Clinical trial results:
Efficacy and Safety of FIAsp Compared to Insulin Aspart in Combination with Insulin Glargine and Metformin in Adults with Type 2 Diabetes

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2010-024051-93
Trial protocol	GB SK
Global end of trial date	22 January 2015

Results information

Result version number	v1 (current)
This version publication date	27 July 2016
First version publication date	27 July 2016

Trial information

Trial identification

Sponsor protocol code	NN1218-3853

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01819129
WHO universal trial number (UTN)	U1111-1118-2509
Other trial identifiers	Clinical Trials Registry - India ID: CTRI/2014/01/004285

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaérd, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 January 2015
Global end of trial reached?	Yes
Global end of trial date	22 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm efficacy of treatment with mealtime faster-acting insulin aspart (FIAsp) in terms of glycaemic control measured by glycosylated haemoglobin (HbA1c) after 26 weeks of randomised treatment, by comparing to meal time insulin aspart, both in combination with once daily insulin glargine and metformin, using a non-inferiority approach.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice and FDA 21 CFR 312.120.

Background therapy:

Metformin: All subjects continued their pre-trial metformin treatment without changing the frequency or dose throughout the trial.

Insulin glargine: Before randomisation, subjects were switched unit-to-unit from their previous basal insulin to once-daily insulin glargine.
During run-in period, the investigator titrated the basal insulin (insulin glargine) on a weekly basis in a treat-to-target fashion. When needed, dose adjustments of basal insulin were allowed after the run-in period also.

Evidence for comparator:

Not applicable

Actual start date of recruitment	09 September 2013
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	Canada: 23
Country: Number of subjects enrolled	Croatia: 16
Country: Number of subjects enrolled	India: 74
Country: Number of subjects enrolled	Israel: 34
Country: Number of subjects enrolled	Russian Federation: 107
Country: Number of subjects enrolled	Serbia: 95
Country: Number of subjects enrolled	United States: 262
Country: Number of subjects enrolled	Slovakia: 54
Country: Number of subjects enrolled	United Kingdom: 24
Worldwide total number of subjects	689
EEA total number of subjects	94

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)	489
From 65 to 84 years	200
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

There were 128 sites in 9 countries, which enrolled subjects in the run-in period, of which 123 sites later assigned subjects to randomised treatment: Canada: 9 sites; Croatia: 6 sites; India: 6 sites; Israel: 6 sites; Russia: 12 sites; Serbia: 9 sites; Slovakia: 5 sites; United Kingdom: 7 sites; United States: 63 sites

Pre-assignment

Screening details:

The trial included a screening visit which took place within 2 weeks prior to the run-in visit, to assess the subject's eligibility. If the subject was found eligible, the subject was to continue in the 8-week run-in period where insulin glargine was initiated and no other oral anti-diabetic treatment than metformin was allowed.

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

Blinding implementation details:

The treatment was double-blinded for the faster aspart and NovoRapid®/NovoLog® arms and insulin glargine and metformin were open-labelled. NovoRapid®/NovoLog® and faster aspart were titrated following the same recommendations, since the trial was double-blinded. In case safety committee recommended unblinding of any data, an independent adhoc group was established to maintain the blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Faster aspart

Arm description:

The subjects in this arm started on 4 units of mealtime faster aspart (subcutaneous (sc)) in combination with once-daily insulin glargine (sc) and metformin (oral) in a basal−bolus regimen. Faster aspart was administered subcutaneously 0−2 minutes before each main meal, hereafter the bolus insulin was titrated to the pre-prandial glycaemic target of 4.0−6.0 mmol/L (71−108 mg/dL) in a treat-to-target fashion in accordance with the titration guideline. Dose adjustments of faster aspart were considered daily based on pre-prandial and bedtime self-measured plasma glucose (SMPG) on the previous day. The investigator assisted the subjects for dose adjustment once weekly and subjects performed self-adjustment for the remaining days of the week. Basal insulin dose adjustments were allowed when needed. Metformin treatment continued without changing the frequency or dose.

Arm type	Experimental
Investigational medicinal product name	Faster-acting insulin aspart
Investigational medicinal product code	
Other name	Insulin aspart
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Faster aspart, 100 units/mL, 3 mL prefilled pen-injector (PDS290), for sc injection. Bolus insulin was titrated to the pre-prandial glycaemic target of 4.0−6.0 mmol/L (71−108 mg/dL) in a treat-to-target fashion.
Faster aspart dose adjustments were considered daily based on pre-prandial and bedtime SMPG on the previous day. Pre-breakfast bolus insulin was adjusted according to the pre-lunch SMPG the previous day; Pre-lunch bolus insulin was adjusted according to the pre-dinner SMPG the previous day; Pre-dinner bolus insulin was adjusted according to the bedtime SMPG the previous day. The adjustments were +1 or -1 if the pre-prandial or bedtime SMPG was >6.0 mmol/L (>108 mg/dL) or <4.0 mmol/L (<71 mg/dL), respectively. No adjustment was done when the pre-prandial or bedtime SMPG was 4.0 - 6.0 mmol/L (71-108 mg/dL).

Arm title	NovoRapid

Arm description:

The subjects in this arm started on 4 units of mealtime NovoRapid®/NovoLog® (sc) in combination with once-daily insulin glargine (sc) and metformin (oral) in a basal−bolus regimen. NovoRapid®/NovoLog® was administered subcutaneously 0−2 minutes before each main meal, hereafter the bolus insulin was titrated to the pre-prandial glycaemic target of 4.0−6.0 mmol/L (71−108 mg/dL) in a treat-to-target fashion in accordance with the titration guideline. Dose adjustments of NovoRapid®/NovoLog® were considered daily based on pre-prandial and bedtime self-measured plasma glucose (SMPG) on the previous day. The investigator assisted the subjects for dose adjustment once weekly and subjects performed self-adjustment for the remaining days of the week. Basal insulin dose adjustments were allowed when needed. Metformin treatment continued without changing the frequency or dose.

Arm type	Active comparator
Investigational medicinal product name	Insulin aspart
Investigational medicinal product code	
Other name	NovoRapid®, NovoLog®
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

NovoRapid®, 100 units/mL, 3 mL prefilled pen-injector (PDS290), for sc injection. Bolus insulin was titrated to the pre-prandial glycaemic target of 4.0−6.0 mmol/L (71−108 mg/dL) in a treat-to-target fashion.
NovoRapid®/NovoLog® dose adjustments were considered daily based on pre-prandial and bedtime SMPG on the previous day. Pre-breakfast bolus insulin was adjusted according to the pre-lunch SMPG the previous day; Pre-lunch bolus insulin was adjusted according to the pre-dinner SMPG the previous day; Pre-dinner bolus insulin was adjusted according to the bedtime SMPG the previous day. The adjustments were +1 or -1 if the pre-prandial or bedtime SMPG was >6.0 mmol/L (>108 mg/dL) or <4.0 mmol/L (<71 mg/dL), respectively. No adjustment was done when the pre-prandial or bedtime SMPG was 4.0 - 6.0 mmol/L (71-108 mg/dL).

Number of subjects in period 1	Faster aspart	NovoRapid
Started	345	344
Exposed	341	341
Completed	301	305
Not completed	44	39
Adverse event, serious fatal	1	1
Consent withdrawn by subject	15	15
Adverse event, non-fatal	1	4
Withdrawal criteria	20	15
Other, due to weight gain and hypoglycaemic events	1	-
Other, subject wanted HbA1c to be >7%	1	-
Other, subject moved out of country	-	1
Lost to follow-up	5	2
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Faster aspart

Reporting group description:

The subjects in this arm started on 4 units of mealtime faster aspart (subcutaneous (sc)) in combination with once-daily insulin glargine (sc) and metformin (oral) in a basal−bolus regimen. Faster aspart was administered subcutaneously 0−2 minutes before each main meal, hereafter the bolus insulin was titrated to the pre-prandial glycaemic target of 4.0−6.0 mmol/L (71−108 mg/dL) in a treat-to-target fashion in accordance with the titration guideline. Dose adjustments of faster aspart were considered daily based on pre-prandial and bedtime self-measured plasma glucose (SMPG) on the previous day. The investigator assisted the subjects for dose adjustment once weekly and subjects performed self-adjustment for the remaining days of the week. Basal insulin dose adjustments were allowed when needed. Metformin treatment continued without changing the frequency or dose.

Reporting group title	NovoRapid

Reporting group description:

The subjects in this arm started on 4 units of mealtime NovoRapid®/NovoLog® (sc) in combination with once-daily insulin glargine (sc) and metformin (oral) in a basal−bolus regimen. NovoRapid®/NovoLog® was administered subcutaneously 0−2 minutes before each main meal, hereafter the bolus insulin was titrated to the pre-prandial glycaemic target of 4.0−6.0 mmol/L (71−108 mg/dL) in a treat-to-target fashion in accordance with the titration guideline. Dose adjustments of NovoRapid®/NovoLog® were considered daily based on pre-prandial and bedtime self-measured plasma glucose (SMPG) on the previous day. The investigator assisted the subjects for dose adjustment once weekly and subjects performed self-adjustment for the remaining days of the week. Basal insulin dose adjustments were allowed when needed. Metformin treatment continued without changing the frequency or dose.

Reporting group values	Faster aspart	NovoRapid	Total
Number of subjects	345	344	689
Age categorical Units: Subjects			
Adults (18-64 years)	241	248	489
From 65-84 years	104	96	200
Age continuous Units: years			
arithmetic mean	59.6	59.4	
standard deviation	± 9.3	± 9.6	-
Gender categorical Units: Subjects			
Female	182	171	353
Male	163	173	336
Body weight Units: kg			
arithmetic mean	89	88.3	
standard deviation	± 16.9	± 16.7	-
HbA1c Units: percentage of haemoglobin			
arithmetic mean	7.96	7.89	
standard deviation	± 0.68	± 0.71	-

End points

End points reporting groups

Reporting group title	Faster aspart

Reporting group description:

The subjects in this arm started on 4 units of mealtime faster aspart (subcutaneous (sc)) in combination with once-daily insulin glargine (sc) and metformin (oral) in a basal−bolus regimen. Faster aspart was administered subcutaneously 0−2 minutes before each main meal, hereafter the bolus insulin was titrated to the pre-prandial glycaemic target of 4.0−6.0 mmol/L (71−108 mg/dL) in a treat-to-target fashion in accordance with the titration guideline. Dose adjustments of faster aspart were considered daily based on pre-prandial and bedtime self-measured plasma glucose (SMPG) on the previous day. The investigator assisted the subjects for dose adjustment once weekly and subjects performed self-adjustment for the remaining days of the week. Basal insulin dose adjustments were allowed when needed. Metformin treatment continued without changing the frequency or dose.

Reporting group title	NovoRapid

Reporting group description:

The subjects in this arm started on 4 units of mealtime NovoRapid®/NovoLog® (sc) in combination with once-daily insulin glargine (sc) and metformin (oral) in a basal−bolus regimen. NovoRapid®/NovoLog® was administered subcutaneously 0−2 minutes before each main meal, hereafter the bolus insulin was titrated to the pre-prandial glycaemic target of 4.0−6.0 mmol/L (71−108 mg/dL) in a treat-to-target fashion in accordance with the titration guideline. Dose adjustments of NovoRapid®/NovoLog® were considered daily based on pre-prandial and bedtime self-measured plasma glucose (SMPG) on the previous day. The investigator assisted the subjects for dose adjustment once weekly and subjects performed self-adjustment for the remaining days of the week. Basal insulin dose adjustments were allowed when needed. Metformin treatment continued without changing the frequency or dose.

Primary: Change from baseline in HbA1c

End point title	Change from baseline in HbA1c

End point description:

The analysis of this efficacy endpoint was based on the full analysis set (FAS). FAS included all randomised subjects. The statistical evaluation of the FAS was to follow the intention-to-treat (ITT) principle and subjects contributed to the evaluation ‘as randomised’. For this endpoint baseline and week 26 have been presented, where week 26 data is end of trial containing last available measurement.

End point type	Primary

End point timeframe:

After 26 weeks of randomised treatment

End point values	Faster aspart	NovoRapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345	344		
Units: percentage				
arithmetic mean (standard deviation)				
Baseline	7.96 (± 0.68)	7.89 (± 0.71)		
Week 26	6.63 (± 0.88)	6.59 (± 0.84)		

Statistical analyses

Statistical analysis title	Primary statistical analysis

Statistical analysis description:

Change from baseline in HbA1c was analysed using a mixed-effect model for repeated measurements including changes from baseline in HbA1c at visit 14, 18, 22, 26, 30 and 36. The model included treatment, region and continuous glucose monitoring (CGM) strata as fixed effects, subject as random effect, HbA1c at baseline as covariate and interaction between all fixed effects and visit, and between the covariate and visit.

Comparison groups	Faster aspart v NovoRapid
Number of subjects included in analysis	689
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.1

Notes:

[1] - The assessment was by comparing the difference of faster aspart vs. NovoRapid®/NovoLog® in change from baseline in HbA1c after 26 weeks of randomised treatment to a non-inferiority limit of 0.4%.

Secondary: Change from baseline in 2-hour PPG increment (meal test)

End point title	Change from baseline in 2-hour PPG increment (meal test)

End point description:

This endpoint was summarised using the FAS. FAS included all randomised subjects. For this endpoint baseline and week 26 have been presented, where week 26 data is end of trial containing last available measurement. Here, 'n' specifies the number of subjects with data available for 2-hour PPG increment at baseline (Faster aspart=338 and NovoRapid=331) and at week 26 (Faster aspart=342 and NovoRapid=342).

End point type	Secondary

End point timeframe:

After 26 weeks of randomised treatment

End point values	Faster aspart	NovoRapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345	344		
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline (n=338,331)	7.57 (± 3.19)	7.34 (± 3.12)		
Week 26 (n=342,342)	4.55 (± 3.13)	4.9 (± 3.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent confirmed hypoglycaemic episodes

End point title	Number of treatment emergent confirmed hypoglycaemic

	episodes

End point description:

A hypoglycaemic episode was defined as treatment-emergent if the onset of the episode was on or after the first day of exposure to randomised treatment and no later than 1 day after the last day of randomised treatment. A severe or blood glucose (BG) confirmed hypoglycaemic episode was an episode that was severe according to the American Diabetes Association (ADA) classification (an episode that required assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions) or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycaemia. This endpoint was summarised using the safety analysis set. Subjects in the safety analysis set contributed to the evaluation 'as treated'.

End point type	Secondary

End point timeframe:

From baseline to 26 weeks of randomised treatment

End point values	Faster aspart	NovoRapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341	341		
Units: Number of episodes				
Severe or BG confirmed	2857	2692		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in body weight

End point title	Change from baseline in body weight

End point description:

This endpoint was summarised using the FAS. FAS included all randomised subjects. For this endpoint baseline and week 26 have been presented, where week 26 data is end of trial containing last available measurement. Here, 'n' specifies the number of subjects with data available for body weight at baseline (Faster aspart=344 and NovoRapid=344) and at week 26 (Faster aspart=345 and NovoRapid=344).

End point type	Secondary

End point timeframe:

After 26 weeks of randomised treatment

End point values	Faster aspart	NovoRapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345	344		
Units: kg				
arithmetic mean (standard deviation)				
Baseline (n=344,344)	89 (± 16.9)	88.3 (± 16.7)		
Week 26 (n=345,344)	91.6 (± 18.2)	90.8 (± 17.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All treatment-emergent adverse events (AEs) were collected from the date on or after the first day of exposure to randomised treatment until no later than 7 days after the last day of randomised treatment.

Adverse event reporting additional description:

Safety analysis set was used for the assessment of safety including AEs. The safety analysis set included all subjects who received at least one dose of test product (faster aspart) or comparator (NovoRapid)."Note: The number of deaths causally related to treatment is the data considered to present under 'total number of deaths resulting from AEs'"

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Faster aspart

Reporting group description:

The subjects in this arm started on 4 units of mealtime faster aspart (sc) in combination with once-daily insulin glargine (sc) and metformin (oral) in a basal−bolus regimen. Faster aspart was administered subcutaneously 0−2 minutes before each main meal, hereafter the bolus insulin was titrated to the pre-prandial glycaemic target of 4.0−6.0 mmol/L (71−108 mg/dL) in a treat-to-target fashion in accordance with the titration guideline. Dose adjustments of faster aspart were considered daily based on pre-prandial and bedtime self-measured plasma glucose (SMPG) on the previous day. The investigator assisted the subjects for dose adjustment once weekly and subjects performed self-adjustment for the remaining days of the week. Basal insulin dose adjustments were allowed when needed. Metformin treatment continued without changing the frequency or dose.

Reporting group title	NovoRapid

Reporting group description:

The subjects in this arm started on 4 units of mealtime NovoRapid®/NovoLog® (sc) in combination with once-daily insulin glargine (sc) and metformin (oral) in a basal−bolus regimen. NovoRapid®/NovoLog® was administered subcutaneously 0−2 minutes before each main meal, hereafter the bolus insulin was titrated to the pre-prandial glycaemic target of 4.0−6.0 mmol/L (71−108 mg/dL) in a treat-to-target fashion in accordance with the titration guideline. Dose adjustments of NovoRapid®/NovoLog® were considered daily based on pre-prandial and bedtime self-measured plasma glucose (SMPG) on the previous day. The investigator assisted the subjects for dose adjustment once weekly and subjects performed self-adjustment for the remaining days of the week. Basal insulin dose adjustments were allowed when needed. Metformin treatment continued without changing the frequency or dose.

Serious adverse events	Faster aspart	NovoRapid	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 341 (4.40%)	24 / 341 (7.04%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cardiac myxoma			
subjects affected / exposed	1 / 341 (0.29%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Refractory anaemia with an excess of blasts			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer stage II			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	2 / 341 (0.59%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 341 (0.29%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	1 / 341 (0.29%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery bypass			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	1 / 341 (0.29%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Investigations			
Arteriogram coronary			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 341 (0.00%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrong drug administered			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 341 (0.29%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina unstable			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 341 (0.29%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myocardial ischaemia			
subjects affected / exposed	1 / 341 (0.29%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery occlusion			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 341 (0.00%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 341 (0.00%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	1 / 341 (0.29%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Aural polyp			
subjects affected / exposed	1 / 341 (0.29%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ischaemic			

subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric polyps			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stasis dermatitis			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 341 (0.29%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cholecystitis infective			
subjects affected / exposed	1 / 341 (0.29%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 341 (0.29%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 341 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	1 / 341 (0.29%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 341 (0.29%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	2 / 341 (0.59%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	4 / 4	5 / 5	
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	49 / 341 (14.37%)	53 / 341 (15.54%)	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	16 / 341 (4.69%)	22 / 341 (6.45%)	
occurrences (all)	19	27	

Nasopharyngitis			
subjects affected / exposed	17 / 341 (4.99%)	24 / 341 (7.04%)	
occurrences (all)	20	27	
Urinary tract infection			
subjects affected / exposed	20 / 341 (5.87%)	13 / 341 (3.81%)	
occurrences (all)	27	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2013	To support the cardiovascular risk assessment and analysis, a 30-day follow-up visit was introduced to collect information on potential major adverse cardiovascular events occurring in the follow-up period and furthermore, smoking history was collected for all subjects at randomisation. Post-trial diabetes treatment was collected after end-of-treatment and was used for causality assessment of AEs and possible cardiovascular events in the follow-up period. The CGM data collection period was increased from 3−7 days to 10−14 days with the simultaneous decrease from 120 to 60 subjects in the CGM subgroup. This was done in order to have more reliable CGM data from individual subjects at fewer clinical sites, thus improving data quality. The ADA classification of hypoglycaemia was updated to reflect the latest ADA classification. Based on a request during the approval of another phase 3a trial in the faster aspart development program, the text was updated so sponsor was not to be contacted prior to breaking the blinded code and also a section about handling of missing data was included. To comply with Clinical Data Interchange Standards Consortium terminology, the final outcome definition of AEs was updated. The master subject information/informed consent form and the CGM diaries were updated according to the protocol implemented changes as applicable.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported