



## 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	v1
This version publication date	01 April 2016
First version publication date	31 July 2015

### Trial information

#### Trial identification

Sponsor protocol code	NN5401-3996
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#### 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:

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**Results analysis stage**

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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:

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**General information about the trial**

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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:

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**Population of trial subjects**

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**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:

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**Subjects enrolled per age group**

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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)	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
<b>Arm title</b>	IDegAsp BID

Arm description:

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

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

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.

<b>Arm title</b>	IDeg once daily (OD) + IAsp
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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.

<b>Number of subjects in period 1</b>	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
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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
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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	159
Body weight Units: Kg			
arithmetic mean	91.2	93.3	
standard deviation	± 17.7	± 15.2	-

## End points

### End points 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.	

### 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 ( $\pm$ 0.13)	-1.42 ( $\pm$ 0.12)		

### Statistical analyses

Statistical analysis title	HbA1c (%) after 26 weeks of treatment
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 <sup>[1]</sup>
P-value	= 0.029 <sup>[2]</sup>
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 ( $\pm$ 0.38)	-1.9 ( $\pm$ 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.

End point title	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
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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  $\leq 3.9$  mmol/L [70 m

End point type	Secondary
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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 treatment emergent nocturnal (00:01-05:59 am) confirmed hypoglycaemic episodes.

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

Nocturnal period is defined as the period between 00:01 and 05:59 a.m. (both included) in which hypoglycaemia can occur.

End point type	Secondary
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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
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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



## 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0, 16.1
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### Reporting groups

Reporting group title	IDegAsp PDS290
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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.

Reporting group title	IDeg OD + IAsp
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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.

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

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

Hypoglycaemic unconsciousness subjects affected / exposed	1 / 136 (0.74%)	1 / 135 (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	1 / 136 (0.74%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Ocular hypertension			
subjects affected / exposed	0 / 136 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumomediastinum			
subjects affected / exposed	0 / 136 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 136 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 136 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 136 (0.00%)	1 / 135 (0.74%)	
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	1 / 136 (0.74%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	IDegAsp PDS290	IDeg OD + IAsp	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 136 (33.82%)	38 / 135 (28.15%)	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 136 (7.35%)	8 / 135 (5.93%)	
occurrences (all)	12	12	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 136 (7.35%)	2 / 135 (1.48%)	
occurrences (all)	10	2	
Fatigue			
subjects affected / exposed	7 / 136 (5.15%)	1 / 135 (0.74%)	
occurrences (all)	7	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 136 (6.62%)	9 / 135 (6.67%)	
occurrences (all)	9	9	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 136 (3.68%)	7 / 135 (5.19%)	
occurrences (all)	5	8	
Pain in extremity			
subjects affected / exposed	8 / 136 (5.88%)	3 / 135 (2.22%)	
occurrences (all)	8	3	
Infections and infestations			
Influenza			
subjects affected / exposed	9 / 136 (6.62%)	5 / 135 (3.70%)	
occurrences (all)	9	7	
Nasopharyngitis			

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



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2012	<p>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.</p> <p>In order to reflect real life practice, it was clarified that 11 days from visit 1 to visit 2 were allowed.</p> <p>The timing of funduscopy/fundus photography and that subjects were not to discard unused trial products was clarified.</p> <p>Due to a change in international trial manager, Protocol Attachment I was updated.</p> <p>Minor inconsistencies in Appendix A were corrected</p>

Notes:

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### 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
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Notes: