Clinical trial results:

A 26-week trial comparing efficacy and safety of insulin degludec/insulin aspart BID and insulin degludec OD plus insulin aspart in subjects with type 2 Diabetes Mellitus treated with basal insulin in need of treatment intensification with mealtime insulin.

Summary

EudraCT number	2012-002346-20	
Trial protocol	AT NO	
Global end of trial date	09 January 2014	
Results information		
Result version number	v2 (current)	
This version publication date	14 April 2016	
First version publication date	31 July 2015	
Version creation reason	Correction of full data set Missing text to be added	

Trial information

Trial identification		
Sponsor protocol code	NN5401-3996	
Additional study identifiers		
ISRCTN number	-	
ClinicalTrials.gov id (NCT number)	NCT01713530	
WHO universal trial number (UTN)	U1111-1130-7135	

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	24 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 January 2014
Global end of trial reached?	Yes
Global end of trial date	09 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to confirm the efficacy of insulin degludec/insulin aspart (IDegAsp) twice daily (BID) in controlling glycaemia after 26 weeks of treatment.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996) and FDA 21 CFR 312.120.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	21 February 2013
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: 36
Country: Number of subjects enrolled	United States: 140
Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Norway: 33
Country: Number of subjects enrolled	Austria: 23
Worldwide total number of subjects	274
EEA total number of subjects	98

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

EU-CTR publication date: 14 April 2016

Adults (18-64 years)	204
From 65 to 84 years	70
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 48 sites in five countries as follows: Algeria (4), Austria (6), France (8), Norway (6), United States (24). In addition, 3 sites (in Austria and US) screened but did not randomise any subjects, and one site in Norway was approved by the institutional review board (IRB) but did not screen any subjects.

Pre-assignment

Screening details:

For both treatment arms, diet and exercise counselling was continued as per the standard of care at the investigational site. During the screening and treatment period, it was not allowed to start any other antidiabetic treatment, change the pre-randomisation OAD (except for the SU/glinides which were to be discontinued at randomisation) or OAD dose

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:	
Not applicable	
Arms	
Are arms mutually exclusive?	Yes
Arm title	IDegAsp BID
Arm description:	
IDegAsp is the soluble co-formulation of daily (BID).	IDeg (70%) and IAsp (30%). IDegAsp was administered twice
Arm type	Experimental
Investigational medicinal product name	IDegAsp
Investigational medicinal product code	
Other name	Insulin degludec, insulin aspart
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use
Docago and administration dotails:	

Dosage and administration details:

IDegAsp 100 U/mL, 3 mL prefilled pen PDS290, for subcutaneous injection. IDegAsp was administered twice daily (BID); either with breakfast and dinner or with lunch and dinner. IDegAsp was injected subcutaneously in the abdomen, upper arm (deltoid area) or thigh. The injection area was to remain the same throughout the trial, but the site within the area was to be changed for each injection.

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Arm title	IDeg once daily (OD) + IAsp

Arm description:

IDeg was administered once daily (OD) at any time of the day. IAsp was administered with the main meals 2–4 times daily in accordance with local labelling.

Arm type	Active comparator
Investigational medicinal product name	IDeg
Investigational medicinal product code	
Other name	Insulin degludec
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

IDeg 100 U/mL, 3 mL prefilled pen PDS290, for subcutaneous injection. IDeg was administered once daily (OD) subcutaneous injection in the thigh, the upper arm (deltoid area) or the abdominal wall and the chosen area of injection had to be the same throughout the trial.

Investigational medicinal product name	IAsp
Investigational medicinal product code	
Other name	insulin aspart
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

IAsp; NovoRapid\$/NovoLog\$, 100 U/mL, 3 mL, FlexPen\$, for subcutaneous injection. IAsp was administered with the main meals 2–4 times daily in accordance with local labelling. The IAsp was injected subcutaneously preferably into the abdominal wall in accordance with local labelling.

Number of subjects in period 1	IDegAsp BID	IDeg once daily (OD) + IAsp	
Started	138	136	
Completed	113	117	
Not completed	25	19	
Adverse event, serious fatal	-	1	
Adverse event, non-fatal	-	4	
Unclassified	4	2	
Protocol deviation	21	12	

Baseline characteristics

Reporting groups

Reporting group title	IDegAsp BID

Reporting group description:

IDegAsp is the soluble co-formulation of IDeg (70%) and IAsp (30%). IDegAsp was administered twice daily (BID).

Reporting group title IDeg once daily (OD) + IAsp

Reporting group description:

IDeg was administered once daily (OD) at any time of the day. IAsp was administered with the main meals 2-4 times daily in accordance with local labelling.

Reporting group values	IDegAsp BID	IDeg once daily (OD) + IAsp	Total	
Number of subjects	138	136	274	
Age categorical				
Units: Subjects				
In utero	0	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	0	
Newborns (0-27 days)	0	0	0	
Infants and toddlers (28 days-23 months)	0	0 0		
Children (2-11 years)	0	0	0	
Adolescents (12-17 years)	0	0	0	
Adults (18-64 years)	104	100	204	
From 65-84 years	34	36	70	
85 years and over	0	0	0	
Age continuous				
Units: years				
arithmetic mean	59.6	59.6		
standard deviation	± 8.3	± 9.2	-	
Gender categorical			_	
Units: Subjects				
Female	65	50	115	
Male	73	86	15986	

End points

End points reporting groups

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Reporting group title	IDegAsp BID
reporting group title	12 09, 100 212

Reporting group description:

IDegAsp is the soluble co-formulation of IDeg (70%) and IAsp (30%). IDegAsp was administered twice daily (BID).

Reporting group title IDeg once daily (OD) + IAsp

Reporting group description:

IDeg was administered once daily (OD) at any time of the day. IAsp was administered with the main meals 2–4 times daily in accordance with local labelling.

Primary: Change from baseline in HbA1c (%) End point title Change from baseline in HbA1c (%) End point description: End point type Primary End point timeframe: After 26 weeks of treatment

End point values	IDegAsp BID	IDeg once daily (OD) + IAsp	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	138	136	
Units: percentage			
least squares mean (standard error)	-1.23 (± 0.13)	-1.42 (± 0.12)	

Statistical analyses

Statistical analysis title	HbA1c (%) after 26 weeks of treatment
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Statistical analysis description:

Change from baseline in HbA1c after 26 weeks of treatment was analysed using an Analysis of Variance (ANOVA) method with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA1c as covariates.

Comparison groups	IDegAsp BID v IDeg once daily (OD) + IAsp
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	= 0.029 [2]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.41

Notes:

- [1] The test of mean treatment difference is greater than 0.4%.
- [2] Non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval was below or equal to 0.4%. This was equivalent to using a one-sided test of size 2.5%.

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:		
After 26 weeks of treatment.		

End point values	IDegAsp BID	IDeg once daily (OD) + IAsp	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	136	136	
Units: mmol/L			
least squares mean (standard error)	-2.22 (± 0.38)	-1.9 (± 0.36)	

Statistical analyses

No statistical analyses for this end point

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

Number of treatment emergent hypoglycaemic episodes according to Novo Nordisk definition of confirmed
hypoglycaemic episodes.

End point description:

Novo Nordisk definition for confirmed hypoglycaemic episodes: severe hypoglycaemia and /or a measured plasma glucose (PG)< 3.1 mmol/L (56 mg/dL).

End point type	Secondary
End point timeframe:	
During 26 weeks of treatment	

End point values	IDegAsp BID	IDeg once daily (OD) + IAsp	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	136	135	
Units: Number of episodes	706	841	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent hypoglycaemic episodes according to the American Diabetes Association (ADA) definition

End point title	Number of treatment emergent hypoglycaemic episodes
	according to the American Diabetes Association (ADA)
	definition

End point description:

Categories of hypoglycaemic episode as per ADA definition:

Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured PG concentration \leq 3.9 mmol/L (70 mg/dL).

Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured PG concentration \leq 3.9 mmol/L (70 mg/dL).

Relative hypoglycaemia: An episode during which the person with diabetes mellitus reports any of the typical symptoms of hypoglycaemia, and interprets those as indicative of hypoglycaemia, but with a measured PG concentration >3.9 mmol/L (70 mg/dL).

Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a PG determination (but that was presumably caused by a PG concentration ≤ 3.9 mmol/L [70 mg/dL]).

End point type	Secondary
End point timeframe:	
During 26 weeks of treatment	

End point values	IDegAsp BID	IDeg once daily (OD) + IAsp	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	136	135	
Units: events			
American Diabetes Association (ADA)	2894	2685	
Severe	29	15	
Documented symptomatic	1818	1843	
Asymptomatic	930	728	
Probable symptomatic	26	33	
Relative	91	66	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of tre hypoglycaemic episodes.	eatment emergent nocturnal (00:01-05:59 am) confirmed
End point title	Number of treatment emergent poeturnal (00:01-05:50 am)

	confirmed hypoglycaemic episodes.
End point description:	
Nocturnal period is defined as the period hypoglycaemia can occur.	between 00:01 and 05:59 a.m. (both included) in which
End point type	Secondary
End point timeframe:	
During 26 weeks of treatment	

End point values	IDegAsp BID	IDeg once daily (OD) + IAsp	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	136	135	
Units: Number of episodes	75	96	

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of treatment emergent adverse events (TEAE).

	End point title	Incidence of treatment emergent adverse events (TEAE).
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End point description:

A 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 26 weeks of treatment.

End point values	IDegAsp BID	IDeg once daily (OD) + IAsp	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	136	135	
Units: Event	330	298	

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 (visit 29).

Adverse event reporting additional description:

Safety analysis set included all the subjects receiving at least one dose of the investigational product.

Assessment type	Systematic	
Dictionary used		
Dictionary name	MedDRA	
Dictionary version	16.0, 16.1	

Reporting groups

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Reporting group title	IDeg OD + IAsp

Reporting group description:

IDeg was to be administered OD at any time of the day. It was to be injected subcutaneously in the abdomen, upper arm (deltoid area) or thigh. IAsp was to be administered with the main meals 2-4 times daily in accordance with local labelling.

Reporting group title	IDegAsp PDS290

Reporting group description:

IDegAsp was to be administered either with breakfast and dinner or with lunch and dinner. IDegAsp was to be injected subcutaneously in the abdomen, upper arm (deltoid area) or thigh.

Serious adverse events	IDeg OD + IAsp	IDegAsp PDS290	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 135 (9.63%)	7 / 136 (5.15%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour benign			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (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 Femoral neck fracture			

subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (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	2 / 135 (1.48%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Wrong drug administered			
subjects affected / exposed	2 / 135 (1.48%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0/0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypersomnia			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoglycaemic unconsciousness			1
subjects affected / exposed	1 / 135 (0.74%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	1/1	1/1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Ocular hypertension			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (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			
Pneumomediastinum			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0/0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation]		İ
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (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%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-se	erious adverse events	: 5 %	
Non-serious adverse events	IDeg OD + IAsp	IDegAsp PDS290	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 135 (28.15%)	46 / 136 (33.82%)	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 135 (5.93%)	10 / 136 (7.35%)	
occurrences (all)	12	12	
General disorders and administration site conditions Asthenia			
subjects affected / exposed	2 / 135 (1.48%)	10 / 136 (7.35%)	
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occurrences (all)	2	10	
 Fatigue			
subjects affected / exposed	1 / 135 (0.74%)	7 / 136 (5.15%)	
occurrences (all)	1	7	
Cocarrences (any	1	/	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 135 (6.67%)	9 / 136 (6.62%)	
occurrences (all)	9	9	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	7 / 135 (5.19%)	5 / 136 (3.68%)	
occurrences (all)	8	5	
(4.17)	8	3	
Pain in extremity			
subjects affected / exposed	3 / 135 (2.22%)	8 / 136 (5.88%)	
occurrences (all)	3	8	
Tofactions and infections			
Infections and infestations Influenza			
subjects affected / exposed	E / 12E /2 700/ \	0 / 126 /6 620/ \	
	5 / 135 (3.70%)	9 / 136 (6.62%)	
occurrences (all)	7	9	
Nasopharyngitis			

subjects affected / exposed	12 / 135 (8.89%)	11 / 136 (8.09%)	
occurrences (all)	14	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2012	Due to unforeseen changes in the regulatory environment, India was removed as a participating country and Quintiles Laboratory in Mumbai was removed from Protocol Attachment I. In order to reflect real life practice, it was clarified that 11 days from visit 1 to visit 2 were allowed. The timing of fundoscopy/fundus photography and that subjects were not to discard unused trial products was clarified. Due to a change in international trial manager, Protocol Attachment I was updated. Minor inconsistencies in Appendix A were corrected

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.

None reported

EU-CTR publication date: 14 April 2016

Notes: