Clinical trial results:
Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid® both in combination with Insulin Degludec in Adults with Type 1 Diabetes

Summary

EudraCT number	2015-001047-36
Trial protocol	BG DE AT IT
Global end of trial date	16 August 2017

Results information

Result version number	v1 (current)
This version publication date	30 August 2018
First version publication date	30 August 2018

Trial information

Trial identification

Sponsor protocol code	NN1218-4131

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02500706
WHO universal trial number (UTN)	U1111-1167-9495

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 July 2017
Global end of trial reached?	Yes
Global end of trial date	16 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the effect in terms of glycaemic control of treatment with mealtime faster-acting insulin aspart in combination with insulin degludec in adults with type 1 diabetes mellitus

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) and ICH GCP (1996) and FDA 21 CFR 312.120.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	04 May 2016
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	Austria: 24
Country: Number of subjects enrolled	Bulgaria: 72
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	Germany: 45
Country: Number of subjects enrolled	India: 103
Country: Number of subjects enrolled	Israel: 33
Country: Number of subjects enrolled	Italy: 41
Country: Number of subjects enrolled	Japan: 245
Country: Number of subjects enrolled	Russian Federation: 92
Country: Number of subjects enrolled	Serbia: 38
Country: Number of subjects enrolled	Taiwan: 31
Country: Number of subjects enrolled	United States: 269
Worldwide total number of subjects	1025
EEA total number of subjects	182

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)	964
From 65 to 84 years	61
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 146 sites in 12 countries(number of sites indicates those that both screened and randomised subjects, unless otherwise noted)-Austria(4);Bulgaria(8); Canada(6); Germany(7); India(16); Israel(6); Italy(4); Japan(24); Russian Federation(10); Serbia(3); Taiwan(3); United States(55 sites screened/52 sites randomised subjects)

Pre-assignment

Screening details:

Eligible subjects were enrolled in an 8-week run-in period (1108 subjects) where subjects were switched from previous insulin treatment to insulin degludec once daily,and NovoRapid®/NovoLog® as mealtime bolus insulin. The basal insulin treatment was optimised using treat-to-target approach. 83 subjects were run-in failures and 1025 were randomised.

Period 1

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

Blinding implementation details:

The trial was partly double-blinded. The bolus treatment was double-blind for the mealtime faster aspart and NovoRapid®/NovoLog® treatment arms and open-label for the postmeal faster aspart treatment arm.

Arms

Are arms mutually exclusive?	Yes
Arm title	Faster aspart (meal)

Arm description:

Bolus insulin: Participants received subcutaneous (s.c., into the abdominal wall) injections of faster-acting insulin aspart at mealtime (0−2 minutes before the meal) during 26-week treatment period. Throughout the trial, the insulin was administered at each of the three main meals (i.e. breakfast, lunch and main evening meal). The insulin was titrated to the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0–6.0 mmol/L (71–108 mg/dL) in a treat-to-target fashion.
Basal insulin: Participants continued insulin degludec once daily s.c. injections at the dose optimized during run-in period during 26-week treatment period.

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:

Faster-acting insulin aspart was administered 0−2 minutes before each of the three main meals (i.e. breakfast, lunch and main evening meal). No adjustments of faster-acting insulin aspart dose was performed by the investigator during run-in. During the 26-week treatment period, the investigator focussed on optimising the bolus insulin. The bolus insulin was titrated to the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0–6.0 mmol/L [71–108 mg/dL] in a treat-to-target fashion.

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

Dosage and administration details:

Insulin degludec was administered once daily at any time of the day, preferably at the same time every day and injected subcutaneously into the thigh, or upper arm (deltoid area). During the 8-week run-in period, the investigator focussed on optimising the treatment by using a treat-to-target approach; the basal insulin was titrated by the investigator on a weekly basis to the pre-breakfast glycaemic target of 4.0-5.0 mmol/L (71-90 mg/dL). Further adjustments of the basal insulin dose during the treatment period were done at the discretion of the Investigator, if needed.

Arm title	Faster aspart (post)

Arm description:

Bolus insulin: Participants received s.c. injections of faster-acting insulin aspart at mealtime (injecting the bolus insulin at the end of the meal but no later than 20 minutes after the start of the meal) during 26-week treatment period. Throughout the trial, the insulin was administered at each of the three main meals (i.e. breakfast, lunch and main evening meal). The insulin was titrated to the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0–6.0 mmol/L (71–108 mg/dL) in a treat-to-target fashion.
Basal insulin: Participants continued insulin degludec once daily s.c. injections at the dose optimized during run-in period during 26-week treatment period.

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:

Faster-acting insulin aspart was administered at the end of the meal but no later than 20 minutes after the start of the meal (i.e. breakfast, lunch and main evening meal). No adjustments of faster-acting insulin aspart dose was performed by the investigator during run-in. During the 26-week treatment period, the investigator focussed on optimising the bolus insulin. The bolus insulin was titrated to the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0–6.0 mmol/L [71–108 mg/dL] in a treat-to-target fashion.

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

Dosage and administration details:

Insulin degludec was administered once daily at any time of the day, preferably at the same time every day and injected subcutaneously into the thigh, or upper arm (deltoid area). During the 8-week run-in period, the investigator focussed on optimising the treatment by using a treat-to-target approach; the basal insulin was titrated by the investigator on a weekly basis to the pre-breakfast glycaemic target of 4.0-5.0 mmol/L (71-90 mg/dL). Further adjustments of the basal insulin dose during the treatment period were done at the discretion of the Investigator, if needed.

Arm title	NovoRapid (meal)

Arm description:

After 8-week run-in period, subjects continued using mealtime insulin aspart (NovoRapid®/NovoLog®) s.c. injections at mealtime (0−2 minutes before the meal) during 26-week treatment period. Throughout the trial, the insulin was administered at each of the three main meals (i.e. breakfast, lunch and main evening meal). The insulin was titrated to the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0–6.0 mmol/L (71–108 mg/dL) in a treat-to-target fashion.
Basal insulin: Participants continued insulin degludec once daily s.c. injections at the dose optimized during run-in period during 26-week treatment period.

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

Dosage and administration details:

Insulin aspart was administered 0−2 minutes before each of the three main meals (i.e. breakfast, lunch

and main evening meal). No adjustments of faster-acting insulin aspart dose was performed by the investigator during run-in. During the 26-week treatment period, the investigator focussed on optimising the bolus insulin. The bolus insulin was titrated to the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0–6.0 mmol/L [71–108 mg/dL] in a treat-to-target fashion.

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

Dosage and administration details:

Insulin degludec was administered once daily at any time of the day, preferably at the same time every day and injected subcutaneously into the thigh, or upper arm (deltoid area). During the 8-week run-in period, the investigator focussed on optimising the treatment by using a treat-to-target approach; the basal insulin was titrated by the investigator on a weekly basis to the pre-breakfast glycaemic target of 4.0-5.0 mmol/L (71-90 mg/dL). Further adjustments of the basal insulin dose during the treatment period were done at the discretion of the Investigator, if needed.

Number of subjects in period 1	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)
Started	342	341	342
Exposed	342	341	342
Completed	338	334	335
Not completed	4	7	7
Consent withdrawn by subject	4	6	4
Adverse event, non-fatal	-	-	1
Unclassified	-	-	1
Lost to follow-up	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Faster aspart (meal)
Reporting group description:	
Bolus insulin: Participants received subcutaneous (s.c., into the abdominal wall) injections of faster-acting insulin aspart at mealtime (0−2 minutes before the meal) during 26-week treatment period. Throughout the trial, the insulin was administered at each of the three main meals (i.e. breakfast, lunch and main evening meal). The insulin was titrated to the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0–6.0 mmol/L (71–108 mg/dL) in a treat-to-target fashion. Basal insulin: Participants continued insulin degludec once daily s.c. injections at the dose optimized during run-in period during 26-week treatment period.	
Reporting group title	Faster aspart (post)
Reporting group description:	
Bolus insulin: Participants received s.c. injections of faster-acting insulin aspart at mealtime (injecting the bolus insulin at the end of the meal but no later than 20 minutes after the start of the meal) during 26-week treatment period. Throughout the trial, the insulin was administered at each of the three main meals (i.e. breakfast, lunch and main evening meal). The insulin was titrated to the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0–6.0 mmol/L (71–108 mg/dL) in a treat-to-target fashion. Basal insulin: Participants continued insulin degludec once daily s.c. injections at the dose optimized during run-in period during 26-week treatment period.	
Reporting group title	NovoRapid (meal)
Reporting group description:	
After 8-week run-in period, subjects continued using mealtime insulin aspart (NovoRapid®/NovoLog®) s.c. injections at mealtime (0−2 minutes before the meal) during 26-week treatment period. Throughout the trial, the insulin was administered at each of the three main meals (i.e. breakfast, lunch and main evening meal). The insulin was titrated to the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0–6.0 mmol/L (71–108 mg/dL) in a treat-to-target fashion. Basal insulin: Participants continued insulin degludec once daily s.c. injections at the dose optimized during run-in period during 26-week treatment period.	

Reporting group values	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)
Number of subjects	342	341	342
Age Categorical Units: Subjects			
Adults (18-64 years)	322	319	323
From 65-84 years	20	22	19
Age Continuous Units: years			
arithmetic mean	41.48	41.02	40.77
standard deviation	± 14.42	± 14.59	± 14.22
Gender Categorical Units: Subjects			
Female	158	155	163
Male	184	186	179

Reporting group values	Total		
Number of subjects	1025		
Age Categorical Units: Subjects			
Adults (18-64 years)	964		
From 65-84 years	61		

Age Continuous Units: years arithmetic mean standard deviation	- 		
Gender Categorical Units: Subjects			
Female	476		
Male	549		

End points

End points reporting groups

Reporting group title	Faster aspart (meal)

Reporting group description:

Bolus insulin: Participants received subcutaneous (s.c., into the abdominal wall) injections of faster-acting insulin aspart at mealtime (0−2 minutes before the meal) during 26-week treatment period. Throughout the trial, the insulin was administered at each of the three main meals (i.e. breakfast, lunch and main evening meal). The insulin was titrated to the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0–6.0 mmol/L (71–108 mg/dL) in a treat-to-target fashion.
Basal insulin: Participants continued insulin degludec once daily s.c. injections at the dose optimized during run-in period during 26-week treatment period.

Reporting group title	Faster aspart (post)

Reporting group description:

Bolus insulin: Participants received s.c. injections of faster-acting insulin aspart at mealtime (injecting the bolus insulin at the end of the meal but no later than 20 minutes after the start of the meal) during 26-week treatment period. Throughout the trial, the insulin was administered at each of the three main meals (i.e. breakfast, lunch and main evening meal). The insulin was titrated to the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0–6.0 mmol/L (71–108 mg/dL) in a treat-to-target fashion.
Basal insulin: Participants continued insulin degludec once daily s.c. injections at the dose optimized during run-in period during 26-week treatment period.

Reporting group title	NovoRapid (meal)

Reporting group description:

After 8-week run-in period, subjects continued using mealtime insulin aspart (NovoRapid®/NovoLog®) s.c. injections at mealtime (0−2 minutes before the meal) during 26-week treatment period. Throughout the trial, the insulin was administered at each of the three main meals (i.e. breakfast, lunch and main evening meal). The insulin was titrated to the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0–6.0 mmol/L (71–108 mg/dL) in a treat-to-target fashion.
Basal insulin: Participants continued insulin degludec once daily s.c. injections at the dose optimized during run-in period during 26-week treatment period.

Primary: Change from baseline in HbA1c

End point title	Change from baseline in HbA1c

End point description:

Change from baseline (week 0) in HbA1c was evaluated after 26 weeks of randomisation. The results are based on the last in-trial value, which included the last available measurement in the in-trial period. In-trial period: the observation period from date of randomisation until last trial-related subject-site contact. Analysis was based on FAS. Number of subjects analysed=subject with data available for HbA1c.

End point type	Primary

End point timeframe:

26 weeks after randomisation

End point values	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	342	341	342	
Units: percentage of HbA1c				
arithmetic mean (standard deviation)	-0.12 (± 0.64)	0.005 (± 0.64)	-0.09 (± 0.65)	

Statistical analyses

Statistical analysis title	Faster aspart (meal) vs. NovoRapid (meal)

Statistical analysis description:

The endpoint was analysed using an analysis of variance model after multiple imputation assuming treatment according to randomisation. The model includes treatment, region and bolus adjusting method at randomisation as factors, and baseline HbA1c as a covariate.

Comparison groups	NovoRapid (meal) v Faster aspart (meal)
Number of subjects included in analysis	684
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.001 [2]
Method	ANOVA model after multiple imputation
Parameter estimate	Treatment difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.07

Notes:

[1] - Stepwise hierarchical testing procedure was applied for confirmatory endpoints:
Step 1: Primary analysis: HbA1c non-inferiority of mealtime faster aspart versus mealtime NovoRapid®/NovoLog®.

Non-inferiority of mealtime faster aspart was considered confirmed if the upper boundary of the two-sided 95% CI was below or equal to 0.4%
[2] - p-values are from the 1-sided test for non-inferiority evaluated at the 2.5% level

Statistical analysis title	Faster aspart (meal) vs. NovoRapid (meal)

Statistical analysis description:

The endpoint was analysed using an analysis of variance model after multiple imputation assuming treatment according to randomisation. The model includes treatment, region and bolus adjusting method at randomisation as factors, and baseline HbA1c as a covariate.

Comparison groups	Faster aspart (meal) v NovoRapid (meal)
Number of subjects included in analysis	684
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.633 [4]
Method	ANOVA model after multiple imputation
Parameter estimate	Treatment difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.07

Notes:

[3] - Stepwise hierarchical testing procedure was applied for confirmatory endpoints:
Step 4: HbA1c superiority of mealtime faster aspart versus mealtime NovoRapid®/NovoLog®.

Superiority was to be confirmed if the upper boundary of the two-sided 95% CI of the mean treatment difference (mealtime faster aspart minus mealtime NovoRapid®/NovoLog®) was below 0%-points
[4] - p-value from the 2-sided test for treatment difference evaluated at the 5% level

Statistical analysis title	Faster aspart (post) vs. NovoRapid (meal)

Statistical analysis description:

The endpoint was analysed using an analysis of variance model after multiple imputation assuming treatment according to randomisation. The model includes treatment, region and bolus adjusting method at randomisation as factors, and baseline HbA1c as a covariate.

Comparison groups	Faster aspart (post) v NovoRapid (meal)
Number of subjects included in analysis	683
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	< 0.001 [6]
Method	ANOVA model after multiple imputation
Parameter estimate	Treatment difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.19

Notes:

[5] - Stepwise hierarchical testing procedure was applied for confirmatory endpoints:
Step 2: HbA1c non-inferiority of postmeal faster aspart versus mealtime NovoRapid®/NovoLog®.

Non-inferiority of postmeal faster aspart was considered confirmed if the upper boundary of the two-sided 95% CI was below or equal to 0.4%
[6] - p-values are from the 1-sided test for non-inferiority evaluated at the 2.5% level

Secondary: Change from baseline in 1-hour post prandial glucose increment (meal test)

End point title	Change from baseline in 1-hour post prandial glucose increment (meal test)

End point description:

The 1-hour PPG increment was analysed based on the laboratory-measured values in the meal test, and was derived using the 1-hour PPG measurement minus the pre-prandial plasma glucose (PG). The results are based on the last in-trial value, which included the last available measurement in the in-trial period. Analysis was based on FAS. Number of subjects analysed=subject with data available for 1-hour PPG and pre-prandial PG.

End point type	Secondary

End point timeframe:

26 weeks after randomisation

End point values	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	332	332	326	
Units: mmol/L				
arithmetic mean (standard deviation)	-1.13 (± 4.04)	1.04 (± 3.53)	-0.15 (± 3.78)	

Statistical analyses

Statistical analysis title	Faster aspart (meal) vs. NovoRapid (meal)

Statistical analysis description:

Change from baseline in postprandial glucose increment (meal test) is analysed using an analysis of variance model. The model includes treatment, region and bolus adjusting method at randomisation as factors, and baseline postprandial glucose increment as a covariate.

Comparison groups	Faster aspart (meal) v NovoRapid (meal)
Number of subjects included in analysis	658
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001 [8]
Method	ANOVA
Parameter estimate	Treatment difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.36
upper limit	-0.45

Notes:

[7] - Stepwise hierarchical testing procedure was applied for confirmatory endpoints:
Step 3: 1-hour postprandial glucose (PPG) increments superiority of mealtime faster aspart versus mealtime NovoRapid®/NovoLog.

Superiority was confirmed if the upper boundary of the two-sided 95% CI of the mean treatment difference (mealtime faster aspart minus mealtime NovoRapid®/NovoLog®) was below 0.
[8] - p-value from the 2-sided test for treatment difference evaluated at the 5% level.

Secondary: Change from baseline in 1,5-anhydroglucitol

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

End point description:

The results are based on the last in-trial value, which included the last available measurement in the in-trial period.

End point type	Secondary

End point timeframe:

26 weeks after randomisation

End point values	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	341	336	338	
Units: ug/mL				
arithmetic mean (standard deviation)	0.22 (± 2.23)	-0.15 (± 2.10)	0.22 (± 2.25)	

Statistical analyses

Statistical analysis title	Faster aspart (meal) vs. NovoRapid (meal)

Statistical analysis description:

Change from baseline in 1,5-anhydroglucitol was analysed using an analysis of variance model after multiple imputation assuming treatment according to randomisation. The model includes treatment, region and bolus adjusting method at randomisation as factors, and baseline 1,5-anhydroglucitol as a covariate.

Comparison groups	Faster aspart (meal) v NovoRapid (meal)
Number of subjects included in analysis	679
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.924 [10]
Method	ANOVA model after multiple imputation
Parameter estimate	Treatment difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.34

Notes:

[9] - Stepwise hierarchical testing procedure was applied for confirmatory endpoints:
Step 5: 1,5-anhydroglucitol superiority of mealtime faster aspart versus mealtime NovoRapid®/NovoLog®.

Superiority was to be confirmed if the lower boundary of the two-sided 95% CI of the mean treatment difference (mealtime faster aspart minus mealtime NovoRapid®/NovoLog®) was above 0.

[10] - p-values are from the 2-sided test for treatment difference evaluated at the 5% level.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 to week 26 (+7 days)

Adverse event reporting additional description:

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 seven days after the last day of randomised treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Faster aspart (post)

Reporting group description:

Bolus insulin: Participants received s.c. injections of faster-acting insulin aspart at mealtime (injecting the bolus insulin at the end of the meal but no later than 20 minutes after the start of the meal) during 26-week treatment period. Throughout the trial, the insulin was administered at each of the three main meals (i.e. breakfast, lunch and main evening meal). The insulin was titrated to the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0–6.0 mmol/L (71–108 mg/dL) in a treat-to-target fashion.
Basal insulin: Participants continued insulin degludec once daily s.c. injections at the dose optimized during run-in period during 26-week treatment period.

Reporting group title	NovoRapid (meal)

Reporting group description:

After 8-week run-in period, subjects continued using mealtime insulin aspart (NovoRapid®/NovoLog®) s.c. injections at mealtime (0−2 minutes before the meal) during 26-week treatment period. Throughout the trial, the insulin was administered at each of the three main meals (i.e. breakfast, lunch and main evening meal). The insulin was titrated to the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0–6.0 mmol/L (71–108 mg/dL) in a treat-to-target fashion.
Basal insulin: Participants continued insulin degludec once daily s.c. injections at the dose optimized during run-in period during 26-week treatment period.

Reporting group title	Faster aspart (meal)

Reporting group description:

subcutaneous (s.c., into the abdominal wall) injections of faster-acting insulin aspart at mealtime (0−2 minutes before the meal) during 26-week treatment period. Throughout the trial, the insulin was administered at each of the three main meals (i.e. breakfast, lunch and main evening meal). The insulin was titrated to the glycaemic target of pre-prandial and bedtime plasma glucose between 4.0–6.0 mmol/L (71–108 mg/dL) in a treat-to-target fashion.
Basal insulin: Participants continued insulin degludec once daily s.c. injections at the dose optimized during run-in period during 26-week treatment period.

Serious adverse events	Faster aspart (post)	NovoRapid (meal)	Faster aspart (meal)
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 341 (4.99%)	17 / 342 (4.97%)	20 / 342 (5.85%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			

subjects affected / exposed	0 / 341 (0.00%)	0 / 342 (0.00%)	1 / 342 (0.29%)
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 fluctuation			
subjects affected / exposed	0 / 341 (0.00%)	1 / 342 (0.29%)	0 / 342 (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
Injury, poisoning and procedural complications			
Extradural haematoma			
subjects affected / exposed	0 / 341 (0.00%)	0 / 342 (0.00%)	1 / 342 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 341 (0.00%)	0 / 342 (0.00%)	1 / 342 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 341 (0.00%)	1 / 342 (0.29%)	0 / 342 (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
Forearm fracture			
subjects affected / exposed	1 / 341 (0.29%)	0 / 342 (0.00%)	0 / 342 (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
Postoperative ileus			
subjects affected / exposed	1 / 341 (0.29%)	0 / 342 (0.00%)	0 / 342 (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
Radius fracture			
subjects affected / exposed	0 / 341 (0.00%)	0 / 342 (0.00%)	1 / 342 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Road traffic accident			
subjects affected / exposed	1 / 341 (0.29%)	0 / 342 (0.00%)	0 / 342 (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
Skull fractured base			
subjects affected / exposed	0 / 341 (0.00%)	0 / 342 (0.00%)	1 / 342 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 341 (0.00%)	0 / 342 (0.00%)	1 / 342 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 341 (0.00%)	0 / 342 (0.00%)	1 / 342 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrong drug administered			
subjects affected / exposed	0 / 341 (0.00%)	2 / 342 (0.58%)	0 / 342 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Haemorrhoid operation			
subjects affected / exposed	0 / 341 (0.00%)	0 / 342 (0.00%)	1 / 342 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia repair			
subjects affected / exposed	0 / 341 (0.00%)	1 / 342 (0.29%)	0 / 342 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 341 (0.29%)	0 / 342 (0.00%)	0 / 342 (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

Diabetic neuropathy			
subjects affected / exposed	0 / 341 (0.00%)	0 / 342 (0.00%)	1 / 342 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic coma			
subjects affected / exposed	0 / 341 (0.00%)	1 / 342 (0.29%)	0 / 342 (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	1 / 341 (0.29%)	0 / 342 (0.00%)	2 / 342 (0.58%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic unconsciousness			
subjects affected / exposed	3 / 341 (0.88%)	2 / 342 (0.58%)	2 / 342 (0.58%)
occurrences causally related to treatment / all	3 / 3	1 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	2 / 341 (0.59%)	0 / 342 (0.00%)	0 / 342 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 341 (0.29%)	0 / 342 (0.00%)	0 / 342 (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
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 341 (0.00%)	0 / 342 (0.00%)	1 / 342 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 341 (0.00%)	0 / 342 (0.00%)	1 / 342 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 341 (0.00%)	1 / 342 (0.29%)	0 / 342 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 341 (0.00%)	0 / 342 (0.00%)	1 / 342 (0.29%)
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 and connective tissue disorders			
Bursitis			
subjects affected / exposed	1 / 341 (0.29%)	0 / 342 (0.00%)	0 / 342 (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
Collagen disorder			
subjects affected / exposed	0 / 341 (0.00%)	0 / 342 (0.00%)	1 / 342 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	1 / 341 (0.29%)	0 / 342 (0.00%)	0 / 342 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 341 (0.00%)	1 / 342 (0.29%)	0 / 342 (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
Trigger finger			
subjects affected / exposed	0 / 341 (0.00%)	0 / 342 (0.00%)	1 / 342 (0.29%)
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			
Cellulitis			

subjects affected / exposed	1 / 341 (0.29%)	0 / 342 (0.00%)	0 / 342 (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
Diverticulitis			
subjects affected / exposed	0 / 341 (0.00%)	1 / 342 (0.29%)	0 / 342 (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
Pilonidal cyst			
subjects affected / exposed	1 / 341 (0.29%)	0 / 342 (0.00%)	0 / 342 (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
Urinary tract infection			
subjects affected / exposed	0 / 341 (0.00%)	1 / 342 (0.29%)	0 / 342 (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
Metabolism and nutrition disorders			
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 341 (0.29%)	1 / 342 (0.29%)	1 / 342 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	3 / 341 (0.88%)	6 / 342 (1.75%)	8 / 342 (2.34%)
occurrences causally related to treatment / all	6 / 6	5 / 6	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia unawareness			
subjects affected / exposed	1 / 341 (0.29%)	0 / 342 (0.00%)	0 / 342 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	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 (post)	NovoRapid (meal)	Faster aspart (meal)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	152 / 341 (44.57%)	161 / 342 (47.08%)	154 / 342 (45.03%)
Investigations			
Blood glucose decreased			
subjects affected / exposed	67 / 341 (19.65%)	68 / 342 (19.88%)	58 / 342 (16.96%)
occurrences (all)	83	82	81
Infections and infestations			
Influenza			
subjects affected / exposed	14 / 341 (4.11%)	10 / 342 (2.92%)	21 / 342 (6.14%)
occurrences (all)	14	10	22
Upper respiratory tract infection			
subjects affected / exposed	26 / 341 (7.62%)	27 / 342 (7.89%)	30 / 342 (8.77%)
occurrences (all)	34	34	38
Viral upper respiratory tract infection			
subjects affected / exposed	70 / 341 (20.53%)	80 / 342 (23.39%)	73 / 342 (21.35%)
occurrences (all)	100	118	101

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2016	1. Introduction of estimands into the protocol with emphasis on using the in-trial observation period for the primary estimand: Significant changes to statistical analysis section to accommodate this (primary analysis, sensitivity analysis, wording of endpoints). Differentiation between trial drug discontinuation and trial discontinuation. 2. Introduction of premature discontinuation visit into trial design. 3. Addition of sections describing criteria for run-in failure and for premature discontinuation of trial product. 4. Addition of sections describing how subjects that discontinue trial product prematurely should be followed and how a subject can withdraw from the trial. 5. Addition of section describing choice of non-inferiority margin. 6. Order of hierarchical testing changed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported