Clinical trial results:
Efficacy and Safety of Continuous Subcutaneous Insulin Infusion of Faster-acting Insulin Aspart compared to NovoRapid® in Adults with Type 1 Diabetes

Summary

EudraCT number	2010-024054-11
Trial protocol	NL DE BE FR SI GB
Global end of trial date	21 July 2017

Results information

Result version number	v1 (current)
This version publication date	25 July 2018
First version publication date	25 July 2018

Trial information

Trial identification

Sponsor protocol code	NN1218-3854

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02825251
WHO universal trial number (UTN)	U1111-1118-2480

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 June 2017
Global end of trial reached?	Yes
Global end of trial date	21 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the effect of CSII treatment with faster aspart in terms of glycaemic control by comparing it to CSII treatment with NovoRapid®/NovoLog®, in adults with Type 1 Diabetes Mellitus (T1DM), using a non-inferiority approach.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki Amended 2013 and ICH Good Clinical Practice (1996), including archiving of essential documents and 21 CFR 312.120.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	06 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 36
Country: Number of subjects enrolled	Canada: 45
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	Germany: 63
Country: Number of subjects enrolled	Netherlands: 20
Country: Number of subjects enrolled	Russian Federation: 55
Country: Number of subjects enrolled	Slovenia: 33
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	United States: 158
Worldwide total number of subjects	472
EEA total number of subjects	214

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	432
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 92 sites in 9 countries as follows: Belgium (7), Canada (8), France (10), Germany (9), Netherlands (9), Russian Federation (11), Slovenia (2), United Kingdom (6), and United States (30). One (1) site in the Netherlands screened, but didn't randomise any subject.

Pre-assignment

Screening details:

There was a 4-week run-in period primarily for reinforcement of subject training in trial procedures, diabetes education and collecting baseline assessments. Subjects remained on their pre-trial insulin treatment during the run-in period.

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	Investigator, Subject

Blinding implementation details:

As the trial was blinded with regard to faster aspart and NovoRapid®, only dispensing unit numbers (DUNs) allocated by the interactive voice/web response system (IV/WRS) were dispensed to the subject. Trial products were packaged in non-subject specific boxes.

Arms

Are arms mutually exclusive?	Yes
Arm title	Faster aspart

Arm description:

The subjects received faster aspart (basal-bolus regimen) by continuous subcutaneous insulin infusion (CSII) for 16 weeks.

Arm type	Experimental
Investigational medicinal product name	Insulin aspart
Investigational medicinal product code	
Other name	Fiasp®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Doses of basal and bolus insulin and timing of bolus dose were individually adjusted and thus no maximum dose of insulin was specified. Basal rate insulin adjustment: The purpose of adjusting the basal rates was to ensure that blood glucose (BG) was kept between 4.0–6.0 mmol/L [71–108 mg/dL] while in a fasting state and during the night. Bolus insulin titration: It was recommended that mealtime bolus insulin was titrated based on carbohydrate-counting using the Bolus Wizard® according to their usual practice and according to instructions from the investigator. Meal-time dosing was defined as bolus infusion initiated 0-2 minutes before a meal.

Arm title	NovoRapid

Arm description:

The subjects received insulin aspart (NovoRapid®/NovoLog®: basal-bolus regimen) by CSII for 16 weeks.

Arm type	Active comparator
Investigational medicinal product name	Insulin aspart
Investigational medicinal product code	
Other name	NovoRapid®, NovoLog®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Doses of basal and bolus insulin and timing of bolus dose were individually adjusted and thus no maximum dose of insulin was specified. Basal rate insulin adjustment: The purpose of adjusting the basal rates was to ensure that BG was kept between 4.0–6.0 mmol/L [71–108 mg/dL] while in a fasting state and during the night. Bolus insulin titration: It was recommended that meal-time bolus insulin was titrated based on carbohydrate-counting using the Bolus Wizard® according to their usual practice and according to instructions from the investigator. Meal-time dosing was defined as bolus infusion initiated 0-2 minutes before a meal.

Number of subjects in period 1	Faster aspart	NovoRapid
Started	236	236
Completed	233	230
Not completed	3	6
Consent withdrawn by subject	1	4
Adverse event, non-fatal	-	1
Unclassified	2	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Faster aspart
Reporting group description:	
The subjects received faster aspart (basal-bolus regimen) by continuous subcutaneous insulin infusion (CSII) for 16 weeks.	
Reporting group title	NovoRapid
Reporting group description:	
The subjects received insulin aspart (NovoRapid®/NovoLog®: basal-bolus regimen) by CSII for 16 weeks.	

Reporting group values	Faster aspart	NovoRapid	Total
Number of subjects	236	236	472
Age Categorical Units: Subjects			
Adults (18-64 years)	213	219	432
From 65-84 years	23	17	40
Age Continuous Units: years			
arithmetic mean	43.3	43.6	
standard deviation	± 14.8	± 14.7	-
Gender Categorical Units: Subjects			
Female	133	136	269
Male	103	100	203

End points

End points reporting groups

Reporting group title	Faster aspart
Reporting group description:	
The subjects received faster aspart (basal-bolus regimen) by continuous subcutaneous insulin infusion (CSII) for 16 weeks.	
Reporting group title	NovoRapid
Reporting group description:	
The subjects received insulin aspart (NovoRapid®/NovoLog®: basal-bolus regimen) by CSII for 16 weeks.	

Primary: Change from baseline in glycosylated haemoglobin (HbA1c)

End point title	Change from baseline in glycosylated haemoglobin (HbA1c)
End point description:	
Change from baseline (week 0) in HbA1c was evaluated 16 weeks after randomisation. The results are based on the last in-trial value, which included the last available measurement in the in-trial period. In-trial period: the observation period from date of randomisation until last trial-related subject-site contact. Results are based on the FAS, which included all randomised subjects. Number of subjects analysed = Number of subjects contributed to the analysis.	
End point type	Primary
End point timeframe:	
16 weeks after randomisation	

End point values	Faster aspart	NovoRapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	236		
Units: Percentage (%) of HbA1c				
arithmetic mean (standard deviation)				
Baseline	7.49 (± 0.55)	7.49 (± 0.53)		
Change from baseline	-0.06 (± 0.50)	-0.14 (± 0.44)		

Statistical analyses

Statistical analysis title	Faster aspart versus NovoRapid
Statistical analysis description:	
Change from baseline in HbA1c was analysed using an analysis of variance model after multiple imputation assuming treatment according to randomisation. The model included treatment, strata (use of own continuous glucose monitoring), previous insulin use, and region as factors, and baseline HbA1c as a covariate. Non-inferiority of faster aspart was considered confirmed if the upper limit of the two-sided 95 % CI for the true treatment-difference D (faster aspart minus NovoRapid®) was below 0.4 %.	
Comparison groups	Faster aspart v NovoRapid

Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Treatment difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.17

Secondary: Change from baseline in 1-hour PPG increment (meal test)

End point title	Change from baseline in 1-hour PPG increment (meal test)

End point description:

Change from baseline (week 0) in 1-hour postprandial glucose (PPG) increment was evaluated 16 weeks after randomisation. The results are based on the last in-trial value, which included the last available measurement in the in-trial period. Results are based on the FAS, which included all randomised subjects. Number of subjects analysed (N) = Number of subjects contributed to the analysis.

End point type	Secondary

End point timeframe:

16 weeks after randomisation

End point values	Faster aspart	NovoRapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	236		
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline (N = 235, 235)	4.67 (± 3.09)	4.62 (± 3.00)		
Change from baseline (N = 228, 227)	-0.89 (± 3.44)	0.05 (± 3.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in 1,5-anhydroglucitol

End point title	Change from baseline in 1,5-anhydroglucitol

End point description:

Change from baseline (week 0) in 1,5-anhydroglucitol was evaluated 16 weeks after randomisation. The results are based on the last in-trial value, which included the last available measurement in the in-trial period. Results are based on the FAS, which included all randomised subjects. Number of subjects analysed (N) = Number of subjects contributed to the analysis.

End point type	Secondary

End point timeframe:

16 weeks after randomisation

End point values	Faster aspart	NovoRapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	236		
Units: ug/mL				
arithmetic mean (standard deviation)				
Baseline (N = 233, 234)	4.20 (± 2.34)	4.13 (± 2.14)		
Change from baseline (N = 233, 234)	0.14 (± 1.48)	0.25 (± 1.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of time spent in low IG (≤3.9 mmol/L [70 mg/dL]) during CGM

End point title	Change from baseline of time spent in low IG (≤3.9 mmol/L [70 mg/dL]) during CGM

End point description:

Change from baseline (week 0) in low interstitial glucose (IG) (≤3.9 mmol/L [70 mg/dL]) during continuous glucose monitoring (CGM) was evaluated 16 weeks after randomisation. The results are based on the last in-trial value, which included the last available measurement in the in-trial period. Results are based on the FAS, which included all randomised subjects. Number of subjects analysed (N) = Number of subjects contributed to the analysis.

End point type	Secondary

End point timeframe:

16 weeks after randomisation

End point values	Faster aspart	NovoRapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	236		
Units: min/day				
arithmetic mean (standard deviation)				
Baseline (N = 236, 236)	85.42 (± 65.20)	79.88 (± 60.46)		
Change from baseline (N = 234, 231)	-6.96 (± 55.29)	2.85 (± 58.56)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 to Week 16 + 7 days. Results are based on the safety analysis set, which included all subjects receiving at least one dose of the investigational medicinal product (IMP; faster aspart) or its comparator (NovoRapid®).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Faster aspart
Reporting group description: -	
Reporting group title	NovoRapid

Reporting group description: -

Serious adverse events	Faster aspart	NovoRapid	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 236 (2.12%)	8 / 236 (3.39%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Pain management			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoglycaemic seizure			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic unconsciousness			

subjects affected / exposed	1 / 236 (0.42%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal aneurysm			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurodermatitis			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Adenovirus infection			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device breakage			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 236 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketoacidosis			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Faster aspart	NovoRapid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 236 (35.59%)	72 / 236 (30.51%)	
General disorders and administration site conditions			
Infusion site reaction			
subjects affected / exposed	16 / 236 (6.78%)	7 / 236 (2.97%)	
occurrences (all)	26	10	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	12 / 236 (5.08%)	6 / 236 (2.54%)	
occurrences (all)	12	6	
Upper respiratory tract infection			
subjects affected / exposed	17 / 236 (7.20%)	12 / 236 (5.08%)	
occurrences (all)	18	12	
Viral upper respiratory tract infection			

subjects affected / exposed occurrences (all)	48 / 236 (20.34%) 60	50 / 236 (21.19%) 64	

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28918652