Clinical trial results:
Efficacy and safety of fast-acting Insulin Aspart compared to NovoRapid® both in combination with Insulin Degludec with or without metformin in adults with type 2 diabetes (onset® 9)

Summary

EudraCT number	2016-000878-38
Trial protocol	BG CZ ES GR DE HR IT
Global end of trial date	29 January 2019

Results information

Result version number	v1 (current)
This version publication date	13 February 2020
First version publication date	13 February 2020

Trial information

Trial identification

Sponsor protocol code	NN1218-4113

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03268005
WHO universal trial number (UTN)	U1111-1180-0636

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	20 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 January 2019
Global end of trial reached?	Yes
Global end of trial date	29 January 2019
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 fast-acting insulin aspart compared to NovoRapid® both in combination with insulin degludec with or without metformin in adults with type 2 diabetes treated with a basal-bolus regimen, using a non-inferiority approach.

Protection of trial subjects:

The trial was conducted in accordance with Declaration of Helsinki (2013) and ICH Good Clinical Practice (1996), including archiving of essential documents and FDA 21 CFR 312.120.

Background therapy: -

Evidence for comparator:

Not applicable

Actual start date of recruitment	19 September 2017
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	Argentina: 40
Country: Number of subjects enrolled	Bulgaria: 41
Country: Number of subjects enrolled	Canada: 49
Country: Number of subjects enrolled	Czech Republic: 25
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Spain: 70
Country: Number of subjects enrolled	Greece: 57
Country: Number of subjects enrolled	Croatia: 25
Country: Number of subjects enrolled	Italy: 38
Country: Number of subjects enrolled	Korea, Republic of: 58
Country: Number of subjects enrolled	Poland: 60
Country: Number of subjects enrolled	Romania: 44
Country: Number of subjects enrolled	Russian Federation: 64
Country: Number of subjects enrolled	Serbia: 75
Country: Number of subjects enrolled	Slovakia: 42
Country: Number of subjects enrolled	Ukraine: 51
Country: Number of subjects enrolled	United States: 320
Worldwide total number of subjects	1091
EEA total number of subjects	434

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)	625
From 65 to 84 years	461
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 165 sites in 17 countries as follows: Argentina-3, Bulgaria-4, Canada-10, Croatia-4, Czech Republic-4, Germany-6, Greece-8, Italy-4, Poland-6, Republic of Korea-10, Romania-6, Russia-8, Serbia-9, Slovakia-5, Spain-8, Ukraine-6 and United States (US)-62. Two sites in the US screened but didn't randomise any subject.

Pre-assignment

Screening details:

There was a 12-week run-in period primarily for optimisation of the basal insulin and reinforcement of subject training in trial procedures, diabetes education and dietary training. During the run-in period, the investigator focused on optimising the basal insulin treatment using a treat-to-target approach.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Faster aspart

Arm description:

Subjects received faster aspart along with insulin degludec (basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose.

Arm type	Experimental
Investigational medicinal product name	Faster aspart
Investigational medicinal product code	
Other name	Fiasp®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin degludec dose was adjusted weekly by the investigator in the run-in period based on the mean of three pre-breakfast SMPG values measured on the last two days prior to and on the day of contact. If one of the SMPG values were below target (< 4.0 mmol/L or 71 mg/dL) then the insulin degludec dose was adjusted according to the titration guideline specified in the protocol. Faster aspart was titrated from randomisation (week 0) and onwards, twice weekly to reach the glycaemic target of pre-prandial and bedtime PG between 4.0-6.0 mmol/L (71 - 108 mg/dL) in a treat-to-target fashion. Insulin degludec was administered once daily, at any time of the day but preferably the same time every day, into the thigh or upper arm. Faster aspart was injected 0-2 minutes prior to meals, into the abdominal wall.

Arm title	NovoRapid

Arm description:

Subjects received insulin aspart (NovoRapid®/NovoLog®: basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose.

Arm type	Experimental
Investigational medicinal product name	Insulin aspart
Investigational medicinal product code	
Other name	NovoLog®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin degludec dose was adjusted weekly by the investigator in the run-in period based on the mean of three pre-breakfast SMPG values measured on the last two days prior to and on the day of contact. If one of the SMPG values were below target (< 4.0 mmol/L or 71 mg/dL) then the insulin degludec dose was adjusted according to the titration guideline specified in the protocol. NovoRapid was titrated from randomisation (week 0) and onwards, twice weekly to reach the glycaemic target of pre-prandial and bedtime PG between 4.0-6.0 mmol/L (71 - 108 mg/dL) in a treat-to-target fashion. Insulin degludec was administered once daily, at any time of the day but preferably the same time every day, into the thigh or upper arm. NovoRapid was injected 0-2 minutes prior to meals, into the abdominal wall.

Number of subjects in period 1	Faster aspart	NovoRapid
Started	546	545
Completed	531	531
Not completed	15	14
Adverse event, serious fatal	2	1
Consent withdrawn by subject	11	11
Lost to follow-up	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Faster aspart
Reporting group description:	
Subjects received faster aspart along with insulin degludec (basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose.	
Reporting group title	NovoRapid
Reporting group description:	
Subjects received insulin aspart (NovoRapid®/NovoLog®: basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose.	

Reporting group values	Faster aspart	NovoRapid	Total
Number of subjects	546	545	1091
Age categorical			
Units: Subjects			
Adults (18-64 years)	301	324	625
From 65-84 years	240	221	461
85 years and over	5	0	5
Age Continuous			
Units: Years			
arithmetic mean	62.6	62.1	
standard deviation	± 8.6	± 8.8	-
Sex: Female, Male			
Gender Categorical			
Units: Participants			
Male	265	289	554
Female	281	256	537
HbA1c			
Glycosylated haemoglobin			
Units: %-points			
arithmetic mean	7.15	7.05	
standard deviation	± 0.77	± 0.70	-

End points

End points reporting groups

Reporting group title	Faster aspart

Reporting group description:

Subjects received faster aspart along with insulin degludec (basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose.

Reporting group title	NovoRapid

Reporting group description:

Subjects received insulin aspart (NovoRapid®/NovoLog®: basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose.

Primary: Change from baseline in HbA1c

End point title	Change from baseline in HbA1c

End point description:

Change from baseline (week 0) in glycosylated haemoglobin (HbA1c) was evaluated at week 16. The endpoint was evaluated based on data from the in-trial observation period. In-trial observation period was from date of randomisation and until last trial-related participant-site contact.

End point type	Primary

End point timeframe:

16 weeks after randomisation

End point values	Faster aspart	NovoRapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	544	539		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)	-0.15 (± 0.62)	-0.09 (± 0.60)		

Statistical analyses

Statistical analysis title	Faster aspart vs NovoRapid

Statistical analysis description:

Change from baseline in HbA1c was analysed using an analysis of variance model after multiple imputation assuming treatment according to randomisation. The model included treatment, region and metformin use at baseline (Yes/No) as factors, and baseline HbA1c as a covariate.

Comparison groups	Faster aspart v NovoRapid
Number of subjects included in analysis	1083
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.31
Method	ANOVA
Parameter estimate	Treatment difference
Point estimate	-0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.03

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

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

End point description:

Change from baseline (week 0) in 1-hour postprandial glucose (PPG) increment was evaluated after 16 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 observation period was from date of randomisation and until last trial-related participant-site contact.

End point type	Secondary

End point timeframe:

16 weeks after randomisation

End point values	Faster aspart	NovoRapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	519	523		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.43 (± 2.45)	0.08 (± 2.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in 1,5-anhydroglucitol

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

End point description:

Change from baseline (week 0) in 1,5-anhydroglucitol was evaluated after 16 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 observation period was from date of randomisation and until last trial-related participant-site contact.

End point type	Secondary

End point timeframe:

16 weeks after randomisation

End point values	Faster aspart	NovoRapid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	534	531		
Units: mmol/L				
arithmetic mean (standard deviation)	1.38 (± 3.10)	0.89 (± 3.31)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 to Week 16 + 7 days. All reported AEs are treatment emergent (i.e., TEAE).

Adverse event reporting additional description:

Results are based on the SAS. All presented AEs are TEAEs which were recorded during the exposure to trial products. AEs with onset during the on-treatment observation period were considered treatment-emergent. Number of deaths causally related to treatment' is the data considered to present under 'total number of deaths resulting from AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Faster aspart

Reporting group description:

Subjects received Faster aspart along with insulin degludec (basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose. Insulin degludec dose was adjusted weekly by the investigator in the run-in period based on the mean of three pre-breakfast SMPG values measured on the last two days prior to and on the day of contact. If one of the SMPG values were below target (< 4.0 mmol/L or 71 mg/dL) then the insulin degludec dose was adjusted according to the titration guideline specified in the protocol. Faster aspart was titrated from randomisation (week 0) and onwards, twice weekly to reach the glycaemic target of pre-prandial and bedtime PG between 4.0-6.0 mmol/L (71 - 108 mg/dL) in a treat-to-target fashion.

Reporting group title	NovoRapid

Reporting group description:

Subjects received insulin aspart (NovoRapid®/NovoLog®: basal-bolus regimen) with or without metformin for 16 weeks. Before the treatment period was a 12-week run-in period in which the investigator optimised basal insulin dose. Insulin degludec dose was adjusted weekly by the investigator in the run-in period based on the mean of three pre-breakfast SMPG values measured on the last two days prior to and on the day of contact. If one of the SMPG values were below target (< 4.0 mmol/L or 71 mg/dL) then the insulin degludec dose was adjusted according to the titration guideline specified in the protocol. NovoRapid was titrated from randomisation (week 0) and onwards, twice weekly to reach the glycaemic target of pre-prandial and bedtime PG between 4.0-6.0 mmol/L (71 - 108 mg/dL) in a treat-to-target fashion.

Serious adverse events	Faster aspart	NovoRapid	
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 544 (6.99%)	40 / 544 (7.35%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatocellular carcinoma			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein occlusion			

subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose ulceration			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Aortic valve replacement			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel decompression			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rehabilitation therapy			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitrectomy			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 544 (0.00%)	2 / 544 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delusion			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rapid eye movements sleep abnormal			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Cardiac stress test abnormal			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Accidental overdose			
subjects affected / exposed	2 / 544 (0.37%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 544 (0.18%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrong product administered			
subjects affected / exposed	1 / 544 (0.18%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 544 (0.37%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 544 (0.00%)	2 / 544 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 544 (0.18%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 544 (0.18%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 544 (0.18%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 544 (0.18%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 544 (0.37%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 544 (0.00%)	2 / 544 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	0 / 544 (0.00%)	2 / 544 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebellar infarction			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic neuropathy			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 544 (0.00%)	2 / 544 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			

subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic unconsciousness			
subjects affected / exposed	3 / 544 (0.55%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 544 (0.37%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular parkinsonism			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemorrhagic anaemia			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Colitis			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyclic vomiting syndrome			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigger finger			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gangrene			
subjects affected / exposed	0 / 544 (0.00%)	2 / 544 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 544 (0.37%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 544 (0.00%)	2 / 544 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 544 (0.18%)	0 / 544 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 544 (0.00%)	1 / 544 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	4 / 544 (0.74%)	3 / 544 (0.55%)	
occurrences causally related to treatment / all	2 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Faster aspart	NovoRapid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 544 (5.88%)	33 / 544 (6.07%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	32 / 544 (5.88%)	33 / 544 (6.07%)	
occurrences (all)	35	36	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2017	Criteria for premature discontinuation of trial products was updated with 2 additional criteria: Lack of efficacy Unacceptable adverse event (including toxicity) The master agreement for amendment form was updated to version 2 to include the title of the original protocol and not only the title of the amendment. Both version 1 and 2 was used to document agreement of amendment 1.
28 February 2018	Replacement of eDiary requirements with paper diary requirements including change of trial BGM. Throughout the protocol "eDiary" was replaced with "diary". Clarification to titration guideline section Information was provided to investigators in a memo dated 30-Nov-2017 to make it clear that insulin degludec titration was based on SMPGs two days prior to and on day of contact instead of three days prior to contact SI/IC updated with information regarding Personal Data Protection. Minor clarifying updates to protocol text.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable

Notes: