Clinical trial results:
A trial investigating the pharmacokinetic properties of FIAsp in children, adolescents and adults with type 1 diabetes.

Summary

EudraCT number	2011-002104-32
Trial protocol	DE
Global end of trial date	24 July 2014

Results information

Result version number	v1
This version publication date	16 March 2016
First version publication date	08 February 2015

Trial information

Trial identification

Sponsor protocol code	NN1218-3888

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02035371
WHO universal trial number (UTN)	U1111-1121-1469

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the total exposure of faster-acting insulin aspart (also known as FIAsp) 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 (2008) and ICH Good Clinical Practice (1996) and FDA 21 CFR 312.120.

Background therapy:

Not applicable.

Evidence for comparator:

Not Applicable

Actual start date of recruitment	13 January 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: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	13
Adults (18-64 years)	15
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted at one site in Germany (single centre study).

Pre-assignment

Screening details:

Not applicable.

Period 1

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

Blinding implementation details:

The trial was randomised, single-centre, double-blind, single-dose, two-period cross-over trial.

Arms

Are arms mutually exclusive?	No
Arm title	Faster-acting insulin aspart first, then NovoRapid

Arm description:

Subjects received faster-acting insulin aspart followed by NovoRapid.

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

Dosage and administration details:

Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

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

Dosage and administration details:

Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

Arm title	NovoRapid first, then faster-acting insulin aspart

Arm description:

Subjects received NovoRapid first, followed by faster-acting insulin aspart.

Arm type	crossover assignment
Investigational medicinal product name	NovoRapid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Trial product dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously

in the abdomen.

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

Dosage and administration details:

Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

Number of subjects in period 1	Faster-acting insulin aspart first, then NovoRapid	NovoRapid first, then faster-acting insulin aspart
Started	21	19
Completed	19	19
Not completed	2	0
Difficulty in blood sampling in rescheduled visit	1	-
Protocol deviation	1	-

Period 2

Period 2 title	Period 2- completers
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This was randomised, single- centre, double- blind ,single dose ,two- period cross over trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	NovoRapid first, then faster-acting insulin aspart

Arm description:

Subjects received NovoRapid first followed by faster-acting insulin aspart.

Arm type	crossover assignment
Investigational medicinal product name	NovoRapid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

Investigational medicinal product name	Faster-acting insulin aspart
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

Arm title	Faster-acting insulin aspart first, then NovoRapid

Arm description:

Subjects received faster- acting insulin aspart first, followed by NovoRapid.

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

Dosage and administration details:

Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

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

Dosage and administration details:

Trial products dose level were 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

Number of subjects in period 2	NovoRapid first, then faster-acting insulin aspart	Faster-acting insulin aspart first, then NovoRapid
Started	19	19
Completed	19	19

Period 3

Period 3 title	Period 3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This trial was randomised, double-blind, single centre, single dose, two-period , cross over study.

Arms

Are arms mutually exclusive?	No

Arm title	Faster-acting insulin aspart: Children (6-11 years)

Arm description:

Subjects received faster-acting Insulin aspart followed by NovoRapid.

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

Dosage and administration details:

Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

Arm title	Faster-acting insulin aspart: Adolescents (12-17 years)

Arm description:

Subjects received faster-acting Insulin aspart followed by NovoRapid.

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

Dosage and administration details:

Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

Arm title	Faster-acting insulin aspart: Adults (18-64 years)

Arm description:

Subjects received faster-acting Insulin aspart followed by NovoRapid.

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

Dosage and administration details:

Trial products dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

Arm title	NovoRapid: Children (6-11years)

Arm description:

Subjects received NovoRapid followed by faster-acting Insulin aspart.

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

Dosage and administration details:

Trial product dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

Arm title	NovoRapid: Adolescents (12-17 years)

Arm description:

Subjects received NovoRapid followed by faster-acting Insulin aspart.

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

Dosage and administration details:

Trial product, the dose level was 0.2 U/kg body weight. The trial product were administered subcutaneously in the abdomen.

Arm title	NovoRapid: Adults (18-64 years)

Arm description:

Subjects received NovoRapid followed by faster-acting insulin aspart.

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

Dosage and administration details:

Trial product dose level was 0.2 U/kg body weight. The trial products were administered subcutaneously in the abdomen.

Number of subjects in period 3	Faster-acting insulin aspart: Children (6-11 years)	Faster-acting insulin aspart: Adolescents (12-17 years)	Faster-acting insulin aspart: Adults (18-64 years)
Started	12	13	15
Completed	12	13	13
Not completed	0	0	2
Difficulty in blood sampling in rescheduled visit	-	-	1
Protocol deviation	-	-	1

Number of subjects in period 3	NovoRapid: Children (6-11years)	NovoRapid: Adolescents (12-17 years)	NovoRapid: Adults (18-64 years)
Started	12	13	13
Completed	12	13	13
Not completed	0	0	0
Difficulty in blood sampling in rescheduled visit	-	-	-
Protocol deviation	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Period 1

Reporting group description:

Each subject were randomly allocated to a treatment sequence consisting of 2 dosing visits separated by a wash-out period of 3-22 days.

Reporting group values	Period 1	Total	
Number of subjects	40	40	
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)	12	12	
Adolescents (12-17 years)	13	13	
Adults (18-64 years)	15	15	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	18	18	
Male	22	22	

End points

End points reporting groups

Reporting group title	Faster-acting insulin aspart first, then NovoRapid
Reporting group description:	
Subjects received faster-acting insulin aspart followed by NovoRapid.	
Reporting group title	NovoRapid first, then faster-acting insulin aspart
Reporting group description:	
Subjects received NovoRapid first, followed by faster-acting insulin aspart.	
Reporting group title	NovoRapid first, then faster-acting insulin aspart
Reporting group description:	
Subjects received NovoRapid first followed by faster-acting insulin aspart.	
Reporting group title	Faster-acting insulin aspart first, then NovoRapid
Reporting group description:	
Subjects received faster- acting insulin aspart first, followed by NovoRapid.	
Reporting group title	Faster-acting insulin aspart: Children (6-11 years)
Reporting group description:	
Subjects received faster-acting Insulin aspart followed by NovoRapid.	
Reporting group title	Faster-acting insulin aspart: Adolescents (12-17 years)
Reporting group description:	
Subjects received faster-acting Insulin aspart followed by NovoRapid.	
Reporting group title	Faster-acting insulin aspart: Adults (18-64 years)
Reporting group description:	
Subjects received faster-acting Insulin aspart followed by NovoRapid.	
Reporting group title	NovoRapid: Children (6-11years)
Reporting group description:	
Subjects received NovoRapid followed by faster-acting Insulin aspart.	
Reporting group title	NovoRapid: Adolescents (12-17 years)
Reporting group description:	
Subjects received NovoRapid followed by faster-acting Insulin aspart.	
Reporting group title	NovoRapid: Adults (18-64 years)
Reporting group description:	
Subjects received NovoRapid followed by faster-acting insulin aspart.	

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

End point title	AUCIAsp, 0–12h, area under the serum insulin aspart concentration-time curve from 0 to 12 hours
End point description:	
Area under the serum insulin aspart concentration-time curve.	
End point type	Primary
End point timeframe:	
0-12 hours	

End point values	Faster-acting insulin aspart: Children (6-11 years)	Faster-acting insulin aspart: Adolescents (12-17 years)	Faster-acting insulin aspart: Adults (18-64 years)	NovoRapid: Children (6-11years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	15	12
Units: pmol h/L				
median (full range (min-max))	380.45 (308.26 to 562.02)	504.66 (411.56 to 717.09)	687.68 (465.16 to 913.32)	455.59 (250.63 to 539.3)

End point values	NovoRapid: Adolescents (12-17 years)	NovoRapid: Adults (18-64 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: pmol h/L				
median (full range (min-max))	510.56 (371.26 to 821.21)	686.89 (500.51 to 861.14)		

Statistical analyses

Statistical analysis title	AUC (0-12h) Faster Aspart : Children/Adults

Statistical analysis description:

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

Comparison groups	Faster-acting insulin aspart: Children (6-11 years) v Faster-acting insulin aspart: Adults (18-64 years)
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other[1]
Method	Mixed models analysis
Parameter estimate	Geometric-mean ratio
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.69

Notes:

[1] - Exploratory comparison

Statistical analysis title	AUC (0-12h) Faster Aspart : Adolescents/Adults

Statistical analysis description:

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

Comparison groups	Faster-acting insulin aspart: Adolescents (12-17 years) v Faster-acting insulin aspart: Adults (18-64 years)
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[2]
Method	Mixed models analysis
Parameter estimate	Geometric-mean ratio
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	0.9

Notes:

[2] - Exploratory comparison

Statistical analysis title	AUC (0-12h) NovoRapid: Children/Adults

Statistical analysis description:

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

Comparison groups	NovoRapid: Children (6-11years) v NovoRapid: Adults (18-64 years)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other[3]
Method	Mixed models analysis
Parameter estimate	Geometric-mean ratio
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.7

Notes:

[3] - Exploratory comparison

Statistical analysis title	AUC (0-12h) NovoRapid : Adolescents/Adults

Statistical analysis description:

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

Comparison groups	NovoRapid: Adolescents (12-17 years) v NovoRapid: Adults (18-64 years)

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other[4]
Method	Mixed models analysis
Parameter estimate	Geometric-mean ratio
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.87

Notes:

[4] - Exploratory comparison

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

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

End point description:

Maximum observed serum insulin aspart concentration.

End point type	Secondary

End point timeframe:

From 0-12hours

End point values	Faster-acting insulin aspart: Children (6-11 years)	Faster-acting insulin aspart: Adolescents (12-17 years)	Faster-acting insulin aspart: Adults (18-64 years)	NovoRapid: Children (6-11years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	15	12
Units: pmol/L				
median (full range (min-max))	255.1 (160.8 to 380.1)	276.8 (165 to 458.2)	257.7 (149.1 to 502.3)	271.65 (113 to 412.9)

End point values	NovoRapid: Adolescents (12-17 years)	NovoRapid: Adults (18-64 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: pmol/L				
median (full range (min-max))	261.3 (155.4 to 400.1)	267.3 (154.2 to 430.3)		

Statistical analyses

Statistical analysis title	Cmax Faster aspart : Children/Adults

Statistical analysis description:

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

Comparison groups	Faster-acting insulin aspart: Children (6-11 years) v Faster-acting insulin aspart: Adults (18-64 years)
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other[5]
Method	Mixed models analysis
Parameter estimate	Geometric-mean ratio
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.17

Notes:

[5] - Exploratory comparison

Statistical analysis title	Cmax Faster aspart : Adolescents/Adults

Statistical analysis description:

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

Comparison groups	Faster-acting insulin aspart: Adolescents (12-17 years) v Faster-acting insulin aspart: Adults (18-64 years)
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[6]
Method	Mixed models analysis
Parameter estimate	Geometric-mean ratio
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.26

Notes:

[6] - Exploratory comparison

Statistical analysis title	Cmax NovoRapid : Children/Adults

Statistical analysis description:

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

Comparison groups	NovoRapid: Children (6-11years) v NovoRapid: Adults (18-64

	years)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other[7]
Method	Mixed models analysis
Parameter estimate	Geometric-mean ratio
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.18

Notes:

[7] - Exploratory comparison

Statistical analysis title	Cmax NovoRapid : Adolescents/Adults

Statistical analysis description:

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

Comparison groups	NovoRapid: Adolescents (12-17 years) v NovoRapid: Adults (18-64 years)
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other[8]
Method	Mixed models analysis
Parameter estimate	Geometric-mean ratio
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.17

Notes:

[8] - Exploratory comparison

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events were collected at visit 2 (Day 1 and Day 2),visit 3 (Day 1, Day 2, 3-22 days after V2, D2), and Follow-up visit (7-22 days after V3, D2).

Adverse event reporting additional description:

Safety analysis set included all subjects receiving at least one dose of the IMP or its comparator. Subjects in the safety analysis set contributed to the evaluation "as treated".

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Faster-acting insulin aspart: Children (6-11years)

Reporting group description:

Subjects received faster-acting insulin aspart followed by NovoRapid.

Reporting group title	Faster-acting insulin aspart: Adolescents (12-17 years)

Reporting group description:

Subjects received faster-acting insulin aspart followed by NovoRapid.

Reporting group title	Faster-acting insulin aspart: Adults (18-64 years)

Reporting group description:

Subjects received faster-acting insulin aspart followed by NovoRapid.

Reporting group title	NovoRapid: Children (6-11years)

Reporting group description:

Subjects received NovoRapid followed by faster-acting insulin aspart.

Reporting group title	NovoRapid: Adolescents (12-17 years)

Reporting group description:

Subjects received NovoRapid followed by faster-acting insulin aspart.

Reporting group title	NovoRapid: Adults (18-64 years)

Reporting group description:

Subjects received NovoRapid followed by faster-acting insulin aspart.

Serious adverse events	Faster-acting insulin aspart: Children (6-11years)	Faster-acting insulin aspart: Adolescents (12-17 years)	Faster-acting insulin aspart: Adults (18-64 years)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	NovoRapid: Children (6-11years)	NovoRapid: Adolescents (12-17 years)	NovoRapid: Adults (18-64 years)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 13 (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: 5 %

Non-serious adverse events	Faster-acting insulin aspart: Children (6-11years)	Faster-acting insulin aspart: Adolescents (12-17 years)	Faster-acting insulin aspart: Adults (18-64 years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)	2 / 13 (15.38%)	3 / 15 (20.00%)
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Catheter site haematoma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Nausea			

subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	0 / 15 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	NovoRapid: Children (6-11years)	NovoRapid: Adolescents (12-17 years)	NovoRapid: Adults (18-64 years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	2 / 13 (15.38%)	2 / 13 (15.38%)
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Catheter site haematoma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2014	One substantial amendment was made to the protocol, and this occurred after first patient first visit. The changes introduced in the amendment were 1.Extension of the maximum time allowed between visits in order to provide more flexibility in the scheduling of patients to attend visits From 3−21 days to 3−22 days between the screening visit (V1) and the first dosing visit (V2). From 3−12 days to 3−22 days between dosing visits (V2 and V3). From 7−21 days to 7−22 days between the second dosing visit (V3) and the follow-up visit (V4) 2. The timing of the fundoscopy assessment at the screening visit (V1) was extended to allow assessment up until the day before the first dosing visit (V2), day 1 to provide more flexibility in the screening of subjects. 3. Addition of dose to the information collected for concomitant medication, in order to be consistent with the concomitant medication form.

Notes:

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.

Not applicable

Notes: