Clinical trial results:
A 38 week trial comparing effect and safety of insulin degludec/insulin aspart vs. insulin glargine plus insulin aspart in subjects with type 2 diabetes treated with basal insulin with or without oral antidiabetic treatment in need of treatment intensification

Summary

EudraCT number	2015-004768-12
Trial protocol	CZ
Global end of trial date	24 December 2017

Results information

Result version number	v1 (current)
This version publication date	23 December 2018
First version publication date	23 December 2018

Trial information

Trial identification

Sponsor protocol code	NN5401-4266

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02906917
WHO universal trial number (UTN)	U1111-1175-7895

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	22 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2017
Global end of trial reached?	Yes
Global end of trial date	24 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the effect of insulin degludec/insulin aspart once daily versus insulin glargine once daily in combination with insulin aspart once daily in controlling glycaemia after 26 weeks in subjects with type 2 diabetes mellitus treated with basal insulin with or without oral antidiabetic treatment in need of treatment intensification.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (64th World Medical Association (WMA) Assembly, October 2013), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (10 June 1996) and 21 United States Code of Federal Regulations (CFR) 312.120.

Background therapy:

The following products were regarded as non-investigational medicinal products (non-IMPs) in this trial: Oral antidiabetic drugs (OADs) and washout insulins. OADs: Subjects were allowed to take the following OADs throughout the treatment period (week 0-38): 1) Metformin, 2) α-glucosidase-inhibitors, 3) Dipeptidyl peptidase-IV (DPP-4) inhibitors, 4) sodium/glucose co-transporter 2 (SGLT-2) inhibitors, and 5) Oral combination products (of the allowed individual OADs above).
Washout insulins: The 'washout' insulin products used in the follow-up period between the end-of-treatment visit (week 38) and the 7-day follow-up visit (week 39) are as follows: 1) Human isophane insulin (NPH) (Insulatard®, Protaphane®, Novolin® N), 2) Biphasic insulin aspart 30 (BIAsp 30) (NovoMix® 30, NovoLog® Mix 70/30), and 3) Insulin aspart (NovoRapid®/NovoLog®).

Evidence for comparator:

Not applicable.

Actual start date of recruitment	20 September 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	Algeria: 46
Country: Number of subjects enrolled	Czech Republic: 60
Country: Number of subjects enrolled	India: 51
Country: Number of subjects enrolled	Russian Federation: 110
Country: Number of subjects enrolled	Serbia: 46
Country: Number of subjects enrolled	Turkey: 66
Country: Number of subjects enrolled	United States: 153
Worldwide total number of subjects	532
EEA total number of subjects	60

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)	383
From 65 to 84 years	149
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 71 sites in 7 countries, as follows: Algeria (4), Czech Republic (6), India (10), Russian Federation (11), Serbia (5), Turkey (7), and United States (28). Additionally, 1 site in the United States screened, but didn't randomise any subject.

Pre-assignment

Screening details:

Not applicable.

Period 1

Period 1 title	Initiation period (Week 0-26)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Insulin degludec/insulin aspart

Arm description:

Subjects received Insulin degludec/insulin aspart (IDegAsp) once daily (OD) with or without OAD(s) for 26 weeks (week 0-26).

Arm type	Experimental
Investigational medicinal product name	Insulin degludec/insulin aspart
Investigational medicinal product code	
Other name	Ryzodeg®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IDegAsp OD was administered with the largest meal each day. Subjects switching from pre-trial basal insulin OD or more to IDegAsp OD at trial entry were to transfer unit-to-unit.

Arm title	Insulin glargine + insulin aspart

Arm description:

Subjects received Insulin glargine (IGlar) OD and insulin aspart (IAsp) OD with or without OAD(s) for 26 weeks (week 0-26).

Arm type	Active comparator
Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	
Other name	Lantus®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IGlar OD was administered in accordance with local labelling. Subjects switching from pre-trial basal insulin OD to IGlar OD were to transfer unit-to-unit to IGlar, while subjects switching from basal insulin more than OD to IGlar OD were to reduce the initial total daily dose by 20% or according to local labelling.

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:

IAsp OD was administered with the largest meal. IAsp was to be initiated at 4 units.

Number of subjects in period 1	Insulin degludec/insulin aspart	Insulin glargine + insulin aspart
Started	267	265
Exposed	265	263
Completed	261	254
Not completed	6	11
Consent withdrawn by subject	3	4
Adverse event, non-fatal	1	-
Unclassified	1	3
Lost to follow-up	1	4

Period 2

Period 2 title	Intensification period (Week 26-38)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Insulin degludec/insulin aspart

Arm description:

Subjects received IDegAsp OD/twice a day (BID) with or without OAD(s) for 12 weeks (week 26-38).

Arm type	Experimental
Investigational medicinal product name	Insulin degludec/insulin aspart
Investigational medicinal product code	
Other name	Ryzodeg®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IDegAsp OD/BID was administered with the largest meal(s) each day (in the case of BID dosing, one meal being dinner) based on individual needs.

Arm title	Insulin glargine + insulin aspart

Arm description:	
Subjects received IGlar OD and IAsp 1−3 times daily with or without OAD(s) for 12 weeks (week 26-38).	
Arm type	Active comparator
Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	
Other name	Lantus®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
IGlar OD was administered in accordance with local labelling.	
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:	
IAsp 1−3 times daily was administered with main meals based on individual needs.	

Number of subjects in period 2	Insulin degludec/insulin aspart	Insulin glargine + insulin aspart
Started	261	254
Completed	252	247
Not completed	9	7
Adverse event, serious fatal	-	2
Consent withdrawn by subject	3	2
Unclassified	3	2
Lost to follow-up	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Insulin degludec/insulin aspart
Reporting group description:	
Subjects received Insulin degludec/insulin aspart (IDegAsp) once daily (OD) with or without OAD(s) for 26 weeks (week 0-26).	
Reporting group title	Insulin glargine + insulin aspart
Reporting group description:	
Subjects received Insulin glargine (IGlar) OD and insulin aspart (IAsp) OD with or without OAD(s) for 26 weeks (week 0-26).	

Reporting group values	Insulin degludec/insulin aspart	Insulin glargine + insulin aspart	Total
Number of subjects	267	265	532
Age Categorical Units: Subjects			
Adults (18-64 years)	203	180	383
From 65-84 years	64	85	149
Age Continuous Units: years			
arithmetic mean	58.2	59.2	
standard deviation	± 8.9	± 9.1	-
Gender Categorical Units: Subjects			
Female	142	128	270
Male	125	137	262

End points

End points reporting groups

Reporting group title	Insulin degludec/insulin aspart
Reporting group description:	
Subjects received Insulin degludec/insulin aspart (IDegAsp) once daily (OD) with or without OAD(s) for 26 weeks (week 0-26).	
Reporting group title	Insulin glargine + insulin aspart
Reporting group description:	
Subjects received Insulin glargine (IGlar) OD and insulin aspart (IAsp) OD with or without OAD(s) for 26 weeks (week 0-26).	
Reporting group title	Insulin degludec/insulin aspart
Reporting group description:	
Subjects received IDegAsp OD/twice a day (BID) with or without OAD(s) for 12 weeks (week 26-38).	
Reporting group title	Insulin glargine + insulin aspart
Reporting group description:	
Subjects received IGlar OD and IAsp 1−3 times daily with or without OAD(s) for 12 weeks (week 26-38).	
Subject analysis set title	Insulin degludec/insulin aspart
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received IDegAsp OD with or without OAD(s) for 26 weeks (week 0-26 (Initiation period; period-1)).	
Subject analysis set title	Insulin glargine + insulin aspart
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received IGlar OD and IAsp OD with or without OAD(s) for 26 weeks (week 0-26 (Initiation period; period-1)).	
Subject analysis set title	Insulin degludec/insulin aspart
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received treatment for 38 weeks as per the following sequence: 1) Initiation period (period-1, week 0−26): IDegAsp OD was administered with or without OAD(s). 2) Intensification period (period-2, week 26−38): IDegAsp OD/BID was administered with or without OAD(s).	
Subject analysis set title	Insulin glargine + insulin aspart
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received treatment for 38 weeks as per the following sequence: 1) Initiation period (period-1, week 0−26): IGlar OD and IAsp OD was administered with or without OAD(s). 2) Intensification period (period-2, week 26−38): IGlar OD and IAsp 1−3 times daily was administered with or without OAD(s).	
Subject analysis set title	Insulin degludec/insulin aspart
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received treatment for 38 weeks as per the following sequence: 1) Initiation period (period-1, week 0−26): IDegAsp OD was administered with or without OAD(s). 2) Intensification period (period-2, week 26−38): IDegAsp OD/BID was administered with or without OAD(s).	
Subject analysis set title	Insulin glargine + insulin aspart
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received treatment for 38 weeks as per the following sequence: 1) Initiation period (period-1, week 0−26): IGlar OD and IAsp OD was administered with or without OAD(s). 2) Intensification period (period-2, week 26−38): IGlar OD and IAsp 1−3 times daily was administered with or without OAD(s).	

Primary: Change in glycosylated haemoglobin (HbA1c) (%) - Week 26

End point title	Change in glycosylated haemoglobin (HbA1c) (%) - Week 26

End point description:

Change from baseline (week 0) in glycosylated haemoglobin (HbA1c) was evaluated 26 weeks after randomisation. Results are based on the full analysis set (FAS), which included all randomised subjects. 'n' represents the 'number of subjects analysed' at specified time point, which is the number of subjects contributed to the analysis at specified time point.

End point type	Primary

End point timeframe:

From baseline after 26 weeks

End point values	Insulin degludec/insulin aspart	Insulin glargine + insulin aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267	265		
Units: % of HbA1c				
arithmetic mean (standard deviation)				
Baseline (week 0): n=261, 264	8.2 (± 0.8)	8.1 (± 0.7)		
Change from baseline (week 26): n=251, 248	-1.1 (± 0.9)	-1.1 (± 0.8)		

Statistical analyses

Statistical analysis title	Change in HbA1c (%) - Week 26

Statistical analysis description:

The response and change from baseline in response are analysed on 1000 complete, imputed data sets after multiple imputation for each treatment arm separately. A penalty of 0.4% is added to the week 26 values for all premature treatment discontinued subjects and subject with missing HbA1c values at week 26 in the IDegAsp arm. Each of the imputed data sets are analysed through an analysis of covariance (ANCOVA).

Comparison groups	Insulin glargine + insulin aspart v Insulin degludec/insulin aspart
Number of subjects included in analysis	532
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	Treatment contrast
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.21

Notes:

[1] - Non-inferiority of IDegAsp OD versus IGlar OD + IAsp OD was considered confirmed if the 95% confidence interval for the mean treatment difference was entirely below 0.4%. Treatment, region, sex, previous insulin treatment and previous OAD treatment as categorical fixed effects and baseline response and age as covariate.

[2] - One-sided p-value for test of non-inferiority.

Secondary: Responder (Yes/No) for HbA1c <7% - Week 26

End point title	Responder (Yes/No) for HbA1c <7% - Week 26

End point description:

Participants achieving (yes/no) HbA1c <7% was evaluated 26 weeks after randomisation. Results are based on the FAS. 'n' represents the 'number of subjects analysed' at specified time point, which is the number of subjects contributed to the analysis at specified time point.

End point type	Secondary

End point timeframe:

After 26 weeks

End point values	Insulin degludec/insulin aspart	Insulin glargine + insulin aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267	265		
Units: Number of participants				
Yes: n=241, 242	120	120		
No: n=241, 242	121	122		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in HbA1c (%) - Week 38

End point title	Change from baseline in HbA1c (%) - Week 38

End point description:

Change from baseline (week 0) in HbA1c was evaluated 38 weeks after randomisation. Results are based on the FAS. 'n' represents the 'number of subjects analysed' at specified time point, which is the number of subjects contributed to the analysis at specified time point.

End point type	Secondary

End point timeframe:

After 38 weeks

End point values	Insulin degludec/insulin aspart	Insulin glargine + insulin aspart		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	267	265		
Units: % of HbA1c				
arithmetic mean (standard deviation)				
Baseline (week 0): n=261, 264	8.2 (± 0.8)	8.1 (± 0.7)		

Change from baseline (week 38): n=247, 242	-1.2 (± 0.9)	-1.2 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Responder (Yes/No) for HbA1c <7% - Week 38

End point title	Responder (Yes/No) for HbA1c <7% - Week 38

End point description:

Participants achieving (yes/no) HbA1c <7% was evaluated 38 weeks after randomisation. Results are based on the FAS. 'n' represents the 'number of subjects analysed' at specified time point, which is the number of subjects contributed to the analysis at specified time point.

End point type	Secondary

End point timeframe:

After 38 weeks

End point values	Insulin degludec/insulin aspart	Insulin glargine + insulin aspart		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	267	265		
Units: Number of participants				
Yes: n=234, 233	139	140		
No: n=234, 233	95	93		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment-emergent severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes - 26 weeks

End point title	Number of treatment-emergent severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes - 26 weeks

End point description:

Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes were analysed during week 0-26. Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the American Diabetes Association (ADA) classification or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. Treatment emergent: hypoglycaemic episodes were defined as treatment emergent if the onset of the episode occurred on or after the first day of trial product administration, and no later than 7 calendar days after the last day on trial product. Results are based on the safety analysis set, which included all subjects receiving at least one dose of the investigational product (IDegAsp) or comparator (IGlar).

End point type	Secondary

End point timeframe:

During 26 weeks

End point values	Insulin degludec/insulin aspart	Insulin glargine + insulin aspart		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	265	263		
Units: Episodes	329	376		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes - 38 weeks

End point title	Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes - 38 weeks

End point description:

Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes were analysed during week 0-38. Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia. Treatment emergent: hypoglycaemic episodes were defined as treatment emergent if the onset of the episode occurred on or after the first day of trial product administration, and no later than 7 calendar days after the last day on trial product. Results are based on the safety analysis set.

End point type	Secondary

End point timeframe:

During 38 weeks

End point values	Insulin degludec/insulin aspart	Insulin glargine + insulin aspart		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	265	263		
Units: Episodes	537	640		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of treatment-emergent adverse events (TEAEs)

End point title	Incidence of treatment-emergent adverse events (TEAEs)

End point description:

Number of TEAEs were analysed during week 0-38. Treatment emergent: An adverse event that had an onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. If an event had an onset date before the first day of exposure on

randomised treatment and increased in severity during the treatment period, or if it had an onset date within 7 days after the last drug date, then this event was also to be considered as a TEAE. Results are based on the safety analysis set.

End point type	Secondary

End point timeframe:

During 38 weeks

End point values	Insulin degludec/insulin aspart	Insulin glargine + insulin aspart		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	265	263		
Units: Events	614	525		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 to week 38 (treatment period) + 7 days (follow-up period).

Adverse event reporting additional description:

All presented adverse events are treatment emergent (i.e., TEAEs). Results are based on the safety analysis set. Number of deaths causally related to treatment' is the data considered to present under 'total number of deaths resulting from adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Insulin glargine + insulin aspart

Reporting group description:

Subjects received treatment for 38 weeks as per the following sequence: 1) Initiation period (period-1, week 0−26): IGlar OD and IAsp OD was administered with or without OAD(s). 2) Intensification period (period-2, week 26−38): IGlar OD and IAsp 1−3 times daily was administered with or without OAD(s).

Reporting group title	Insulin degludec/insulin aspart

Reporting group description:

Subjects received treatment for 38 weeks as per the following sequence: 1) Initiation period (period-1, week 0−26): IDegAsp OD was administered with or without OAD(s). 2) Intensification period (period-2, week 26−38): IDegAsp OD/BID was administered with or without OAD(s).

Serious adverse events	Insulin glargine + insulin aspart	Insulin degludec/insulin aspart	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 263 (7.60%)	18 / 265 (6.79%)	
number of deaths (all causes)	2	0	
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 / 263 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			

subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
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	2 / 263 (0.76%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pituitary tumour benign			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia repair			
subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (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			
Non-cardiac chest pain			
subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (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			
Asthma			

subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (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	1 / 263 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 263 (0.38%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 263 (0.38%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
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 / 263 (0.38%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIth nerve paralysis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 263 (0.76%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric polyps			
subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Hidradenitis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (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			
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal mass			
subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			

subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	1 / 263 (0.38%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			

subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 263 (0.38%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 265 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Insulin glargine + insulin aspart	Insulin degludec/insulin aspart	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 263 (21.67%)	74 / 265 (27.92%)	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 263 (6.08%)	27 / 265 (10.19%)	
occurrences (all)	23	52	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 263 (3.42%)	16 / 265 (6.04%)	
occurrences (all)	9	17	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	22 / 263 (8.37%)	36 / 265 (13.58%)	
occurrences (all)	27	49	
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	17 / 263 (6.46%) 17	15 / 265 (5.66%) 17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2017	Following are the key changes done to the protocol amendment: 1) Extension of the recruitment period; planned last patient last visit (LPLV) changed from 16-Nov-2017 to 12-Dec-2017. 2) Clarification of adverse event (AE) collection during follow-up. 3) Clarification of data collection for antidiabetic concomitant medications and other concomitant medications. 4) Addition of supportive secondary endpoint: HbA1c responders without severe or BG confirmed symptomatic hypoglycaemia. 5) Implementation of a new standard for statistical data handling in line with new requirements from US Food and Drug Administration (FDA) (changes to the statistical analysis of hypoglycaemic rate during the maintenance period). 6) Correction of errors. 7) Provision of clarifications/specification of processes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported