EU Clinical Trials Register

Clinical trial results:
A trial comparing the efficacy and safety of two different titration algorithms for insulin degludec/insulin aspart in subjects with type 2 diabetes mellitus previously treated with insulin glargine

Summary

EudraCT number	2012-000373-23
Trial protocol	DE
Global end of trial date	22 August 2013

Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	28 July 2015

Trial information

Trial identification

Sponsor protocol code	NN5401-3941

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01680341
WHO universal trial number (UTN)	U1111-1127-4114

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 August 2013
Global end of trial reached?	Yes
Global end of trial date	22 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the efficacy of the insulin degludec/insulin aspart (IDegAsp) twice daily (BID) simple titration algorithm in controlling glycaemia with respect to change from baseline in glycosylated haemoglobin (HbA1c) after 26 weeks of treatment.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice and EN ISO 14155 Part 1 and 2.

Background therapy:

While entering the treatment period the subjects discontinued IGlar and sulfonylurea (SU)/glinides (if administered) but continued treatment with other OADs as prescribed. i.e. metformin, DPP-4 inhibitor or alpha-glucosidase inhibitor.

Evidence for comparator:

Not applicable

Actual start date of recruitment	31 August 2012
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	Germany: 39
Country: Number of subjects enrolled	Algeria: 35
Country: Number of subjects enrolled	Malaysia: 33
Country: Number of subjects enrolled	Turkey: 10
Country: Number of subjects enrolled	United States: 155
Worldwide total number of subjects	272
EEA total number of subjects	39

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	202
From 65 to 84 years	70
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 43 sites in 5 countries as follows: 3 sites in Algeria, 5 sites in Germany, 3 sites in Malaysia, 3 sites in Turkey, 29 sites in United States.

Pre-assignment

Screening details:

At screening, subjects were on IGlar and up to 3 OADs (metformin, DPP-4 inhibitor, SU/glinides or alpha-glucosidase inhibitor) therapy. These pre-trial assignments were ongoing from ≥12 weeks prior to randomisation and doses were stabilised in this period of time.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label trial. There was no blinding of investigators or subjects. An open label trial design was chosen since all subjects in both treatment arms were to receive insulin treatment with IDegAsp BID and since blinding of the different titration algorithms would not have been possible.

Arms

Are arms mutually exclusive?	Yes
Arm title	IDegAsp Simple

Arm description:

Subjects received insulin treatment with IDegAsp (co-formulated basal-bolus injection), for a treatment period of 26 weeks, using the simple titration algorithm. IDegAsp doses were self-titrated, twice weekly (at intervals of 3-4 days) based upon a single pre-breakfast and single pre-dinner self-measured plasma glucose (SMPG) values. The titration of the morning dose was to be based on the previous evening's pre-dinner SMPG measurement and the titration of the dinner dose was to be based on the pre-breakfast SMPG measurement taken on the day of titration.

Arm type	Experimental
Investigational medicinal product name	IDegAsp
Investigational medicinal product code	
Other name	Insulin degludec and Insulin aspart
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Twice weekly self-titration at intervals of 3-4 days, based upon a single pre-breakfast and pre-dinner SMPG (self-measured plasma glucose) value, with subcutaneous (s.c., under the skin) administration.

Arm title	IDegAsp Stepwise

Arm description:

Subjects received insulin treatment with IDegAsp (co-formulated basal-bolus injection), for a treatment period of 26 weeks, using the step-wise titration algorithm. IDegAsp doses were self-titrated, once weekly, based on lowest of 3 pre-breakfast and 3 pre-dinner self-measured plasma glucose (SMPG) values, (measurements on 3 consecutive days prior to titration). The titration of the morning dose was to be based on the pre-dinner SMPG measurements and the titration of the dinner dose was to be based on the pre-breakfast SMPG measurements.

Arm type	Experimental
Investigational medicinal product name	IDegAsp
Investigational medicinal product code	
Other name	Insulin degludec and Insulin aspart
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Once weekly self-titration based upon the lowest of 3 pre-breakfast and 3 pre-dinner SMPG (self-measured plasma glucose) values, with subcutaneous (s.c., under the skin) administration.

Number of subjects in period 1	IDegAsp Simple	IDegAsp Stepwise
Started	136	136
Completed	115	119
Not completed	21	17
Adverse event, serious fatal	1	1
Adverse event, non-fatal	2	1
Unclassified	18	15

Baseline characteristics

Reporting groups

Reporting group title	IDegAsp Simple

Reporting group description:

Subjects received insulin treatment with IDegAsp (co-formulated basal-bolus injection), for a treatment period of 26 weeks, using the simple titration algorithm. IDegAsp doses were self-titrated, twice weekly (at intervals of 3-4 days) based upon a single pre-breakfast and single pre-dinner self-measured plasma glucose (SMPG) values. The titration of the morning dose was to be based on the previous evening's pre-dinner SMPG measurement and the titration of the dinner dose was to be based on the pre-breakfast SMPG measurement taken on the day of titration.

Reporting group title	IDegAsp Stepwise

Reporting group description:

Subjects received insulin treatment with IDegAsp (co-formulated basal-bolus injection), for a treatment period of 26 weeks, using the step-wise titration algorithm. IDegAsp doses were self-titrated, once weekly, based on lowest of 3 pre-breakfast and 3 pre-dinner self-measured plasma glucose (SMPG) values, (measurements on 3 consecutive days prior to titration). The titration of the morning dose was to be based on the pre-dinner SMPG measurements and the titration of the dinner dose was to be based on the pre-breakfast SMPG measurements.

Reporting group values	IDegAsp Simple	IDegAsp Stepwise	Total
Number of subjects	136	136	272
Age categorical			
Units: Subjects			
Adults (18-64 years)	105	97	202
From 65-84 years	31	39	70
Age continuous			
Units: years			
arithmetic mean	58.8	59.1	
standard deviation	± 9.8	± 9.4	-
Gender categorical			
Units: Subjects			
Female	60	53	113
Male	76	83	159
Body Weight			
Units: Kg			
arithmetic mean	89.4	89.4	
standard deviation	± 19.3	± 17.4	-
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean	31.7	31.5	
standard deviation	± 4.8	± 4.7	-
Duration of Diabetes			
Units: Years			
arithmetic mean	13	11.2	
standard deviation	± 7	± 6.7	-
HbA1c			
Units: Percentage (%)			
arithmetic mean	8.2	8.2	
standard deviation	± 0.9	± 0.9	-
Fasting Plasma Glucose (FPG)			
Units: mmol/L			

arithmetic mean	7.8	8.1	
standard deviation	± 2.3	± 3	-

End points

End points reporting groups

Reporting group title	IDegAsp Simple

Reporting group description:

Subjects received insulin treatment with IDegAsp (co-formulated basal-bolus injection), for a treatment period of 26 weeks, using the simple titration algorithm. IDegAsp doses were self-titrated, twice weekly (at intervals of 3-4 days) based upon a single pre-breakfast and single pre-dinner self-measured plasma glucose (SMPG) values. The titration of the morning dose was to be based on the previous evening's pre-dinner SMPG measurement and the titration of the dinner dose was to be based on the pre-breakfast SMPG measurement taken on the day of titration.

Reporting group title	IDegAsp Stepwise

Reporting group description:

Subjects received insulin treatment with IDegAsp (co-formulated basal-bolus injection), for a treatment period of 26 weeks, using the step-wise titration algorithm. IDegAsp doses were self-titrated, once weekly, based on lowest of 3 pre-breakfast and 3 pre-dinner self-measured plasma glucose (SMPG) values, (measurements on 3 consecutive days prior to titration). The titration of the morning dose was to be based on the pre-dinner SMPG measurements and the titration of the dinner dose was to be based on the pre-breakfast SMPG measurements.

Primary: Change from baseline in HbA1c (%)

End point title	Change from baseline in HbA1c (%)

End point description:

Change from baseline in HbA1c (%) after 26 weeks of treatment.

End point type	Primary

End point timeframe:

At end of 26 weeks of treatment

End point values	IDegAsp Simple	IDegAsp Stepwise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: Percentage				
least squares mean (standard error)	-1.45 (± 0.09)	-1.33 (± 0.09)		

Statistical analyses

Statistical analysis title	Change from baseline in HbA1c (%).

Statistical analysis description:

Change from baseline in HbA1c after 26 weeks of treatments is analysed using an ANOVA method with treatment, sex and region as fixed effects, and age and baseline HbA1c as covariates.

Comparison groups	IDegAsp Simple v IDegAsp Stepwise

Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	1-sided
upper limit	0.11
Variability estimate	Standard error of the mean

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 in fasting plasma glucose (FPG) after 26 weeks of treatment.	
End point type	Secondary
End point timeframe:	
At end of 26 weeks of treatment	

End point values	IDegAsp Simple	IDegAsp Stepwise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: mmol/L				
least squares mean (standard error)	-1.68 (± 0.23)	-1.98 (± 0.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects achieving HbA1c< 7.0%

End point title	Proportion of subjects achieving HbA1c< 7.0%
End point description:	
Proportion of subjects achieving HbA1c< 7.0% at end of 26 weeks of treatment.	
End point type	Secondary
End point timeframe:	
At end of 26 weeks of treatment	

End point values	IDegAsp Simple	IDegAsp Stepwise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: Number of subjects	91	85		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with HbA1c< 7.0% without confirmed hypoglycaemic episodes

End point title	Proportion of subjects with HbA1c< 7.0% without confirmed hypoglycaemic episodes

End point description:

Proportion of subjects with HbA1c< 7.0% without confirmed hypoglycaemic episodes during the last 12 weeks of treatment or within 7 days from last randomised treatment including only subjects exposed for at least 12 weeks.

End point type	Secondary

End point timeframe:

At end of 26 weeks of treatment.

End point values	IDegAsp Simple	IDegAsp Stepwise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	125		
Units: Number of subjects	31	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Self-measured plasma glucose measurements (SMPGs) of the 8-point profiles

End point title	Self-measured plasma glucose measurements (SMPGs) of the 8-point profiles

End point description:

Self-measured plasma glucose measurements (SMPGs) of the 8-point profiles at the end of 26 weeks of treatment.
(N: Number of subjects)
1. Before breakfast: N in IDegAsp Simple = 134, IDegAsp Step wise = 131
2. 90 minutes after start of breakfast : N in IDegAsp Simple = 129, IDegAsp Step wise = 126
3. Before lunch: N in IDegAsp Simple = 131, IDegAsp Step wise = 126
4. 90 minutes after start of lunch: N in IDegAsp Simple = 128, IDegAsp Step wise = 127
5. Before main evening meal: N in IDegAsp Simple = 133, IDegAsp Step wise = 128
6. 90 minutes after main evening meal: N in IDegAsp Simple = 127, IDegAsp Step wise = 128
7. Before bedtime: N in IDegAsp Simple = 121, IDegAsp Step wise = 116
8. Before breakfast the following day: N in IDegAsp Simple = 135, IDegAsp Step wise = 131

End point type	Secondary

End point timeframe:

At the end of 26 weeks of treatment

End point values	IDegAsp Simple	IDegAsp Stepwise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: mmol/L				
least squares mean (standard error)				
Before breakfast	6.55 (± 0.2)	6.61 (± 0.2)		
90 minutes after start of breakfast	8.18 (± 0.28)	8.07 (± 0.29)		
Before lunch	6.8 (± 0.26)	6.48 (± 0.26)		
90 minutes after start of lunch	8.91 (± 0.27)	8.57 (± 0.27)		
Before main evening meal	7.59 (± 0.26)	7.27 (± 0.27)		
90 minutes after main evening meal	8.74 (± 0.31)	8.89 (± 0.31)		
Before bedtime	7.89 (± 0.3)	8.17 (± 0.31)		
Before breakfast the following day	6.41 (± 0.19)	6.51 (± 0.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Self-measured plasma glucose measurements (SMPGs) of the Mean of the 8-point profile

End point title	Self-measured plasma glucose measurements (SMPGs) of the Mean of the 8-point profile

End point description:

Self-measured plasma glucose measurements (SMPGs) of the mean of the 8-point profile at end of 26 weeks of treatment.

End point type	Secondary

End point timeframe:

At end of 26 weeks of treatment.

End point values	IDegAsp Simple	IDegAsp Stepwise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	132		
Units: mmol/L				
least squares mean (standard error)	7.69 (± 0.19)	7.72 (± 0.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Self-measured Prandial plasma glucose (SMPGs) increment from 8-point profile

End point title	Self-measured Prandial plasma glucose (SMPGs) increment from 8-point profile

End point description:

Self-measured Prandial plasma glucose (SMPGs) increment from 8-point profile at end of 26 weeks of treatment.
(N: Number of subjects)
1. Mean of SMPG increment-All Meal: N in IDegAsp Simple = 130, N in IDegAsp Step wise = 129
2. SMPG increment-Breakfast: N in IDegAsp Simple = 131, N in IDegAsp Step wise = 129
3. SMPG increment-Lunch: N in IDegAsp Simple = 132, N in IDegAsp Step wise = 129
4. SMPG increment-Evening Meal: N in IDegAsp Simple = 130, N in IDegAsp Step wise = 127

End point type	Secondary

End point timeframe:

At end of 26 weeks of treatment

End point values	IDegAsp Simple	IDegAsp Stepwise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: mmol/L				
least squares mean (standard error)				
Mean of SMPG increment: All Meal	2.21 (± 0.18)	2.26 (± 0.19)		
SMPG increment - Breakfast	2.61 (± 0.29)	2.28 (± 0.29)		
SMPG increment - Lunch	2.7 (± 0.3)	2.42 (± 0.31)		
SMPG increment: Evening Meal	1.62 (± 0.31)	2.04 (± 0.32)		

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:

A treatment emergent adverse event (TEAE) was defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment.

End point type	Secondary

End point timeframe:

During 28 weeks of trial

End point values	IDegAsp Simple	IDegAsp Stepwise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[1]	134[2]		
Units: Number	242	286		

Notes:

[1] - 242 adverse events were reported in 87 subjects.

[2] - 286 adverse events were reported in 89 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent confirmed hypoglycaemic episodes according to the Novo Nordisk definition for confirmed hypoglycaemic episodes

End point title	Number of treatment emergent confirmed hypoglycaemic episodes according to the Novo Nordisk definition for confirmed hypoglycaemic episodes

End point description:

Number of treatment emergent confirmed hypoglycaemic episodes according to the Novo Nordisk definition for confirmed hypoglycaemic episodes (severe hypoglycaemia and/or a measured PG < 3.1 mmol/L (< 56 mg/dL) during 28 weeks of trial.

End point type	Secondary

End point timeframe:

During 28 weeks of trial

End point values	IDegAsp Simple	IDegAsp Stepwise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[3]	134[4]		
Units: Number	552	323		

Notes:

[3] - 552 confirmed hypoglycaemic episodes were reported by 93 subjects.

[4] - 323 confirmed hypoglycaemic episodes were reported by 78 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent hypoglycaemic episodes according to the American Diabetes Association (ADA) definition ≤ 3.9 mmol/L (≤ 70 mg/dL)

End point title	Number of treatment emergent hypoglycaemic episodes according to the American Diabetes Association (ADA) definition ≤ 3.9 mmol/L (≤ 70 mg/dL)

End point description:

Number of treatment emergent hypoglycaemic episodes according to the American Diabetes Association (ADA) definition ≤ 3.9 mmol/L (≤ 70 mg/dL).

End point type	Secondary

End point timeframe:

During 28 weeks of trial

End point values	IDegAsp Simple	IDegAsp Stepwise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[5]	134[6]		
Units: Number	2226	1270		

Notes:

[5] - 2226 hypoglycaemic episodes were reported by 122 subjects.

[6] - 1270 hypoglycaemic episodes were reported by 113 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent confirmed hypoglycaemic episodes in the maintenance period

End point title	Number of treatment emergent confirmed hypoglycaemic episodes in the maintenance period

End point description:

Number of treatment emergent confirmed hypoglycaemic episodes in the maintenance period (from week 16 to end of trial including follow-up).
N = Number of subjects
1. Confirmed episodes: N in IDegAsp Simple = 64, N in IDegAsp Step wise = 50
2. ADA classified episodes: N in IDegAsp Simple = 109, N in IDegAsp Step wise = 94
3. ADA unclassifiable episodes: N in IDegAsp Simple = 3, N in IDegAsp Step wise = 4

End point type	Secondary

End point timeframe:

From week 16 to end of trial including follow-up

End point values	IDegAsp Simple	IDegAsp Stepwise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	124		
Units: Number				
Confirmed episodes	230	143		
ADA classified episodes	902	529		
ADA unclassifiable episodes	6	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent nocturnal (00:01-05:59) confirmed hypoglycaemic episodes

End point title	Number of treatment emergent nocturnal (00:01-05:59) confirmed hypoglycaemic episodes

End point description:

Number of treatment emergent nocturnal (00:01-05:59) confirmed hypoglycaemic episodes during 28 weeks of trial. (N: Number of subjects)
1. Confirmed episodes: N in IDegAsp Simple = 37, N in IDegAsp Step wise = 24
2. ADA classifiable episodes: N in IDegAsp Simple = 71, N in IDegAsp Step wise = 46
3. ADA Unclassifiable episodes: N in IDegAsp Simple = 0, N in IDegAsp Step wise = 0

End point type	Secondary

End point timeframe:

During 28 weeks of trial

End point values	IDegAsp Simple	IDegAsp Stepwise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	134		
Units: Number				
Confirmed episodes	82	49		
ADA classifiable episodes	245	128		
ADA unclassifiable episodes	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from the first trial-related activity after the subject had signed the informed consent until the end of the post-treatment follow-up period.

Adverse event reporting additional description:

An adverse event is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	IDegAsp Simple

Reporting group description:

Subjects received insulin treatment with IDegAsp (co-formulated basal-bolus injection), for a treatment period of 26 weeks, using the simple titration algorithm. IDegAsp doses were self-titrated, twice weekly (at intervals of 3-4 days) based on single pre-breakfast and single pre-dinner self-measured plasma glucose (SMPG) levels, with subcutaneous (s.c., under the skin) administration.

Reporting group title	IDegAsp Stepwise

Reporting group description:

Subjects received insulin treatment with IDegAsp (co-formulated basal-bolus injection), for a treatment period of 26 weeks, using the step-wise titration algorithm. IDegAsp doses were self-titrated, once weekly, based on lowest of 3 pre-breakfast and 3 pre-dinner self-measured plasma glucose (SMPG) levels, with subcutaneous (s.c., under the skin) administration.

Serious adverse events	IDegAsp Simple	IDegAsp Stepwise	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 135 (5.19%)	10 / 134 (7.46%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 135 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 135 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			

subjects affected / exposed	0 / 135 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 135 (0.74%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 135 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 135 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 135 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 135 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	0 / 135 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 135 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	0 / 135 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 135 (0.74%)	0 / 134 (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 / 135 (0.74%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 135 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 135 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 135 (0.74%)	0 / 134 (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			
Hypoglycaemia			
subjects affected / exposed	2 / 135 (1.48%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	IDegAsp Simple	IDegAsp Stepwise	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 135 (33.33%)	53 / 134 (39.55%)	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 135 (6.67%)	8 / 134 (5.97%)	
occurrences (all)	10	8	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 135 (3.70%)	8 / 134 (5.97%)	
occurrences (all)	7	12	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 135 (4.44%)	8 / 134 (5.97%)	
occurrences (all)	6	9	
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 135 (4.44%)	7 / 134 (5.22%)	
occurrences (all)	6	7	
Influenza			
subjects affected / exposed	5 / 135 (3.70%)	12 / 134 (8.96%)	
occurrences (all)	5	12	
Nasopharyngitis			
subjects affected / exposed	12 / 135 (8.89%)	20 / 134 (14.93%)	
occurrences (all)	16	23	
Upper respiratory tract infection			
subjects affected / exposed	14 / 135 (10.37%)	10 / 134 (7.46%)	
occurrences (all)	16	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23710902