments, i.e. with one single dose of BC human insulin containing 0.2 U·kg BW, and one single dose of Human insulin (Huminsulin Normal®), containing 0.2 U·kg BW human insulin, and one single dose of insulin lispro (Humalog®), containing 0.2 U·kg BW insulin lispro on three separate dosing visits and during euglycemic clamp procedures. The three dosing visits were separated by a wash-out period of 3 to 15 days.	
Subject analysis set title	Safety Analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects who received at least one dose of one of the IMP	
Subject analysis set title	BC Human insulin
Subject analysis set type	Full analysis
Subject analysis set description:	
Subject who received at least one dose of BC Human insulin	
Subject analysis set title	Human insulin
Subject analysis set type	Full analysis
Subject analysis set description:	
subject who received at least one dose of Human insulin	
Subject analysis set title	Insulin lispro
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects who received at least one dose of insulin lispro	

Primary: AUCins(0-1h)

End point title	AUCins(0-1h)
End point description:	
Area under the human insulin serum concentration - time curve from t=0 to 1 hour.	
End point type	Primary
End point timeframe:	
From t=0 to t=1 hour after IMP administration.	

End point values	BC Human insulin	Human insulin		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	36		
Units: h*mU/L				
arithmetic mean (standard deviation)	26.0 (± 14.3)	15.5 (± 9.7)		

Statistical analyses

Statistical analysis title	BC Human insulin vs Human insulin
Comparison groups	Human insulin v BC Human insulin

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS Mean Ratio
Point estimate	1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.47
upper limit	2.07

Notes:

[1] - Difference

Secondary: AUCins(0-last)

End point title	AUCins(0-last)

End point description:

Area under the human insulin / insulin lispro serum concentration - time curve from t=0 to the last measurable insulin / insulin lispro serum concentration

End point type	Secondary

End point timeframe:

Time curve from t=0 to the last measurable insulin / insulin lispro serum concentration

End point values	BC Human insulin	Human insulin	Insulin lispro	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	35	36	37	
Units: h*mU/L				
arithmetic mean (standard deviation)	158.33 (± 47.043)	152.47 (± 32.690)	183.08 (± 41.679)	

Statistical analyses

Statistical analysis title	BC Human insulin vs Human insulin
Comparison groups	BC Human insulin v Human insulin
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.6548
Method	ANOVA
Parameter estimate	LS Mean Ratio
Point estimate	1.016

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9453
upper limit	1.0922

Notes:

[2] - Difference

Statistical analysis title	BC Human insulin vs insulin lispro
Comparison groups	BC Human insulin v Insulin lispro
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS Mean Ratio
Point estimate	0.857
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.815
upper limit	0.9006

Notes:

[3] - Absence of differences

Secondary: Tonset of appearance	
End point title	Tonset of appearance
End point description:	
Time from t=0 to the first time human insulin / insulin lispro serum concentration is equal or superior to lower limit of quantification (LLOQ)	
End point type	Secondary
End point timeframe:	
From t=0 to t=10 hours	

End point values	BC Human insulin	Human insulin	Insulin lispro	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	35	36	37	
Units: Hour				
arithmetic mean (standard deviation)	0.088 (± 0.0421)	0.211 (± 0.1416)	0.119 (± 0.0611)	

Statistical analyses

Statistical analysis title	BC Human insulin vs Human insulin
Comparison groups	Human insulin v BC Human insulin

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehman estimate
Point estimate	-0.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1333
upper limit	-0.0667

Notes:

[4] - Difference

Statistical analysis title	BC Human insulin vs insulin lispro
Comparison groups	BC Human insulin v Insulin lispro
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehman estimate
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0667
upper limit	0

Notes:

[5] - Absence of differences

Secondary: Cmax ins	
End point title	Cmax ins
End point description:	
Maximum observed human insulin / insulin lispro serum concentration	
End point type	Secondary
End point timeframe:	
From t=0 to t=10 hours	

End point values	BC Human insulin	Human insulin	Insulin lispro	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	35	36	
Units: mU/L				
arithmetic mean (standard deviation)	44.270 (± 19.784)	39.492 (± 16.556)	83.078 (± 39.685)	

Statistical analyses

Statistical analysis title	BC Human insulin vs Human insulin
Comparison groups	BC Human insulin v Human insulin
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.0122
Method	ANOVA
Parameter estimate	LS Mean Ratio
Point estimate	1.133
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.0296
upper limit	1.2458

Notes:

[6] - Difference

Statistical analysis title	BC Human insulin vs insulin lispro
Comparison groups	BC Human insulin v Insulin lispro
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS Mean Ratio
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5179
upper limit	0.5849

Notes:

[7] - Absence of differences

Secondary: AUC-GIR 0-Last	
End point title	AUC-GIR 0-Last

End point description:

Area under the glucose infusion rate time curve from 0 hours until the end of clamp.

End point type	Secondary

End point timeframe:

From t=0 up to t=10 hours

End point values	BC Human insulin	Human insulin	Insulin lispro	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	36	36	37	
Units: mg/kg				
arithmetic mean (standard deviation)	1294.2 (± 610.90)	1255.8 (± 612.64)	1295.3 (± 464.40)	

Statistical analyses

Statistical analysis title	BC Human insulin vs Human insulin
Comparison groups	Human insulin v BC Human insulin
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.5814
Method	ANOVA
Parameter estimate	LS Mean Ratio
Point estimate	1.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9306
upper limit	1.1343

Notes:

[8] - Difference

Statistical analysis title	BC Human insulin vs insulin lispro
Comparison groups	Insulin lispro v BC Human insulin
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.3622
Method	ANOVA
Parameter estimate	LS Mean Ratio
Point estimate	0.959
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8894
upper limit	1.035

Notes:

[9] - Absence of difference

Secondary: T onset of Action

End point title	T onset of Action
End point description: Time from t=0 hours until blood glucose concentration has decreased by 5 mg·dL 1 (0.3 mmol·L 1) from baseline	
End point type	Secondary
End point timeframe: From t=0 up to 10 hours	

End point values	BC Human insulin	Human insulin	Insulin lispro	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	35	36	37	
Units: Hour				
arithmetic mean (standard deviation)	0.469 (± 0.1744)	0.822 (± 0.3369)	0.555 (± 0.1721)	

Statistical analyses

Statistical analysis title	BC Human insulin vs Human insulin
Comparison groups	BC Human insulin v Human insulin
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehman estimate
Point estimate	-0.333
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	-0.2167

Notes:

[10] - Difference

Statistical analysis title	BC Human insulin vs insulin lispro
Comparison groups	BC Human insulin v Insulin lispro
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.0024
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehman estimate
Point estimate	-0.083

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1667
upper limit	-0.0333

Notes:
[11] - Absence of differences

Secondary: GIRmax

End point title	GIRmax

End point description:
Maximum glucose infusion rate

End point type	Secondary

End point timeframe:
From t=0 up to t=10 hours

End point values	BC Human insulin	Human insulin	Insulin lispro	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	36	36	37	
Units: mg/kg/min				
arithmetic mean (standard deviation)	4.622 (± 2.4718)	4.209 (± 2.4950)	6.487 (± 2.5341)	

Statistical analyses

Statistical analysis title	BC Human insulin vs Human insulin
Comparison groups	BC Human insulin v Human insulin
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	< 0.023
Method	ANOVA
Parameter estimate	LS Mean Ratio
Point estimate	1.124
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.0173
upper limit	1.2413

Notes:
[12] - Difference

Statistical analysis title	BC Human insulin vs insulin lispro
Comparison groups	BC Human insulin v Insulin lispro

Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANOVA
Parameter estimate	LS Mean Ratio
Point estimate	0.682
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6281
upper limit	0.7411

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first IMP (study drug) dose to safety follow-up visit.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1
Reporting groups	
Reporting group title	BC Human Insulin
Reporting group description: -	
Reporting group title	Human insulin
Reporting group description: -	
Reporting group title	Insulin lispro
Reporting group description: -	

Serious adverse events	BC Human Insulin	Human insulin	Insulin lispro
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 37 (0.00%)	0 / 37 (0.00%)	0 / 37 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	BC Human Insulin	Human insulin	Insulin lispro
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 37 (8.11%)	5 / 37 (13.51%)	4 / 37 (10.81%)
Injury, poisoning and procedural complications			
Phlebitis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 37 (2.70%)	1 / 37 (2.70%)
occurrences (all)	0	1	1
Injection site erythema			
subjects affected / exposed	0 / 37 (0.00%)	1 / 37 (2.70%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 37 (5.41%)	2 / 37 (5.41%)	4 / 37 (10.81%)
occurrences (all)	2	2	4
Vision blurred			
subjects affected / exposed	0 / 37 (0.00%)	1 / 37 (2.70%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 37 (0.00%)	1 / 37 (2.70%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 37 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Psychiatric disorders			
Hyperventilation			
subjects affected / exposed	0 / 37 (0.00%)	1 / 37 (2.70%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 37 (0.00%)	0 / 37 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 37 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 37 (2.70%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 37 (0.00%)	2 / 37 (5.41%)
occurrences (all)	2	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 August 2014	Two additionnal arms with different doses of BC Human insulin at different doses were cancelled. This amendment was in place before the start of study recruitment / study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported