



Clinical trial results:

Efficacy and Safety of FIAsp compared to insulin aspart both in Combination with insulin detemir in Adults with Type 1 Diabetes

Summary

EudraCT number	2010-024049-53
Trial protocol	BE HU CZ GB DE PL FI
Global end of trial date	11 June 2015

Results information

Result version number	v1 (current)
This version publication date	26 June 2016
First version publication date	26 June 2016

Trial information

Trial identification

Sponsor protocol code	NN1218-3852
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01831765
WHO universal trial number (UTN)	U1111-1118-2442

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 June 2015
Global end of trial reached?	Yes
Global end of trial date	11 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm efficacy of treatment with meal time faster-acting insulin aspart (FIAsp) in terms of glycaemic control measured by change from baseline in glycosylated haemoglobin (HbA1c) after 26 weeks of randomised treatment by comparing it to meal time insulin aspart both in combination with insulin detemir, using a non-inferiority approach.

Protection of trial subjects:

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

Background therapy:

Insulin detemir, a long-acting insulin analogue was used as part of a basal–bolus insulin regimen. During run-in, insulin detemir was titrated in a treat-to-target fashion on a weekly basis to the prebreakfast glycaemic target of 4.0–5.0 mmol/L (71–90 mg/dL) and the predinner glycaemic target of 4.0–6.0 mmol/L (71–108 mg/dL) if the subject was on a twice daily regimen, in accordance with the titration guideline. When needed, dose adjustments of basal insulin were allowed after the run-in period at the discretion of the investigator. However, changing the dose frequency after randomisation was not allowed.

Evidence for comparator:

Not applicable

Actual start date of recruitment	26 August 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	Poland: 66
Country: Number of subjects enrolled	United Kingdom: 60
Country: Number of subjects enrolled	Belgium: 27
Country: Number of subjects enrolled	Czech Republic: 48
Country: Number of subjects enrolled	Finland: 28
Country: Number of subjects enrolled	Germany: 193
Country: Number of subjects enrolled	Hungary: 46
Country: Number of subjects enrolled	United States: 603
Country: Number of subjects enrolled	Canada: 72
Worldwide total number of subjects	1143
EEA total number of subjects	468

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)	1057
From 65 to 84 years	86
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 165 sites in 9 countries, as follows: Belgium: 5 sites, Canada: 12 sites, Czech Republic: 5 sites; Finland: 6 sites; Germany: 25 sites; Hungary: 5 sites; Poland: 6 sites; United Kingdom: 9 sites; United States: 92 sites.

Pre-assignment

Screening details:

Screening visit was within 2 weeks prior to run-in visit to assess subject's eligibility. Visit 2 (week - 8), subjects confirmed eligible enrolled in 8-week run-in period during which basal insulin treatment was optimised using treat-to-target approach. All subjects received once/twice daily insulin detemir and NovoRapid®/NovoLog® during 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	Subject, Investigator

Blinding implementation details:

The treatment was double-blinded for the mealtime faster aspart and NovoRapid®/NovoLog® arms and open-labelled for the postmeal faster aspart arm all in combination with open label insulin detemir. 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 (meal)

Arm description:

The subjects in this arm were administered mealtime faster aspart in combination with once or twice daily insulin detemir in a basal-bolus regimen. Mealtime faster aspart was administered subcutaneously 0–2 minutes before each main meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.

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 U/mL solution for subcutaneous injection was provided in a prefilled 3 mL PDS290 peninjector (blinded for the mealtime arm). Insulin detemir (Levemir®), 100 U/mL solution for subcutaneous injection was provided in a 3 mL FlexPen®. The dose of faster aspart was titrated to the premeal or bedtime glycaemic target of 4.0–6.0 mmol/L (71–108 mg/dL) using either predefined bolus-dosing algorithm or using principles of flexible dosing based on the meal carbohydrate content. Bolus titration took place twice weekly for subjects who followed the pre-defined bolus dosing algorithms. At the scheduled visit, the investigator titrated based on the previous 3 or 4 days and the subject titrated based on the remaining data as appropriate between scheduled visit as instructed by the investigator. Subjects using the principles of flexible dosing based on the meal carbohydrate content continued to do so, and adjusted the dose several times daily.

Arm title	Faster aspart (post)
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Arm description:

The subjects in this arm were administered postmeal faster aspart in combination with once or twice daily insulin detemir in a basal-bolus regimen. Postmeal faster aspart was administered subcutaneously 20 minutes after the start of the meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.

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 U/mL solution for subcutaneous injection was provided in a prefilled 3 mL PDS290 peninjector (open-label for the postmeal arm). Insulin detemir (Levemir®), 100 U/mL solution for subcutaneous injection was provided in a 3 mL FlexPen®. The dose of faster aspart was titrated to the premeal or bedtime glycaemic target of 4.0–6.0 mmol/L (71–108 mg/dL) using either using a predefined bolus-dosing algorithm or using the principles of flexible dosing based on the meal carbohydrate content. Bolus titration took place twice weekly for subjects who followed the pre-defined bolus dosing algorithms. At the scheduled visit, the investigator titrated based on the last 3 or 4 previous days and the subject titrated based on the remaining data as appropriate between scheduled visit as instructed by the investigator. Subjects using the principles of flexible dosing based on the meal carbohydrate content continued to do so, and adjusted the dose several times daily.

Arm title	NovoRapid (meal)
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Arm description:

The subjects in this arm were administered mealtime NovoRapid®/NovoLog® in combination with once or twice daily insulin detemir in a basal-bolus regimen. Mealtime NovoRapid®/NovoLog® was administered subcutaneously 0–2 minutes before each main meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.

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®/NovoLog®, 100 U/mL solution for subcutaneous injection was provided in a prefilled 3 mL PDS290 pen-injector. Insulin detemir (Levemir®), 100 U/mL solution for subcutaneous injection was provided in a 3 mL FlexPen®. The dose of NovoRapid®/NovoLog® was titrated to the premeal or bedtime glycaemic target of 4.0–6.0 mmol/L (71–108 mg/dL) using either using a predefined bolus-dosing algorithm or using the principles of flexible dosing based on the meal carbohydrate content. Bolus titration took place twice weekly for subjects who followed the pre-defined bolus dosing algorithms. At the scheduled visit, the investigator titrated based on the previous 3 or 4 days and the subject titrated based on the remaining data as appropriate between scheduled visit as instructed by the investigator. Subjects using the principles of flexible dosing based on the meal carbohydrate content continued to do so, and adjusted the dose several times daily.

Number of subjects in period 1	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)
Started	381	382	380
Completed 26 weeks	351	355	356
Completed 52 weeks	337	0 ^[1]	338
Completed	337	355	338
Not completed	44	27	42
Adverse event, serious fatal	-	1	1
Consent withdrawn by subject	22	7	17
Other, sponsor and PI decided to close site	1	1	-
Adverse event, non-fatal	5	3	3
Withdrawal criteria	12	10	16
Pregnancy	1	1	2
Lost to follow-up	2	3	3
Other, sponsor withdrew subject	-	1	-
Lack of efficacy	1	-	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This group did not continue in the study after 26 weeks. The completed subjects for this group represents the treatment period till 26 weeks, while completed for other groups represents treatment period till 52 weeks.

Baseline characteristics

Reporting groups

Reporting group title	Faster aspart (meal)
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Reporting group description:

The subjects in this arm were administered mealtime faster aspart in combination with once or twice daily insulin detemir in a basal–bolus regimen. Mealtime faster aspart was administered subcutaneously 0–2 minutes before each main meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.

Reporting group title	Faster aspart (post)
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Reporting group description:

The subjects in this arm were administered postmeal faster aspart in combination with once or twice daily insulin detemir in a basal–bolus regimen. Postmeal faster aspart was administered subcutaneously 20 minutes after the start of the meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.

Reporting group title	NovoRapid (meal)
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Reporting group description:

The subjects in this arm were administered mealtime NovoRapid®/NovoLog® in combination with once or twice daily insulin detemir in a basal-bolus regimen. Mealtime NovoRapid®/NovoLog® was administered subcutaneously 0–2 minutes before each main meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.

Reporting group values	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)
Number of subjects	381	382	380
Age categorical			
Units: Subjects			
Adults (18-64 years)	346	359	352
From 65-84 years	35	23	28
Age continuous			
Units: years			
arithmetic mean	46.1	43.5	43.7
standard deviation	± 13.8	± 13.7	± 14
Gender categorical			
Units: Subjects			
Female	166	163	142
Male	215	219	238
Body weight			
Units: kg			
arithmetic mean	78.56	80.49	80.15
standard deviation	± 14.89	± 15.93	± 15.21
HbA1c			
Units: % of haemoglobin			
arithmetic mean	7.62	7.63	7.58

standard deviation	± 0.71	± 0.72	± 0.68
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Reporting group values	Total		
Number of subjects	1143		
Age categorical Units: Subjects			
Adults (18-64 years)	1057		
From 65-84 years	86		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	471		
Male	672		
Body weight Units: kg arithmetic mean standard deviation	-		
HbA1c Units: % of haemoglobin arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Faster aspart (meal)
Reporting group description: The subjects in this arm were administered mealtime faster aspart in combination with once or twice daily insulin detemir in a basal–bolus regimen. Mealtime faster aspart was administered subcutaneously 0–2 minutes before each main meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.	
Reporting group title	Faster aspart (post)
Reporting group description: The subjects in this arm were administered postmeal faster aspart in combination with once or twice daily insulin detemir in a basal–bolus regimen. Postmeal faster aspart was administered subcutaneously 20 minutes after the start of the meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.	
Reporting group title	NovoRapid (meal)
Reporting group description: The subjects in this arm were administered mealtime NovoRapid®/NovoLog® in combination with once or twice daily insulin detemir in a basal-bolus regimen. Mealtime NovoRapid®/NovoLog® was administered subcutaneously 0–2 minutes before each main meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation.	
Subject analysis set title	Faster aspart (meal)-as treated
Subject analysis set type	Safety analysis
Subject analysis set description: The subjects in this arm were administered mealtime faster aspart in combination with once or twice daily insulin detemir in basal–bolus regimen. Mealtime faster aspart was administered subcutaneously 0–2 minutes before each main meal. Subjects who prior to screening had used principles of flexible dosing based on meal carbohydrate content, and who were assessed by investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during treatment period. All other subjects were to use predefined bolus-dosing algorithm to adjust bolus dose during treatment period. Additional bolus dosing was allowed at investigator's recommendation. A total of 5 subjects were randomised to the postmeal faster aspart arm but had consistently throughout the trial taken their bolus insulin before the meal, hence were included as treated in the safety analysis set for this arm (number of subjects: 386).	
Subject analysis set title	Faster aspart (post)-as treated
Subject analysis set type	Safety analysis
Subject analysis set description: The subjects in this arm were administered postmeal faster aspart in combination with once or twice daily insulin detemir in basal–bolus regimen. Postmeal faster aspart was administered subcutaneously 20 minutes after start of meal. Subjects who prior to screening had used principles of flexible dosing based on meal carbohydrate content, and who were assessed by investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during treatment period. All other subjects were to use predefined bolus-dosing algorithm to adjust bolus dose during treatment period. Additional bolus dosing was allowed at investigator's recommendation. A total of 5 subjects were randomised to the postmeal faster aspart arm but had consistently throughout the trial taken their bolus insulin before the meal, hence were included as treated and included in the mealtime faster aspart arm instead (number of subjects: 377).	
Subject analysis set title	NovoRapid (meal)-as treated
Subject analysis set type	Safety analysis

Subject analysis set description:

The subjects in this arm were administered mealtime NovoRapid®/NovoLog® in combination with once or twice daily insulin detemir in a basal-bolus regimen. Mealtime NovoRapid®/NovoLog® was administered subcutaneously 0–2 minutes before each main meal. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation. Number of subjects in this arm: 380.

Primary: Change from baseline in HbA1c

End point title	Change from baseline in HbA1c
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End point description:

Change from baseline in HbA1c after 26 weeks of randomised treatment.

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
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End point timeframe:

After 26 weeks of randomised treatment

End point values	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	380	
Units: percentage				
arithmetic mean (standard deviation)				
Baseline	7.62 (± 0.71)	7.63 (± 0.72)	7.58 (± 0.68)	
Week 26	7.31 (± 0.77)	7.51 (± 0.77)	7.42 (± 0.78)	

Statistical analyses

Statistical analysis title	Primary statistical analysis
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Statistical analysis description:

Change from baseline in HbA1c analysed using a mixed-effect model for repeated measurements including visit 14, 18, 22, 26, 30, 34 and 36. The model included treatment, region and strata (combination of bolus adjusting method, basal treatment regimen and continuous glucose monitoring (CGM) and frequently sampled meal test subgroup) as fixed effects, subject as random effect, baseline HbA1c as covariate and interaction between all fixed effects and visit, and between the covariate and visit.

Comparison groups	Faster aspart (meal) v NovoRapid (meal)
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Number of subjects included in analysis	761
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Analysis specification	Pre-specified
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Analysis type	non-inferiority ^[1]
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Parameter estimate	Mean difference (final values)
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Point estimate	-0.15
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Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	-0.07

Notes:

[1] - Noninferiority was considered confirmed if the upper boundary of the two-sided 95% CI was below or equal to 0.4% or equivalent if the p-value for noninferiority for the one-sided test of null hypothesis (H0): $D > 0.4\%$ against the alternative hypothesis (HA): $D \leq 0.4\%$, was less than or equal to 2.5%, where D is the mean treatment difference (mealtime faster aspart minus NovoRapid®/NovoLog®).

Statistical analysis title	Primary statistical analysis
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Statistical analysis description:

Change from baseline in HbA1c analysed using a mixed-effect model for repeated measurements including visit 14, 18, 22, 26, 30, 34 and 36. The model included treatment, region and strata (combination of bolus adjusting method, basal treatment regimen and continuous glucose monitoring (CGM) and frequently sampled meal test subgroup) as fixed effects, subject as random effect, baseline HbA1c as covariate and interaction between all fixed effects and visit, and between the covariate and visit.

Comparison groups	Faster aspart (post) v NovoRapid (meal)
Number of subjects included in analysis	762
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.12

Notes:

[2] - Noninferiority was considered confirmed if the upper boundary of the two-sided 95% CI was below or equal to 0.4% or equivalent if the p-value for noninferiority for the one-sided test of null hypothesis (H0): $D > 0.4\%$ against the alternative hypothesis (HA): $D \leq 0.4\%$, was less than or equal to 2.5%, where D is the mean treatment difference (postmeal faster aspart minus NovoRapid®/NovoLog®).

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

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

Change from baseline in 2-hour PPG increments after 26 weeks of randomised treatment (meal test). The analysis of this efficacy endpoint was based on 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 (meal) = 379, Faster aspart (post) = 377 and NovoRapid (meal) = 375) and at week 26 (Faster aspart (meal) = 381, Faster aspart (post) = 382 and NovoRapid (meal) = 380).

End point type	Secondary
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End point timeframe:

After 26 weeks of randomised treatment

End point values	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	380	
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline (n = 379, 377, 375)	6.06 (± 5.16)	6.06 (± 4.9)	6.24 (± 4.81)	
Week 26 (n = 381, 382, 380)	5.88 (± 4.67)	6.73 (± 4.67)	6.55 (± 4.78)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in HbA1c (post meal arm)

End point title	Change from baseline in HbA1c (post meal arm) ^[3]
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End point description:

Change from baseline in HbA1c (post meal arm) after 26 weeks of randomised treatment. 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.

End point type	Secondary
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End point timeframe:

After 26 weeks of randomised treatment

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The change from baseline in HbA1c was analysed here for the postmeal faster aspart versus NovoRapid®/NovoLog® and hence the data is provided for the faster aspart (post) and the NovoRapid (meal) arm.

End point values	Faster aspart (post)	NovoRapid (meal)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	382	380		
Units: Percentage				
arithmetic mean (standard deviation)				
Baseline	7.63 (± 0.72)	7.58 (± 0.68)		
Week 26	7.51 (± 0.77)	7.42 (± 0.78)		

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
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End point description:

Number of treatment-emergent severe or BG confirmed hypoglycaemic episodes from baseline until week 26. 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. Severe or BG confirmed is an episode that is severe according to the American Diabetes Association (ADA) classification (an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions) or BG confirmed by a PG value <3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycaemia. This endpoint was summarized using the safety analysis set.

End point type	Secondary
End point timeframe:	
From baseline until 26 weeks of randomised treatment	

End point values	Faster aspart (meal)-as treated	Faster aspart (post)-as treated	NovoRapid (meal)-as treated	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	386	377	380	
Units: Number of episodes				
Severe or BG confirmed	5899	5443	5865	

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:	
Change from baseline in body weight after 26 weeks of randomised treatment. 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 (meal) = 381, Faster aspart (post) = 382 and NovoRapid (meal) = 378) and at week 26 (Faster aspart (meal) = 381, Faster aspart (post) = 382 and NovoRapid (meal) = 380).	
End point type	Secondary
End point timeframe:	
After 26 weeks of randomised treatment	

End point values	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	381	382	380	
Units: kg				
arithmetic mean (standard deviation)				
Baseline (n=381, 382, 378)	78.56 (± 14.89)	80.49 (± 15.93)	80.21 (± 15.21)	
Week 26 (n=381, 382, 380)	79.21 (± 15.25)	81.17 (± 16.45)	80.69 (± 15.44)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events

End point title	Adverse events
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End point description:

All treatment emergent adverse events (TEAEs) from baseline until 52 weeks of randomised treatment. A TEAE was defined as an event that had an onset date on or after the first day of exposure to randomised treatment, and no later than 7 days after the last day of randomised treatment.

End point type	Secondary
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End point timeframe:

From the first day of exposure to randomised treatment and until 26 +1 weeks [faster aspart (post)] or until 26+26+1 weeks [faster aspart (meal) and NovoRapid®/NovoLog® (meal)].

End point values	Faster aspart (meal)-as treated	Faster aspart (post)-as treated	NovoRapid (meal)-as treated	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	386	377	380	
Units: event rate/100 patient yrs of exposure				
number (not applicable)	445.8	441	411	

Statistical analyses

No statistical analyses for this end point

Secondary: HbA1c

End point title	HbA1c ^[4]
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End point description:

Change from baseline in HbA1c (%) after 52 weeks of randomised treatment. This endpoint was summarised using the FAS. FAS included all randomised subjects. The statistical evaluation of the FAS was to follow the ITT principle and subjects contributed to the evaluation 'as randomised'. For this endpoint, baseline and week 52 have been presented, where week 52 data is the end of trial containing last available measurement.

End point type	Secondary
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End point timeframe:

After 52 weeks of randomised treatment

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The change from baseline in HbA1c after 52 weeks of randomised treatment is reported

here. The subjects in the postmeal arm did not enter the additional 26-week treatment period and hence the data is provided for the faster aspart (meal) and the NovoRapid (meal) arm.

End point values	Faster aspart (meal)	NovoRapid (meal)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	381	380		
Units: percentage				
arithmetic mean (standard deviation)				
Baseline	7.62 (± 0.71)	7.58 (± 0.68)		
Week 52	7.51 (± 0.83)	7.58 (± 0.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Postprandial glucose (PPG)

End point title	Postprandial glucose (PPG) ^[5]
End point description:	
Change from baseline in PPG and PPG increment (meal test) after 52 weeks of randomised treatment. This endpoint was summarised using the FAS. FAS included all randomised subjects. For this endpoint, baseline and week 52 have been presented, where week 52 data is the end of trial containing last available measurement. Here, 'n' specifies the number of subjects with data available for PPG at baseline [Faster aspart (meal) =379 and NovoRapid (meal) =379] and at week 52 [Faster aspart (meal) =380 and NovoRapid (meal) =380]. The number of subjects with data available for PPG increment at 120 mins at baseline [Faster aspart (meal) =379 and NovoRapid (meal) =379] and at week 52 [Faster aspart (meal) =380 and NovoRapid (meal) =380] is also presented.	
End point type	Secondary
End point timeframe:	
After 52 weeks of randomised treatment	

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The change from baseline in PPG and PPG increment (meal test) for mealtime faster aspart group and the NovoRapid®/NovoLog® group after 52 weeks of randomised treatment is reported here. The subjects in the postmeal arm did not enter the additional 26-week treatment period and hence the data is provided for the faster aspart (meal) and the NovoRapid (meal) arm.

End point values	Faster aspart (meal)	NovoRapid (meal)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	381	380		
Units: mmol/L				
arithmetic mean (standard deviation)				
PPG at 120 minutes (Baseline) (n=379,379)	14.51 (± 6.09)	14.14 (± 5.69)		
PPG at 120 minutes (Week 52) (n=380,380)	14.26 (± 5.76)	14.51 (± 6.02)		
PPG increment at 120 mins (Baseline) (n=379,375)	6.06 (± 5.16)	6.24 (± 4.81)		
PPG increment at 120 mins(Week 52) (n=381,380)	5.71 (± 4.92)	6.14 (± 4.86)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Until 52 (26+26) weeks of treatment + 1 week of follow-up for faster aspart (meal) and NovoRapid®/NovoLog®(meal) or until 26 weeks of treatment + 1 week of follow-up for faster aspart (post).

Adverse event reporting additional description:

All TEAEs are summarised. A TEAE defined as an event that had an onset date on or after first day of exposure to randomised treatment, and no later than 7 days after the last day of randomised treatment. Note: number of deaths causally related to treatment is the data considered to present under 'total number of deaths resulting from adverse events'.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Faster aspart (meal)-as treated
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Reporting group description:

The subjects in this arm were administered mealtime faster aspart in combination with once or twice daily insulin detemir in a basal-bolus regimen. Mealtime faster aspart was administered subcutaneously 0-2 minutes before each main meal for 52 weeks. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation. A total of 5 subjects were randomised to the postmeal faster aspart arm but had consistently throughout the trial taken their bolus insulin before the meal, hence were included as treated in the safety analysis set for this arm (number of subjects: 386)

Reporting group title	Faster aspart (post)-as treated
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Reporting group description:

The subjects in this arm were administered postmeal faster aspart in combination with once or twice daily insulin detemir in a basal-bolus regimen. Postmeal faster aspart was administered subcutaneously 20 minutes after the start of the meal for 26 weeks. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation. A total of 5 subjects were randomised to the postmeal faster aspart arm but had consistently throughout the trial taken their bolus insulin before the meal, hence were included as treated and included in the mealtime faster aspart arm instead (number of subjects: 377).

Reporting group title	NovoRapid (meal)-as treated
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Reporting group description:

The subjects in this arm were administered mealtime NovoRapid®/NovoLog® in combination with once or twice daily insulin detemir in a basal-bolus regimen. Mealtime NovoRapid®/NovoLog® was administered subcutaneously 0-2 minutes before each main meal for 52 weeks. Subjects who, prior to screening, had used the principles of flexible dosing based on the meal carbohydrate content, and who were assessed by the investigator to be adequately trained in this method, were to continue using this method for bolus adjustment during the treatment period. All other subjects were to use a predefined bolus-dosing algorithm to adjust the bolus dose during the treatment period. Additional bolus dosing was allowed at the investigator's recommendation. Number of subjects in this arm: 380.

Serious adverse events	Faster aspart (meal)-as treated	Faster aspart (post)-as treated	NovoRapid (meal)-as treated
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 386 (9.07%)	28 / 377 (7.43%)	33 / 380 (8.68%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aneurysm			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Coronary arterial stent insertion			

subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary revascularisation			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Nasal septum deviation			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood glucose decreased			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular evaluation			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			

subjects affected / exposed	1 / 386 (0.26%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	2 / 386 (0.52%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			

subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrong drug administered			
subjects affected / exposed	1 / 386 (0.26%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 386 (0.26%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic seizure			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic unconsciousness			
subjects affected / exposed	5 / 386 (1.30%)	3 / 377 (0.80%)	4 / 380 (1.05%)
occurrences causally related to treatment / all	7 / 8	3 / 3	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis microscopic			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal fibrosis			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Compartment syndrome			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint stiffness			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscal degeneration			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			

subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal cyst			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 386 (0.26%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 386 (0.00%)	0 / 377 (0.00%)	1 / 380 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis			

subjects affected / exposed	1 / 386 (0.26%)	0 / 377 (0.00%)	2 / 380 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	12 / 386 (3.11%)	11 / 377 (2.92%)	10 / 380 (2.63%)
occurrences causally related to treatment / all	10 / 16	7 / 11	8 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	0 / 386 (0.00%)	1 / 377 (0.27%)	0 / 380 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Faster aspart (meal)-as treated	Faster aspart (post)-as treated	NovoRapid (meal)-as treated
Total subjects affected by non-serious adverse events			
subjects affected / exposed	252 / 386 (65.28%)	189 / 377 (50.13%)	236 / 380 (62.11%)
Injury, poisoning and procedural complications			
Wrong drug administered			
subjects affected / exposed	22 / 386 (5.70%)	18 / 377 (4.77%)	23 / 380 (6.05%)
occurrences (all)	31	20	28
Nervous system disorders			
Headache			
subjects affected / exposed	37 / 386 (9.59%)	26 / 377 (6.90%)	45 / 380 (11.84%)
occurrences (all)	70	41	79
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	27 / 386 (6.99%)	11 / 377 (2.92%)	27 / 380 (7.11%)
occurrences (all)	34	11	33
Nausea			
subjects affected / exposed	28 / 386 (7.25%)	18 / 377 (4.77%)	23 / 380 (6.05%)
occurrences (all)	36	29	34
Vomiting			
subjects affected / exposed	19 / 386 (4.92%)	15 / 377 (3.98%)	25 / 380 (6.58%)
occurrences (all)	23	16	30

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 386 (4.40%)	12 / 377 (3.18%)	20 / 380 (5.26%)
occurrences (all)	21	13	21
Oropharyngeal pain			
subjects affected / exposed	17 / 386 (4.40%)	16 / 377 (4.24%)	23 / 380 (6.05%)
occurrences (all)	22	21	30
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	28 / 386 (7.25%)	15 / 377 (3.98%)	20 / 380 (5.26%)
occurrences (all)	36	17	22
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	20 / 386 (5.18%)	8 / 377 (2.12%)	17 / 380 (4.47%)
occurrences (all)	25	8	21
Influenza			
subjects affected / exposed	22 / 386 (5.70%)	11 / 377 (2.92%)	37 / 380 (9.74%)
occurrences (all)	30	12	54
Nasopharyngitis			
subjects affected / exposed	128 / 386 (33.16%)	90 / 377 (23.87%)	120 / 380 (31.58%)
occurrences (all)	214	111	174
Sinusitis			
subjects affected / exposed	19 / 386 (4.92%)	7 / 377 (1.86%)	28 / 380 (7.37%)
occurrences (all)	21	7	37
Upper respiratory tract infection			
subjects affected / exposed	56 / 386 (14.51%)	28 / 377 (7.43%)	40 / 380 (10.53%)
occurrences (all)	75	31	61
Urinary tract infection			
subjects affected / exposed	20 / 386 (5.18%)	15 / 377 (3.98%)	18 / 380 (4.74%)
occurrences (all)	25	20	29

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 July 2013	A 30-day follow-up period was introduced in order to collect information on potential major cardiovascular events (MACE) to support cardiovascular risk assessment. Furthermore, collection of smoking history (to support cardiovascular risk analysis) and new diabetes treatment after end of trial treatment was introduced for all subjects at randomisation. The continuous glucose monitoring (CGM) data collection period was increased from 3–7 days to 10–14 days with the simultaneous decrease from 180 to 90 subjects in the CGM and frequently sampled meal test subgroup. This was done in order to improve data quality by having more CGM data from individual subjects at fewer clinical sites. The ADA classification of hypoglycaemia was updated to reflect the latest ADA classification. France was replaced by Finland.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported