



## Clinical trial results:

**A 6-week randomised, double-blind, parallel-group trial evaluating compatibility and safety of FIAsp and insulin aspart with an external continuous subcutaneous insulin infusion system in adult subjects with type 1 diabetes**

### Summary

EudraCT number	2013-002233-37
Trial protocol	DE
Global end of trial date	14 May 2014

### Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	26 July 2015

### Trial information

#### Trial identification

Sponsor protocol code	NN1218-3931
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01999322
WHO universal trial number (UTN)	U1111-1143-2316

Notes:

### Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allè, Bagsvaerd, Denmark, 2860
Public contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Global Clinical Registry (GCR,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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	12 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 May 2014
Global end of trial reached?	Yes
Global end of trial date	14 May 2014
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To evaluate the compatibility of faster-acting insulin aspart (FIAsp) and insulin aspart with the external continuous subcutaneous insulin infusion (CSII) system over a 6-week treatment period.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice and 21 CFR 312.120.

Background therapy:

Eligible subjects previously treated with a rapid-acting insulin analogue were to stay on their own NovoRapid®, insulin lispro or insulin glulisine in the screening period, after which all subjects received NovoRapid®, with no additional anti-diabetes treatment allowed, for a 2-week run-in period prior to randomisation.

Evidence for comparator:

Not applicable

Actual start date of recruitment	19 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	United States: 10
Country: Number of subjects enrolled	Germany: 27
Worldwide total number of subjects	37
EEA total number of subjects	27

Notes:

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**Subjects enrolled per age group**

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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)	31
From 65 to 84 years	6
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The trial was conducted at two sites in two countries as follows: USA: one site; Germany one site.

### Pre-assignment

Screening details:

Eligible subjects previously treated with a rapid acting insulin analogue were to stay in their own NovoRapid®, insulin lispro or insulin glulisine in the screening period after which the all subjects received NovoRapid®, with no additional antidiabetics allowed, for a 2-week run-in period prior to randomisation.

### Period 1

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

Blinding implementation details:

This trial was double-blinded. The randomisation in this study was 2:1.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Faster-acting insulin aspart

Arm description:

Subjects received faster-acting insulin aspart for a duration of 6 weeks. The insulin dose adjustments were made based on frequent glucose measurements during contacts with the investigator. The following glycaemic targets were recommended: pre-prandial and bedtime glucose: below 6.0 mmol/L (108 mg/dL) and 2-hr postprandial glucose: below 7.8 mmol/L (140 mg/dL). A 2:1 randomisation following the screening period was selected in order to ensure adequate exposure to faster-acting insulin aspart.

Arm type	Experimental
Investigational medicinal product name	Faster-acting insulin aspart
Investigational medicinal product code	
Other name	INSULIN ASPART
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Faster-acting insulin aspart was provided in 100U/ml 3 mL Penfill® and administered in accordance with the instructions provided by the pump manufacturer, preferably in the abdomen by subcutaneous infusion. Subjects were instructed in how to fill the reservoir from Penfill®. The subjects remained on their own external CSII system. Subjects were instructed to change infusion set and reservoir every 72 hours ( $\pm$  4 hours) and only before 72 hours ( $\pm$  4 hours) if there is any suspicion of occlusion, leakage, unexplained hyperglycaemic episode, infusion site reaction, technical reason or other reason. Infusion sites were to be rotated but the infusion set was to be inserted in a standardised way in a similar position. No maximum dose was specified. Doses were adjusted according to plasma glucose and the bolus dose was calculated manually or by using pump bolus calculator.

<b>Arm title</b>	NovoRapid®
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Arm description:

Subjects received NovoRapid® for a duration of 6 weeks. The insulin dose adjustments were made based on frequent glucose measurements during contacts with the investigator. The following glycaemic targets were recommended: pre-prandial and bedtime glucose: below 6.0 mmol/L (108 mg/dL) and 2-hr postprandial glucose: below 7.8 mmol/L (140 mg/dL).

Arm type	Active comparator
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Investigational medicinal product name	NovoRapid®
Investigational medicinal product code	
Other name	INSULIN ASPART
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

NovoRapid® was provided in 100U/ml 3 ml Penfill® and administered in accordance with the instructions provided by the pump manufacturer, preferably in the abdomen by subcutaneous infusion. The subjects remained on their own external CSII system. Subjects were instructed to change infusion set and reservoir every 72 hours ( $\pm$  4 hours) and only before 72 hours ( $\pm$  4 hours) if there is any suspicion of occlusion, leakage, unexplained hyperglycaemic episode, infusion site reaction, technical reason or other reason. Infusion sites were to be rotated but the infusion set was to be inserted in a standardised way in a similar position. No maximum dose was specified. Doses were adjusted according to plasma glucose and the bolus dose was calculated manually or by using pump bolus calculator.

<b>Number of subjects in period 1</b>	Faster-acting insulin aspart	NovoRapid®
Started	25	12
Completed	24	12
Not completed	1	0
Adverse event, non-fatal	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Faster-acting insulin aspart
Reporting group description:	
Subjects received faster-acting insulin aspart for a duration of 6 weeks. The insulin dose adjustments were made based on frequent glucose measurements during contacts with the investigator. The following glycaemic targets were recommended: pre-prandial and bedtime glucose: below 6.0 mmol/L (108 mg/dL) and 2-hr postprandial glucose: below 7.8 mmol/L (140 mg/dL). A 2:1 randomisation following the screening period was selected in order to ensure adequate exposure to faster-acting insulin aspart.	
Reporting group title	NovoRapid®
Reporting group description:	
Subjects received NovoRapid® for a duration of 6 weeks. The insulin dose adjustments were made based on frequent glucose measurements during contacts with the investigator. The following glycaemic targets were recommended: pre-prandial and bedtime glucose: below 6.0 mmol/L (108 mg/dL) and 2-hr postprandial glucose: below 7.8 mmol/L (140 mg/dL).	

Reporting group values	Faster-acting insulin aspart	NovoRapid®	Total
Number of subjects	25	12	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)	19	12	31
From 65-84 years	6	0	6
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	11	4	15
Male	14	8	22

## End points

### End points reporting groups

Reporting group title	Faster-acting insulin aspart
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Reporting group description:

Subjects received faster-acting insulin aspart for a duration of 6 weeks. The insulin dose adjustments were made based on frequent glucose measurements during contacts with the investigator. The following glycaemic targets were recommended: pre-prandial and bedtime glucose: below 6.0 mmol/L (108 mg/dL) and 2-hr postprandial glucose: below 7.8 mmol/L (140 mg/dL). A 2:1 randomisation following the screening period was selected in order to ensure adequate exposure to faster-acting insulin aspart.

Reporting group title	NovoRapid®
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Reporting group description:

Subjects received NovoRapid® for a duration of 6 weeks. The insulin dose adjustments were made based on frequent glucose measurements during contacts with the investigator. The following glycaemic targets were recommended: pre-prandial and bedtime glucose: below 6.0 mmol/L (108 mg/dL) and 2-hr postprandial glucose: below 7.8 mmol/L (140 mg/dL).

### Primary: Number of microscopically confirmed episodes of infusion set occlusions.

End point title	Number of microscopically confirmed episodes of infusion set occlusions. <sup>[1]</sup>
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End point description:

Microscopy was conducted at the laboratory at routine weekly site visits and if the infusion set was sent in by the subject following a premature change because of leakage, unexplained hyperglycaemia or suspicion of occlusion (observation of a plug).

End point type	Primary
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End point timeframe:

6 weeks of treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There was no specification of an analysis in the protocol or in the statistical analysis plan.

End point values	Faster-acting insulin aspart	NovoRapid®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	12		
Units: Number of subjects	0	0		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of unexplained episodes of hyperglycaemia

End point title	Number of unexplained episodes of hyperglycaemia
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End point description:

Unexplained hyperglycaemia was defined as a confirmed plasma glucose value  $\geq 16.7$  mmol/L (300 mg/dL) and was unexplained (i.e., no apparent medical, dietary, insulin dosage or pump failure reason)

End point type	Secondary
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End point timeframe:  
During 6 weeks of treatment

End point values	Faster-acting insulin aspart	NovoRapid®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	12		
Units: Number of events	28	16		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of possible infusion set occlusions

End point title	Number of possible infusion set occlusions
End point description: Episodes of possible infusion set occlusions were defined as infusion sets changed due to suspicion of occlusion, leakage or unexplained hyperglycaemic episode. Possible occlusion excluded technical reasons. This endpoint was calculated from the recorded date/times of changes of infusion set combined with the subjects' own assessment.	
End point type	Secondary
End point timeframe: During 6 weeks of treatment	

End point values	Faster-acting insulin aspart	NovoRapid®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	12		
Units: Number of episodes	7	0		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of premature infusion set changes

End point title	Number of premature infusion set changes
End point description: A premature infusion set change was defined as not being a routine change. This was defined as an infusion set changed at home due to "suspicion of occlusion", "leakage", "unexplained hyperglycaemic episode", "infusion site reaction", "technical reason", or "other". The change of infusion set at a site visit was considered a routine change unless an occlusion was actually suspected at the site.	
End point type	Secondary



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End point timeframe:

During 6 weeks of treatment.

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<b>End point values</b>	Faster-acting insulin aspart	NovoRapid®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	12		
Units: Number of episodes	21	4		

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAEs to be reported within 24 hours.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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### Reporting groups

Reporting group title	NovoRapid®
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Reporting group description:

Subjects received NovoRapid® for a duration of 6 weeks. The insulin dose adjustments were made based on frequent glucose measurements during contacts with the investigator. The following glycaemic targets were recommended: pre-prandial and bedtime glucose: below 6.0 mmol/L (108 mg/dL) and 2-hr postprandial glucose: below 7.8 mmol/L (140 mg/dL).

Reporting group title	Faster-acting insulin aspart
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Reporting group description:

Subjects received faster-acting insulin aspart for a duration of 6 weeks. The insulin dose adjustments were made based on frequent glucose measurements during contacts with the investigator. The following glycaemic targets were recommended: pre-prandial and bedtime glucose: below 6.0 mmol/L (108 mg/dL) and 2-hr postprandial glucose: below 7.8 mmol/L (140 mg/dL).

Serious adverse events	NovoRapid®	Faster-acting insulin aspart	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 25 (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: 5 %

Non-serious adverse events	NovoRapid®	Faster-acting insulin aspart	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 12 (50.00%)	9 / 25 (36.00%)	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	0 / 12 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Pyrexia			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 25 (4.00%) 1	
Eye disorders Diabetic retinopathy subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 25 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Oropharyngeal pain subjects affected / exposed occurrences (all)  Sinus congestion subjects affected / exposed occurrences (all)  Upper respiratory tract congestion subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2  2 / 12 (16.67%) 2  1 / 12 (8.33%) 1  1 / 12 (8.33%) 1	1 / 25 (4.00%) 1  0 / 25 (0.00%) 0  0 / 25 (0.00%) 0  0 / 25 (0.00%) 0	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)  Rash subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1  1 / 12 (8.33%) 1	0 / 25 (0.00%) 0  0 / 25 (0.00%) 0	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 25 (8.00%) 3	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)  Otitis media	1 / 12 (8.33%) 1	3 / 25 (12.00%) 3	

subjects affected / exposed	1 / 12 (8.33%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 25 (0.00%)	
occurrences (all)	1	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

The trial was designed in accordance with the draft FDA guideline dated 1985, that 15–20 subjects with diabetes given the modified insulin should be included for 6 weeks. However the trial was not powered to detect differences between treatments.

Notes: