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

Summary

EudraCT number	2014-002568-33
Trial protocol	BG CZ EE DE LV LT FI PL IT
Global end of trial date	03 March 2018

Results information

Result version number	v1 (current)
This version publication date	19 September 2018
First version publication date	19 September 2018

Trial information

Trial identification

Sponsor protocol code	NN1218-4101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02670915
WHO universal trial number (UTN)	U1111-1158-1170
Other trial identifiers	Japanese trial registration: JapicCTI-163248

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 February 2018
Global end of trial reached?	Yes
Global end of trial date	03 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the effect of treatment with meal-time faster-acting insulin aspart in terms of glycaemic control by comparing it to meal-time NovoRapid® both in combination with insulin degludec using a non-inferiority approach in children and adolescents with type 1 diabetes.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice, including archiving of essential documents 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	Bulgaria: 48
Country: Number of subjects enrolled	Czech Republic: 36
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Estonia: 17
Country: Number of subjects enrolled	Finland: 13
Country: Number of subjects enrolled	India: 59
Country: Number of subjects enrolled	Israel: 31
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Japan: 66
Country: Number of subjects enrolled	Lithuania: 10
Country: Number of subjects enrolled	Latvia: 13
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Russian Federation: 104
Country: Number of subjects enrolled	Serbia: 20
Country: Number of subjects enrolled	Turkey: 36
Country: Number of subjects enrolled	Ukraine: 60
Country: Number of subjects enrolled	United States: 195

Worldwide total number of subjects	777
EEA total number of subjects	206

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)	347
Adolescents (12-17 years)	430
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 150 sites in 17 countries(number of sites with screened/randomised subjects)-Bulgaria: 4/4; Czech Republic: 6/6; Estonia: 2/2; Finland: 3/3; Germany: 6/6; India: 7/7; Israel: 6/6; Italy: 5/5; Japan: 34/34; Latvia: 1/1; Lithuania: 1/1; Poland: 4/4; Russia: 11/11; Serbia: 4/4; Turkey: 7/7; Ukraine: 9/9; United States: 40/39

Pre-assignment

Screening details:

12 week run-in period (834 subjects): Subjects were switched from previous insulin treatment to insulin degludec once daily, and mealtime NovoRapid®/NovoLog®. Insulin degludec treatment was optimised on a weekly basis to the pre-breakfast glycaemic target of 4.0−8.0 mmol/L. 57 subjects were run-in failures and 777 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	Subject, Investigator

Blinding implementation details:

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

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 pre-meal target of 4.0−8.0 mmol/L, and the bed-time target of 6.7–10 mmol/L 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. Dose adjustment at the discretion of the investigator was allowed if needed. A total of 260 subjects randomized to this arm; however, One subject randomised to the faster aspart (post) group, received mealtime faster aspart throughout the treatment period. Hence, total number of exposed to faster aspart (meal)=261.

Arm type	Experimental
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, preferably at the same time every day and injected subcutaneously. During the 12-week run-in period, insulin degludec treatment was titrated by the investigator on a weekly basis to the pre-breakfast glycaemic target of 4.0−8.0 mmol/L. During the 26-week treatment period, adjustment at the discretion of the investigator was allowed if needed

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). In the 26-week treatment period, the Faster-acting insulin aspart was titrated to the pre-meal target of 4.0−8.0 mmol/L, and the bed-time target of 6.7–10 mmol/L in a treat-to-target fashion.

Arm title	Faster aspart (post)

Arm description:

Participants received s.c. injections of faster-acting insulin aspart at mealtime (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 pre-meal target of 4.0−8.0 mmol/L, and the bed-time target of 6.7–10 mmol/L 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. Dose adjustment at the discretion of the investigator was allowed if needed. A total of 259 subjects randomized to this arm; however, One subject randomised to this group, received mealtime faster aspart throughout the treatment period. Hence, total number of exposed to faster aspart (post)=258.

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 20 minutes after the start of the meal (i.e. breakfast, lunch and main evening meal). In the 26-week treatment period, the Faster-acting insulin aspart was titrated to the pre-meal target of 4.0−8.0 mmol/L, and the bed-time target of 6.7–10 mmol/L 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, preferably at the same time every day and injected subcutaneously. During the 12-week run-in period, insulin degludec treatment was titrated by the investigator on a weekly basis to the pre-breakfast glycaemic target of 4.0−8.0 mmol/L. During the 26-week treatment period, adjustment at the discretion of the investigator was allowed if needed

Arm title	NovoRapid (meal)

Arm description:

After 12-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 pre-meal target of 4.0−8.0 mmol/L, and the bed-time target of 6.7–10 mmol/L 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. Dose adjustment at the discretion of the investigator was allowed if needed.

Arm type	Active comparator
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, preferably at the same time every day and injected subcutaneously. During the 12-week run-in period, insulin degludec treatment was titrated by the investigator on a weekly basis to the pre-breakfast glycaemic target of 4.0−8.0 mmol/L. During the 26-week treatment period, adjustment at the discretion of the investigator was allowed if needed

Investigational medicinal product name	Insulin aspart
Investigational medicinal product code	
Other name	
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). In the 26-week treatment period, the insulin aspart was titrated to the pre-meal target of 4.0−8.0 mmol/L, and the bed-time target of 6.7–10 mmol/L in a treat-to-target fashion.

Number of subjects in period 1	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)
Started	260	259	258
Completed	256	251	253
Not completed	4	8	5
Unclassified	-	3	-
Withdrawal by parent/guardian	4	4	1
Withdrawal by subject	-	1	4

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 pre-meal target of 4.0−8.0 mmol/L, and the bed-time target of 6.7–10 mmol/L 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. Dose adjustment at the discretion of the investigator was allowed if needed. A total of 260 subjects randomized to this arm; however, One subject randomised to the faster aspart (post) group, received mealtime faster aspart throughout the treatment period. Hence, total number of exposed to faster aspart (meal)=261.

Reporting group title	Faster aspart (post)

Reporting group description:

Participants received s.c. injections of faster-acting insulin aspart at mealtime (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 pre-meal target of 4.0−8.0 mmol/L, and the bed-time target of 6.7–10 mmol/L 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. Dose adjustment at the discretion of the investigator was allowed if needed. A total of 259 subjects randomized to this arm; however, One subject randomised to this group, received mealtime faster aspart throughout the treatment period. Hence, total number of exposed to faster aspart (post)=258.

Reporting group title	NovoRapid (meal)

Reporting group description:

After 12-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 pre-meal target of 4.0−8.0 mmol/L, and the bed-time target of 6.7–10 mmol/L 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. Dose adjustment at the discretion of the investigator was allowed if needed.

Reporting group values	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)
Number of subjects	260	259	258
Age Categorical Units: Subjects			
1 - <3 years	2	2	0
3 - <6 years	14	14	14
6 - <12 years	100	100	101
12 - <18 years	144	143	143
Age Continuous Units: years			
arithmetic mean	11.72	11.62	11.70
standard deviation	± 3.74	± 3.65	± 3.44
Gender Categorical Units: Subjects			
Female	126	122	110
Male	134	137	148
Glycosylated haemoglobin (HbA1c) Units: percentage of HbA1c			
arithmetic mean	7.57	7.58	7.53

standard deviation	± 0.80	± 0.84	± 0.83
Fasting plasma glucose (FPG) Units: mmol/L			
arithmetic mean	7.58	8.03	7.79
standard deviation	± 3.56	± 3.35	± 3.48

Reporting group values	Total		
Number of subjects	777		
Age Categorical Units: Subjects			
1 - <3 years	4		
3 - <6 years	42		
6 - <12 years	301		
12 - <18 years	430		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	358		
Male	419		
Glycosylated haemoglobin (HbA1c) Units: percentage of HbA1c			
arithmetic mean			
standard deviation	-		
Fasting plasma glucose (FPG) Units: mmol/L			
arithmetic mean			
standard deviation	-		

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 pre-meal target of 4.0−8.0 mmol/L, and the bed-time target of 6.7–10 mmol/L 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. Dose adjustment at the discretion of the investigator was allowed if needed. A total of 260 subjects randomized to this arm; however, One subject randomised to the faster aspart (post) group, received mealtime faster aspart throughout the treatment period. Hence, total number of exposed to faster aspart (meal)=261.

Reporting group title	Faster aspart (post)

Reporting group description:

Participants received s.c. injections of faster-acting insulin aspart at mealtime (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 pre-meal target of 4.0−8.0 mmol/L, and the bed-time target of 6.7–10 mmol/L 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. Dose adjustment at the discretion of the investigator was allowed if needed. A total of 259 subjects randomized to this arm; however, One subject randomised to this group, received mealtime faster aspart throughout the treatment period. Hence, total number of exposed to faster aspart (post)=258.

Reporting group title	NovoRapid (meal)

Reporting group description:

After 12-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 pre-meal target of 4.0−8.0 mmol/L, and the bed-time target of 6.7–10 mmol/L 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. Dose adjustment at the discretion of the investigator was allowed if needed.

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 full analysis set (FAS) which includes all randomised subjects. 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	260	259	258	
Units: percentage of HbA1c				
arithmetic mean (standard deviation)	0.06 (± 0.80)	0.33 (± 0.83)	0.23 (± 0.82)	

Statistical analyses

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

Statistical analysis description:

The primary analysis was implemented as a statistical model using multiple imputation where the subjects without any available HbA1c measurements at scheduled visits had their change from baseline HbA1c value(s) imputed from the available information from the treatment the subject had been randomised to.

Comparison groups	Faster aspart (meal) v NovoRapid (meal)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.001 [2]
Method	multiple imputation
Parameter estimate	Treatment difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	-0.03

Notes:

[1] - Stepwise hierarchical testing procedure was applied: Step 1-Primary analysis: HbA1c non-inferiority of mealtime faster aspart versus mealtime NovoRapid®/NovoLog® both in combination with insulin degludec. 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 (post) vs. NovoRapid (meal)

Statistical analysis description:

The analysis was implemented as a statistical model using multiple imputation where the subjects without any available HbA1c measurements at scheduled visits had their change from baseline HbA1c value(s) imputed from the available information from the treatment the subject had been randomised to.

Comparison groups	Faster aspart (post) v NovoRapid (meal)
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.001 [4]
Method	multiple imputation
Parameter estimate	Treatment difference
Point estimate	0.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.26

Notes:

[3] - Stepwise hierarchical testing procedure was applied: Step 2-Confirmatory secondary analysis: HbA1c non-inferiority of postmeal faster aspart versus mealtime NovoRapid®/NovoLog® both in combination with insulin degludec. 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%.
[4] - 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 analysis was implemented as a statistical model using multiple imputation where the subjects without any available HbA1c measurements at scheduled visits had their change from baseline HbA1c value(s) imputed from the available information from the treatment the subject had been randomised to.

Comparison groups	Faster aspart (meal) v NovoRapid (meal)
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.007 [6]
Method	multiple imputation
Parameter estimate	Treatment difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	-0.03

Notes:

[5] - Stepwise hierarchical testing procedure was applied: Step 3-Confirmatory secondary analysis: HbA1c superiority of mealtime faster aspart versus mealtime NovoRapid®/NovoLog® both in combination with insulin degludec. Superiority of mealtime faster aspart was considered confirmed if the upper boundary of the two-sided 95% CI was below 0.
[6] - p-values are from the 1-sided test for superiority evaluated at the 2.5% level.

Secondary: Change from baseline in 8-point self-measured plasma glucose (SMPG) profile (8-point profile): - Mean postprandial glucose (PPG) and PPG increment over all three meals

End point title	Change from baseline in 8-point self-measured plasma glucose (SMPG) profile (8-point profile): - Mean postprandial glucose (PPG) and PPG increment over all three meals

End point description:

SMPG values were recorded at 8 time-points: before and after (60 min after the start of the meal) breakfast, lunch, main evening meal, before bedtime, and before breakfast on the next day. PPG was recorded by the subject as part of the two 8-point profiles prior to the visits. PPG increments based on the 8-point profiles were derived separately for PG measurements made 1 hour after the meal. PPG increment for each meal (breakfast, lunch, main evening meal) was derived from the 8-point profile as the difference between PPG values and the PG value before meal. 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=subjects who contributed to the analysis.

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	260	259	258	
Units: mmol/L				
arithmetic mean (standard deviation)				
Change in PPG all meals (n=196, 200, 203)	-0.94 (± 2.55)	0.36 (± 3.17)	-0.21 (± 2.79)	
Change in PPG increment all meals (n=196,197,202)	-0.92 (± 2.92)	0.56 (± 2.88)	0.14 (± 2.75)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in fasting plasma glucose (FPG)

End point title	Change from baseline in fasting plasma glucose (FPG)

End point description:

Change from baseline (week 0) in FPG 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 FPG.

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	173	185	161	
Units: mmol/L				
arithmetic mean (standard deviation)	0.41 (± 5.04)	-0.08 (± 4.49)	-0.13 (± 4.16)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent adverse events (AEs)

End point title	Number of treatment emergent adverse events (AEs)

End point description:

Treatment emergent is defined as an event that has onset up to 7 days after last day of randomised treatment and excluding the events occurring in the run-in period. Results are presented as event rate per 100 patient years of exposure (PYE). Safety analysis set (SAS) includes all subjects receiving at

least one dose of the investigational product or its comparator. Subjects in the safety set will contribute to the evaluation "as treated". One subject was randomised to the postmeal faster aspart group but was exposed to mealtime faster aspart throughout the treatment period. The subject was included in the mealtime faster aspart group for the safety analysis set. Therefore, number of subjects analysed= 261 for Faster aspart (meal), 258 for Faster aspart (post) and 258 for NovoRapid (meal).

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	260	259	258	
Units: Event rate per 100 PYE				
number (not applicable)	448.6	531.1	464.5	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From randomization (week 0) to week 26 + 7 days of follow-up	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20

Reporting groups	
Reporting group title	Faster aspart (meal)
Reporting group description: -	
Reporting group title	Faster aspart (post)
Reporting group description: -	
Reporting group title	NovoRapid (meal)
Reporting group description: -	

Serious adverse events	Faster aspart (meal)	Faster aspart (post)	NovoRapid (meal)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 261 (1.92%)	13 / 258 (5.04%)	9 / 258 (3.49%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 261 (0.38%)	2 / 258 (0.78%)	0 / 258 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Diabetes mellitus management			
subjects affected / exposed	0 / 261 (0.00%)	1 / 258 (0.39%)	0 / 258 (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 disorders			
Palpitations			
subjects affected / exposed	0 / 261 (0.00%)	1 / 258 (0.39%)	0 / 258 (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			

Hypoglycaemic unconsciousness			
subjects affected / exposed	0 / 261 (0.00%)	2 / 258 (0.78%)	0 / 258 (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
Idiopathic partial epilepsy			
subjects affected / exposed	1 / 261 (0.38%)	0 / 258 (0.00%)	0 / 258 (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			
Abdominal pain			
subjects affected / exposed	0 / 261 (0.00%)	0 / 258 (0.00%)	1 / 258 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 261 (0.00%)	0 / 258 (0.00%)	1 / 258 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Adjustment disorder with mixed disturbance of emotion and conduct			
subjects affected / exposed	0 / 261 (0.00%)	1 / 258 (0.39%)	0 / 258 (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
Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	0 / 261 (0.00%)	1 / 258 (0.39%)	0 / 258 (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
Renal colic			
subjects affected / exposed	0 / 261 (0.00%)	1 / 258 (0.39%)	0 / 258 (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			
Epiphysiolysis			

subjects affected / exposed	0 / 261 (0.00%)	1 / 258 (0.39%)	0 / 258 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 261 (0.77%)	0 / 258 (0.00%)	0 / 258 (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
Gastroenteritis			
subjects affected / exposed	0 / 261 (0.00%)	0 / 258 (0.00%)	3 / 258 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal viral infection			
subjects affected / exposed	1 / 261 (0.38%)	0 / 258 (0.00%)	0 / 258 (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
Influenza			
subjects affected / exposed	0 / 261 (0.00%)	1 / 258 (0.39%)	0 / 258 (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
Osteomyelitis			
subjects affected / exposed	0 / 261 (0.00%)	0 / 258 (0.00%)	1 / 258 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 261 (0.38%)	0 / 258 (0.00%)	0 / 258 (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
Tonsillitis			
subjects affected / exposed	0 / 261 (0.00%)	0 / 258 (0.00%)	1 / 258 (0.39%)
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			

Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 261 (0.00%)	0 / 258 (0.00%)	1 / 258 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 261 (0.00%)	2 / 258 (0.78%)	2 / 258 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 261 (0.00%)	0 / 258 (0.00%)	1 / 258 (0.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 261 (0.38%)	2 / 258 (0.78%)	1 / 258 (0.39%)
occurrences causally related to treatment / all	1 / 1	0 / 2	1 / 1
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)	Faster aspart (post)	NovoRapid (meal)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	137 / 261 (52.49%)	149 / 258 (57.75%)	136 / 258 (52.71%)
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 261 (6.13%)	26 / 258 (10.08%)	22 / 258 (8.53%)
occurrences (all)	21	38	35
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	22 / 261 (8.43%)	16 / 258 (6.20%)	18 / 258 (6.98%)
occurrences (all)	26	16	20
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	9 / 261 (3.45%)	21 / 258 (8.14%)	7 / 258 (2.71%)
occurrences (all)	9	24	7
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	10 / 261 (3.83%)	11 / 258 (4.26%)	16 / 258 (6.20%)
occurrences (all)	11	14	21
Oropharyngeal pain			
subjects affected / exposed	10 / 261 (3.83%)	9 / 258 (3.49%)	13 / 258 (5.04%)
occurrences (all)	12	13	16
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	13 / 261 (4.98%)	16 / 258 (6.20%)	19 / 258 (7.36%)
occurrences (all)	15	17	24
Influenza			
subjects affected / exposed	20 / 261 (7.66%)	14 / 258 (5.43%)	14 / 258 (5.43%)
occurrences (all)	28	19	21
Rhinitis			
subjects affected / exposed	10 / 261 (3.83%)	16 / 258 (6.20%)	11 / 258 (4.26%)
occurrences (all)	16	24	16
Upper respiratory tract infection			
subjects affected / exposed	22 / 261 (8.43%)	32 / 258 (12.40%)	26 / 258 (10.08%)
occurrences (all)	31	41	32
Viral infection			
subjects affected / exposed	7 / 261 (2.68%)	9 / 258 (3.49%)	14 / 258 (5.43%)
occurrences (all)	8	11	20
Viral upper respiratory tract infection			
subjects affected / exposed	60 / 261 (22.99%)	53 / 258 (20.54%)	48 / 258 (18.60%)
occurrences (all)	73	79	75

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 March 2016	Added 'or equal to' in the definition of confirming of non-inferiority in trial protocol
06 June 2016	A mistake identified in the blood sampling volume at visit 14 and visit 40 for the subjects participating in the Continuous lucose Monitoring (CGM) and meal test subgroup. Consequently the required minimum weight for participation in the CGM and meal test subgroup was increased to ensure the blood volume collected at visit 14 and visit 40 did not exceed 1% of the subjects total blood volume.
25 February 2017	1. An inaccuracy was identified in the layman language for reporting hypoglycaemic episodes. There was a need to clarify the run-in failure criteria, to provide more guidance on when to report a MESI, and that the FPG sample was to be collected using the FPG home sampling kit no matter if the FPG sample was taken at home or at site. 2. The statistical section was updated to clarify the analyses made for the primary and secondary estimands, the supportive secondary CGM and meal test related efficacy endpoints. A clarification was made to which treatment emergent hypoglycaemic episodes should be included in the analyses. 3. An appendix was updated to reflect the changes that occurred due to the change in CGM supplier shortly before trial initiation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported