Clinical trial results:
A Trial comparing the Pharmacokinetic Properties of Fast-acting Insulin Aspart between Children, Adolescents and Adults with Type 1 Diabetes

Summary

EudraCT number	2017-002014-31
Trial protocol	DE
Global end of trial date	05 July 2018

Results information

Result version number	v1 (current)
This version publication date	05 January 2019
First version publication date	05 January 2019

Trial information

Trial identification

Sponsor protocol code	NN1218-4371

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03407599
WHO universal trial number (UTN)	U1111-1197-0428

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 July 2018
Global end of trial reached?	Yes
Global end of trial date	05 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the total exposure of faster aspart between children, adolescents and adult subjects with type 1 diabetes.

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 Practice, including archiving of essential documents and 21 Code of Federal Regulations (CFR) 312.120.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	08 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 43
Worldwide total number of subjects	43
EEA total number of subjects	43

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)	12
Adolescents (12-17 years)	16
Adults (18-64 years)	15
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:

Not applicable

Period 1

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

Blinding implementation details:

Three sets of black sealed codes/labels containing information about the treatment were prepared for each subject. The sets were kept by the trial site (throughout the entire trial period), the local Novo Nordisk affiliate and the Novo Nordisk Global Safety department.

Arms

Arm title	Total population

Arm description:

Each subject was randomly allocated to a treatment sequence (faster aspart followed by NovoRapid® or NovoRapid® followed by faster aspart) consisting of 2 treatment periods. The two treatment periods (between first dosing visit and second dosing visit) were separated by a wash-out period of 3-22 days.

Arm type	Cross-over (experimental & active comparator)
Investigational medicinal product name	Faster aspart
Investigational medicinal product code	
Other name	Fiasp®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were administered with a single dose of faster aspart 0.2 U/kg body weight just prior to a standard meal. Faster aspart was administered subcutaneously (s.c.) into a lifted skin fold of the lower abdominal wall above the inguinal area (lower lateral parts of the abdomen).

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

Dosage and administration details:

Subjects were administered with a single dose of NovoRapid® 0.2 U/kg body weight just prior to a standard meal. NovoRapid® was administered s.c. into a lifted skin fold of the lower abdominal wall above the inguinal area (lower lateral parts of the abdomen).

Number of subjects in period 1	Total population
Started	43
Completed	43

Baseline characteristics

Reporting groups	
Reporting group title	Total population

Reporting group description:

Each subject was randomly allocated to a treatment sequence (faster aspart followed by NovoRapid® or NovoRapid® followed by faster aspart) consisting of 2 treatment periods. The two treatment periods (between first dosing visit and second dosing visit) were separated by a wash-out period of 3-22 days.

Reporting group values	Total population	Total	
Number of subjects	43	43	
Age Categorical Units: Subjects			
Children (2-11 years)	12	12	
Adolescents (12-17 years)	16	16	
Adults (18-64 years)	15	15	
Age Continuous Units: years			
arithmetic mean	15.2		
standard deviation	± 4.1	-	
Gender Categorical Units: Subjects			
Female	23	23	
Male	20	20	

End points

End points reporting groups

Reporting group title	Total population
Reporting group description: Each subject was randomly allocated to a treatment sequence (faster aspart followed by NovoRapid® or NovoRapid® followed by faster aspart) consisting of 2 treatment periods. The two treatment periods (between first dosing visit and second dosing visit) were separated by a wash-out period of 3-22 days.	
Subject analysis set title	Faster aspart - Children
Subject analysis set type	Full analysis
Subject analysis set description: Children subjects (6–11 years) received single dose of faster aspart in a cross-over manner in both treatment periods 1 and 2.	
Subject analysis set title	Faster aspart - Adolescents
Subject analysis set type	Full analysis
Subject analysis set description: Adolescent subjects (12–17 years) received single dose of faster aspart in a cross-over manner in both treatment periods 1 and 2.	
Subject analysis set title	Faster aspart - Adults
Subject analysis set type	Full analysis
Subject analysis set description: Adult subjects (18–64 years) received single dose of faster aspart in a cross-over manner in both treatment periods 1 and 2.	
Subject analysis set title	NovoRapid® - Children
Subject analysis set type	Full analysis
Subject analysis set description: Children subjects (6–11 years) received single dose of NovoRapid® in a cross-over manner in both treatment periods 1 and 2.	
Subject analysis set title	NovoRapid® - Adolescents
Subject analysis set type	Full analysis
Subject analysis set description: Adolescent subjects (12–17 years) received single dose of NovoRapid® in a cross-over manner in both treatment periods 1 and 2.	
Subject analysis set title	NovoRapid® - Adults
Subject analysis set type	Full analysis
Subject analysis set description: Adult subjects (18–64 years) received single dose of NovoRapid® in a cross-over manner in both treatment periods 1 and 2.	

Primary: AUCIAsp,0–12h, area under the serum insulin aspart concentration-time curve

End point title	AUCIAsp,0–12h, area under the serum insulin aspart concentration-time curve
End point description: This endpoint represents data for the free insulin aspart concentration for AUCIAsp,0–12h. Results are based on the full analysis set (FAS), which included all randomised subjects receiving at least one dose of one of the two investigational medicinal products (IMPs; faster aspart or NovoRapid®). Number of subjects analyzed = subjects with available data.	
End point type	Primary
End point timeframe: From 0 to 12 hours	

End point values	Faster aspart - Children	Faster aspart - Adolescents	Faster aspart - Adults	NovoRapid® - Children
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	16	13	12
Units: pmol*h/L				
geometric mean (geometric coefficient of variation)	493 (± 23)	604 (± 16)	684 (± 15)	499 (± 21)

End point values	NovoRapid® - Adolescents	NovoRapid® - Adults		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	15		
Units: pmol*h/L				
geometric mean (geometric coefficient of variation)	648 (± 20)	690 (± 12)		

Statistical analyses

Statistical analysis title	Children: Faster aspart versus NovoRapid®

Statistical analysis description:

The endpoint was log-transformed and analysed using a linear mixed model with age group, treatment, period, and age group-by-treatment interaction as fixed effects, and subject as a random effect. Due to cross-over design of the study, the following "number of subjects included in analysis" is being erroneously displayed as 24. Actual "number of subjects included in analysis" is 12.

Comparison groups	NovoRapid® - Children v Faster aspart - Children
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment ratio
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.11

Statistical analysis title	Adolescents: Faster aspart versus NovoRapid®

Statistical analysis description:

The endpoint was log-transformed and analysed using a linear mixed model with age group, treatment, period, and age group-by-treatment interaction as fixed effects, and subject as a random effect. Due to cross-over design of the study, the following "number of subjects included in analysis" is being erroneously displayed as 32. Actual "number of subjects included in analysis" is 16.

Comparison groups	Faster aspart - Adolescents v NovoRapid® - Adolescents

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1

Statistical analysis title	Adults: Faster aspart versus NovoRapid®

Statistical analysis description:

The endpoint was log-transformed and analysed using a linear mixed model with age group, treatment, period, and age group-by-treatment interaction as fixed effects, and subject as a random effect. Due to cross-over design of the study, the following "number of subjects included in analysis" is being erroneously displayed as 28. Actual "number of subjects included in analysis" is 15.

Comparison groups	Faster aspart - Adults v NovoRapid® - Adults
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.07

Statistical analysis title	Faster aspart: Children versus adults

Statistical analysis description:

The endpoint was log-transformed and analysed using a linear mixed model with age group, treatment, period, and age group-by-treatment interaction as fixed effects, and subject as a random effect.

Comparison groups	Faster aspart - Children v Faster aspart - Adults
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment ratio
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.83

Statistical analysis title	Faster aspart: Adolescents versus adults
Statistical analysis description:	
The endpoint was log-transformed and analysed using a linear mixed model with age group, treatment, period, and age group-by-treatment interaction as fixed effects, and subject as a random effect.	
Comparison groups	Faster aspart - Adolescents v Faster aspart - Adults
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment ratio
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	0.98

Statistical analysis title	NovoRapid®: Children versus adults
Statistical analysis description:	
The endpoint was log-transformed and analysed using a linear mixed model with age group, treatment, period, and age group-by-treatment interaction as fixed effects, and subject as a random effect.	
Comparison groups	NovoRapid® - Children v NovoRapid® - Adults
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment ratio
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.84

Statistical analysis title	NovoRapid®: Adolescents versus adults
Statistical analysis description:	
The endpoint was log-transformed and analysed using a linear mixed model with age group, treatment, period, and age group-by-treatment interaction as fixed effects, and subject as a random effect.	
Comparison groups	NovoRapid® - Adolescents v NovoRapid® - Adults
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment ratio
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.05

Secondary: Cmax,IAsp, maximum observed serum insulin aspart concentration

End point title	Cmax,IAsp, maximum observed serum insulin aspart concentration

End point description:

This endpoint represents data for the free insulin aspart concentration for Cmax,IAsp. Results are based on the FAS. Number of subjects analyzed = subjects with available data.

End point type	Secondary

End point timeframe:

Not applicable

End point values	Faster aspart - Children	Faster aspart - Adolescents	Faster aspart - Adults	NovoRapid® - Children
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	16	13	12
Units: pmol/L				
geometric mean (geometric coefficient of variation)	258 (± 50)	253 (± 25)	290 (± 18)	256 (± 39)

End point values	NovoRapid® - Adolescents	NovoRapid® - Adults		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	15		
Units: pmol/L				
geometric mean (geometric coefficient of variation)	255 (± 32)	292 (± 20)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Day 1 to day 7 in both the treatment periods. Results are based on the safety analysis set, which included all subjects receiving at least one dose of one of the two IMPs.

Adverse event reporting additional description:

An AE was defined as treatment emergent if, for each treatment period, the onset of the AE was in the period from time of first trial product administration to 7 days (7 times 24 hours) after trial product administration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events with a prevalence of 5% are available for this trial. Number of subjects in individual treatment group with at least one non-serious adverse event areas follows: 3 subjects in faster aspart - children, 4 subjects in faster aspart- adolescents, 1 subject in faster aspart – adults, 2 subjects in NovoRapid® -children,1 subject in NovoRapid® - adolescents, and 1 subject in NovoRapid® - Adults.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 March 2018	The date, time, and dose of the last trial product administration were modified to cover the last insulin administration prior to the hypoglycaemic episode. The amendment allowed the reporting of blood glucose (BG) values via subjects' own BG meters in case they experienced a hypoglycaemic episode outside the clinical site. It was specified that an un-blinded monitor will receive a copy of the randomisation list in order to check that the trial products have been administered in accordance with the planned randomisation. The protocol was updated to specify that the destruction of the trial product will be performed upon completion of the trial after finalization of the drug accountability. It was specified that in case the target plasma glucose level cannot be established before 10:00 hours, the subject can be rescheduled once as per standard procedure. Administration of the meal by intravenous infusion was also allowed in addition to the subcutaneous route.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported