Clinical trial results:
A 26-week, Multinational, Multi-centre, Open-Labelled, Randomised, Parallel, Efficacy and Safety Comparison of Insulin Degludec and Insulin Detemir in children and adolescents 1 to less than 18 years with type 1 Diabetes Mellitus on a basal-bolus regimen with insulin aspart as bolus insulin followed by a 26-week extension investigating long term safety.

Summary

EudraCT number	2011-003148-39
Trial protocol	NL FI DE BG GB IT
Global end of trial date	30 July 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	NN1250-3561

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01513473
WHO universal trial number (UTN)	U1111-1122-4758

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, clinicatrials@novonordisk.com
Scientific contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicatrials@novonordisk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000412-PIP01-08, EMEA-000479-PIP01-08, EMEA-000456-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 February 2013
Global end of trial reached?	Yes
Global end of trial date	30 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the efficacy of insulin degludec (IDeg) administered once daily plus mealtime insulin aspart in controlling glycaemia with respect to change from baseline in HBA1c after 26 weeks of treatment. This is done by comparing the difference in change in HbA1c between insulin degludec (IDeg) + insulin aspart (IAsp) and insulin detemir (IDet) + insulin aspart(IAsp) to a non-inferiority limit of 0.4%, and if non-inferiority is confirmed, to a superiority limit of 0%.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice.

Background therapy:

Not Applicable

Evidence for comparator:

Not Applicable

Actual start date of recruitment	16 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Bulgaria: 30
Country: Number of subjects enrolled	Finland: 16
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Japan: 55
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 16
Country: Number of subjects enrolled	Russian Federation: 51
Country: Number of subjects enrolled	South Africa: 12
Country: Number of subjects enrolled	United States: 101
Worldwide total number of subjects	350
EEA total number of subjects	115

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)	4
Children (2-11 years)	219
Adolescents (12-17 years)	127
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 72 sites in 12 countries as follows:
Bulgaria (2), Finland (5), France (4), Germany (3), Italy (2), Japan (15), Netherlands (5), Republic of Macedonia (2), Russian Federation (6), South Africa (2), United Kingdom (4), United States (22).

Pre-assignment

Screening details:

Not Applicable

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 is an open-label, randomised trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)

Arm description:

Subjects from 1 to less than 18 years of age were randomised into treatment arms, receiving IDeg OD as basal insulin treatment. IDeg was administered subcutaneously OD as basal insulin. IAsp was given as mealtime bolus insulin.
170 subjects completed the main trial,152 subjects included in the extension. 18 subjects did not consent to participate in the extension trial.

Arm type	Experimental
Investigational medicinal product name	IDeg
Investigational medicinal product code	
Other name	Insulin Degludec
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The basal insulin was to be administered with NovoPen® Echo (blue for basal) and in Japan NovoPen® 300 Demi Lime and in the US NovoPen® Junior. In Finland and the UK only, NovoPen® 4 (blue/silver) was used for administration of higher basal insulin doses.IDeg was given once a day at approximately the same time of the day.
Basal insulin titration was done according to the lowest pre-breakfast SMPG value measured on the three days prior to the visit/ phone contact for IDeg.

Investigational medicinal product name	IAsp
Investigational medicinal product code	
Other name	Insulin Aspart
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The bolus insulin was to be administered with NovoPen® Echo (red for bolus), in Japan NovoPen®°300 Demi Apricot and in the US NovoPen® Junior. It was given as mealtime insulin. IAsp titration was done once weekly based on the lowest of three SMPG values measured prior to
the next meal and bedtime on the three days prior to the visit/phone contact.

Arm title	Insulin Detemir (IDet) + Insulin Aspart (IAsp)

Arm description:

Subjects from 1 to less than 18 years of age were randomised into treatment arms, receiving IDet OD or BID (twice daily) as basal insulin treatment and used IAsp as mealtime bolus insulin. 165 subjects

completed the main trial, 128 included in the extension trial. 37 subjects did not consent to participate in the extension trial.

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

Dosage and administration details:

Subjects randomised into the IDet treatment arm continued with their pre-trial dosing scheme (OD or BID). Subjects randomised into the IDet treatment arm were allowed to switch from OD to BID dosing according to Protocol.The basal insulin was to be administered with NovoPen® Echo (blue for basal) and in Japan NovoPen® 300 Demi Lime and in the US NovoPen® Junior. In Finland and the UK only, NovoPen® 4 (blue/silver) was used for administration of higher basal insulin doses.Basal insulin titration was done according to the lowest pre-breakfast SMPG value measured on the three days prior to the visit/ phone contact for IDet OD. For IDet BID the morning dose adjustment was to be based on the lowest pre-dinner SMPG value measured on the three days prior to the visit/phone contact.

Investigational medicinal product name	IAsp
Investigational medicinal product code	
Other name	Insulin Aspart
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The bolus insulin was to be administered with NovoPen® Echo (red for bolus), in Japan NovoPen®°300 Demi Apricot and in the US NovoPen® Junior. It was given as mealtime insulin.IAsp titration was done once weekly based on the lowest of three SMPG values measured prior to the next meal and bedtime on the three days prior to the visit/phone contact.

Number of subjects in period 1	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)
Started	174	176
Completed	151	122
Not completed	23	54
Did not consent to extension trial	18	37
Adverse event, non-fatal	-	3
Withdrawal criteria	5	12
other	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	350	350	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	4	4	
Children (2-11 years)	219	219	
Adolescents (12-17 years)	127	127	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	156	156	
Male	194	194	

End points

End points reporting groups

Reporting group title	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)
Reporting group description:	
Subjects from 1 to less than 18 years of age were randomised into treatment arms, receiving IDeg OD as basal insulin treatment. IDeg was administered subcutaneously OD as basal insulin. IAsp was given as mealtime bolus insulin. 170 subjects completed the main trial,152 subjects included in the extension. 18 subjects did not consent to participate in the extension trial.	
Reporting group title	Insulin Detemir (IDet) + Insulin Aspart (IAsp)
Reporting group description:	
Subjects from 1 to less than 18 years of age were randomised into treatment arms, receiving IDet OD or BID (twice daily) as basal insulin treatment and used IAsp as mealtime bolus insulin. 165 subjects completed the main trial, 128 included in the extension trial. 37 subjects did not consent to participate in the extension trial.	

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:	
After 26 weeks of treatment	

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	176		
Units: percentage				
arithmetic mean (standard deviation)	-0.2 (± 0.95)	-0.31 (± 0.89)		

Statistical analyses

Statistical analysis title	Change from baseline in HbA1c
Comparison groups	Insulin Degludec (IDeg) + Insulin Aspart (IAsp) v Insulin Detemir (IDet) + Insulin Aspart (IAsp)
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANOVA
Parameter estimate	Treatment- Contrast
Point estimate	0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.32

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 FPG after 26 weeks of treatment.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment.

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	160		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.67 (± 5.99)	0.5 (± 8.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent adverse events (TEAEs)

End point title	Number of treatment emergent adverse events (TEAEs)

End point description:

A Treatment Emergent Adverse Event (TEAE) is 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:

After 26 weeks weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: Number of adverse events	810	761		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of hypoglycaemic episodes

End point title	Number of hypoglycaemic episodes

End point description:

Episodes of severe hypoglycaemia or episodes with plasma glucose (PG) ≤3.9mmol/L (70mg/dL) with or without symptoms of hypoglycaemia)during the trial. The number of episodes described in the results section is the sum of the above classifications.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: Number of hypoglycaemic episodes	11712	10991		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of nocturnal hypoglycaemic episodes

End point title	Number of nocturnal hypoglycaemic episodes

End point description:

Episodes of severe hypoglycaemia or episodes with plasma glucose (PG) ≤3.9mmol/L (70mg/dL) with or without symptoms of hypoglycaemia)during the trial. Nocturnal hypoglycaemia- Hypoglycaemic episodes from 11pm-7.00am noted in the subjects.The number of episodes described in the results section is the sum of the above classifications.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: Number of hypoglycaemic episodes	1261	1458		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of self-measured hyperglycaemia

End point title	Number of self-measured hyperglycaemia

End point description:

Episodes of PG >11.1mmol/L (200mg/dL)

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: Number of episodes	31264	31173		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of self measured blood ketones >1.5 mmol/L-capillary blood ketone measurement to be performed if self- measured plasma glucose (SMPG) exceeds 14.0 mmol/L (250 mg/dL)

End point title	Number of self measured blood ketones >1.5 mmol/L-capillary blood ketone measurement to be performed if self- measured plasma glucose (SMPG) exceeds 14.0 mmol/L (250 mg/dL)

End point description:

Blood ketones > 1.5mmol/L (Capillary blood ketone measurement to be performed if self measured plasma glucose (SMPG) exceeds 14.0mmol/L (250mg/dL))after 26 weeks of treatment.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: Number of episodes of ketosis	44	86		

Statistical analyses

No statistical analyses for this end point

Secondary: Steady state plasma concentrations of insulin degludec and insulin detemir

End point title	Steady state plasma concentrations of insulin degludec and insulin detemir

End point description:

Steady state plasma concentrations of insulin degludec and insulin detemir on three different visits (three different weeks) during the trial.

End point type	Secondary

End point timeframe:

During the first 26 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: pmol/L				
arithmetic mean (standard deviation)				
Week 2	4540.4 (± 3999)	3972.2 (± 6721.8)		
Week 12	4148.1 (± 3726.9)	5430.1 (± 9067.7)		
Week 26	4105.6 (± 3456.5)	6377 (± 10930.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in HbA1c (%)

End point title	Change from baseline in HbA1c (%)

End point description:

Change from baseline in HbA1c (%) after 52 weeks of treatments.

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	176		
Units: percentage				
arithmetic mean (standard deviation)	-0.27 (± 1.07)	-0.22 (± 1.03)		

Statistical analyses

No statistical analyses for this end point

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 FPG after 52 weeks of treatment

End point type	Secondary

End point timeframe:

At 52 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	160		
Units: mmol/L				
arithmetic mean (standard deviation)	-1.29 (± 6.53)	1.1 (± 8.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent adverse events (TEAEs)

End point title	Number of treatment emergent adverse events (TEAEs)

End point description:

A Treatment Emergent Adverse Event (TEAE) is 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:

After 52 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: Number of TEAEs	1462	1266		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of hypoglycaemic episodes

End point title	Number of hypoglycaemic episodes

End point description:

Episodes of severe hypoglycaemia or episodes with plasma glucose (PG) ≤3.9mmol/L (70mg/dL) with or without symptoms of hypoglycaemia)during the trial. The number of episodes described in the results section is the sum of the above classifications.

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: Number of hypoglycaemic episodes	21560	18373		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of nocturnal hypoglycaemic episodes

End point title	Number of nocturnal hypoglycaemic episodes

End point description:

Episodes of severe hypoglycaemia or episodes with plasma glucose (PG) ≤3.9mmol/L (70mg/dL) with or without symptoms of hypoglycaemia)during the trial. Nocturnal hypoglycaemia- Hypoglycaemic episodes from 11pm-7.00am noted in the subjects. The number of episodes described in the results section is the sum of the above classifications.

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	176		
Units: Number of hypoglycaemic episodes	2336	2586		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of self measured blood ketones >1.5 mmol/L-capillary blood ketone measurement to be performed if self-measured plasma glucose (SMPG) exceeds 14.0 mmol/L (250 mg/dL)

End point title	Number of self measured blood ketones >1.5 mmol/L-capillary blood ketone measurement to be performed if self-measured plasma glucose (SMPG) exceeds 14.0 mmol/L (250 mg/dL)

End point description:

Blood ketones > 1.5mmo/L (Capillary blood ketone measurement to be performed if self measured plasma glucose (SMPG) exceeds 14.0mmol/L (250mg/dL)) after 52 weeks of treatment.

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: Number of episodes of ketosis	109	161		

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin Aspart specific antibodies

End point title	Insulin Aspart specific antibodies
End point description:	
Antibody measurements : the values presented are week 26 (LOCF)	
End point type	Secondary
End point timeframe:	
After 26 weeks of treatment	

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: % B/T				
arithmetic mean (standard deviation)	1.2 (± 2.6)	1.5 (± 2.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin Aspart specific antibodies

End point title	Insulin Aspart specific antibodies
End point description:	
Antibody measurements : the values presented are week 52 (LOCF)	
End point type	Secondary
End point timeframe:	
After 52 weeks of treatment	

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: % B/T				
arithmetic mean (standard deviation)	1.1 (± 2.6)	1.5 (± 2.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin Detemir specific antibodies

End point title	Insulin Detemir specific antibodies

End point description:

Antibody measurements : the values presented are week 26 (LOCF)

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	175		
Units: % B/T				
arithmetic mean (standard deviation)	()	5.4 (± 5.3)		

Notes:

[1] - The analysis was done for the subjects taking insulin detemir only

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin Detemir specific antibodies

End point title	Insulin Detemir specific antibodies

End point description:

Antibody measurements : the values presented are week 52 (LOCF)

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	175		
Units: % B/T				
arithmetic mean (standard deviation)	()	6.1 (± 6.5)		

Notes:

[2] - The antibody analysis was for subjects taking insulin detemir only.

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin Degludec specific antibodies

End point title	Insulin Degludec specific antibodies

End point description:

Antibody measurements : the values presented are of week 26 (LOCF)

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	0[3]		
Units: % B/T				
arithmetic mean (standard deviation)	0.1 (± 0.4)	()		

Notes:

[3] - The antibody analysis was for the subjects who took insulin degludec only.

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin Degludec specific antibodies

End point title	Insulin Degludec specific antibodies

End point description:

Antibody measurements :the presented values are week 52 (LOCF)

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	0[4]		
Units: % B/T				
arithmetic mean (standard deviation)	0 (± 0.3)	()		

Notes:

[4] - The antibody analysis was done for subjects taking insulin degludec only

Statistical analyses

No statistical analyses for this end point

Secondary: Cross -reacting insulin antibodies to human insulin

End point title	Cross -reacting insulin antibodies to human insulin

End point description:

Antibody measurements : the values presented are week 26 (LOCF)

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: % B/T				
arithmetic mean (standard deviation)	20.8 (± 17.9)	25.8 (± 19.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cross-reacting insulin antibodies to human insulin

End point title	Cross-reacting insulin antibodies to human insulin

End point description: Antibody measurements : the values pressnted are week 52 (LOCF)	
End point type	Secondary
End point timeframe: After 52 weeks of treatment	

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: % B/T				
arithmetic mean (standard deviation)	17.2 (± 17.7)	26 (± 19.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of self-measured hyperglycaemia

End point title	Number of self-measured hyperglycaemia
End point description: Episodes of PG >11.1mmol/L (200mg/dL)	
End point type	Secondary
End point timeframe: After 52 weeks of treatment	

End point values	Insulin Degludec (IDeg) + Insulin Aspart (IAsp)	Insulin Detemir (IDet) + Insulin Aspart (IAsp)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: Number of episodes	58679	52831		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

treatment emergent events (after first trial product administration and no later than 7 days after last trial product administration)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	Insulin Detemir+Insulin Aspart

Reporting group description:

Subjects from 1 to less than 18 years of age were randomised into treatment arms, receiving IDet OD or BID (twice daily) as basal insulin treatment and used IAsp as mealtime bolus insulin. 165 subjects completed the main trial and 37 subjects did not consent to participate in the extension trial.

Reporting group title	Insulin Degludec +Insulin Aspart

Reporting group description:

Subjects from 1 to less than 18 years of age were randomised into treatment arms, receiving IDeg OD as basal insulin treatment. IDeg was administered subcutaneously OD as basal insulin. IAsp was given as mealtime bolus insulin.
170 subjects completed the main trial and 18 subjects did not consent to participate in the extension trial.

Serious adverse events	Insulin Detemir+Insulin Aspart	Insulin Degludec +Insulin Aspart	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 175 (9.14%)	18 / 174 (10.34%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood ketone body increased			
subjects affected / exposed	2 / 175 (1.14%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	
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			
Accidental overdose			

subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	
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 / 175 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic seizure			
subjects affected / exposed	3 / 175 (1.71%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic unconsciousness			
subjects affected / exposed	1 / 175 (0.57%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 175 (0.57%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Faecaloma			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 175 (0.57%)	0 / 174 (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			
Cough			
subjects affected / exposed	1 / 175 (0.57%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	1 / 175 (0.57%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 175 (1.14%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 175 (1.14%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	2 / 175 (1.14%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 175 (0.57%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 175 (0.57%)	0 / 174 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	2 / 175 (1.14%)	5 / 174 (2.87%)	
occurrences causally related to treatment / all	1 / 2	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketosis			
subjects affected / exposed	1 / 175 (0.57%)	1 / 174 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 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 Detemir+Insulin Aspart	Insulin Degludec +Insulin Aspart	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	143 / 175 (81.71%)	146 / 174 (83.91%)	
Investigations			
Blood ketone body increased			
subjects affected / exposed	46 / 175 (26.29%)	31 / 174 (17.82%)	
occurrences (all)	131	78	
Nervous system disorders			
Headache			
subjects affected / exposed	51 / 175 (29.14%)	46 / 174 (26.44%)	
occurrences (all)	121	106	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	28 / 175 (16.00%)	30 / 174 (17.24%)	
occurrences (all)	45	59	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	5 / 175 (2.86%)	10 / 174 (5.75%)	
occurrences (all)	5	12	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 175 (4.57%)	12 / 174 (6.90%)	
occurrences (all)	12	16	
Abdominal pain upper			
subjects affected / exposed	17 / 175 (9.71%)	28 / 174 (16.09%)	
occurrences (all)	30	42	
Diarrhoea			
subjects affected / exposed	17 / 175 (9.71%)	22 / 174 (12.64%)	
occurrences (all)	25	26	
Nausea			
subjects affected / exposed	9 / 175 (5.14%)	13 / 174 (7.47%)	
occurrences (all)	12	18	
Vomiting			

subjects affected / exposed	22 / 175 (12.57%)	26 / 174 (14.94%)	
occurrences (all)	35	38	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	28 / 175 (16.00%)	31 / 174 (17.82%)	
occurrences (all)	41	52	
Nasal congestion			
subjects affected / exposed	7 / 175 (4.00%)	13 / 174 (7.47%)	
occurrences (all)	13	17	
Oropharyngeal pain			
subjects affected / exposed	34 / 175 (19.43%)	29 / 174 (16.67%)	
occurrences (all)	50	45	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	5 / 175 (2.86%)	11 / 174 (6.32%)	
occurrences (all)	5	16	
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 175 (4.57%)	9 / 174 (5.17%)	
occurrences (all)	11	10	
Ear infection			
subjects affected / exposed	11 / 175 (6.29%)	9 / 174 (5.17%)	
occurrences (all)	11	11	
Gastroenteritis			
subjects affected / exposed	22 / 175 (12.57%)	15 / 174 (8.62%)	
occurrences (all)	25	19	
Gastroenteritis viral			
subjects affected / exposed	8 / 175 (4.57%)	10 / 174 (5.75%)	
occurrences (all)	13	15	
Influenza			
subjects affected / exposed	18 / 175 (10.29%)	16 / 174 (9.20%)	
occurrences (all)	21	19	
Nasopharyngitis			
subjects affected / exposed	67 / 175 (38.29%)	72 / 174 (41.38%)	
occurrences (all)	141	177	
Pharyngitis			

subjects affected / exposed	9 / 175 (5.14%)	6 / 174 (3.45%)	
occurrences (all)	13	7	
Rhinitis			
subjects affected / exposed	14 / 175 (8.00%)	12 / 174 (6.90%)	
occurrences (all)	23	19	
Sinusitis			
subjects affected / exposed	6 / 175 (3.43%)	9 / 174 (5.17%)	
occurrences (all)	6	13	
Upper respiratory tract infection			
subjects affected / exposed	24 / 175 (13.71%)	34 / 174 (19.54%)	
occurrences (all)	58	56	
Viral infection			
subjects affected / exposed	10 / 175 (5.71%)	6 / 174 (3.45%)	
occurrences (all)	18	8	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	17 / 175 (9.71%)	26 / 174 (14.94%)	
occurrences (all)	31	62	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 November 2011	The corrections to the text for the definition of confirmed hypoglycaemia and conversion of FPG from mmol/dL to mg/dL. In addition it is stated that Novo Nordisk will supply NPH insulin to Japan, Italy and the US.
06 March 2012	The revisions to the text to further describe and clarify the endpoints measured in the extension period of the trial. All subjects who completed 26 weeks of treatment (main period) were encouraged to continue in an extension of the trial under similar conditions, for an additional 6 months (extension period). Subjects were to continue the 6 month extension period according to the treatment allocation in the main period and all efficacy analyses based on the full 12 months period (two times 26 weeks of treatment) will be regarded as supportive. An informed consent covering the extension period must be obtained prior to any activities related to the extension period. An additional secondary endpoint, measurement of insulin antibodies (IDeg specific, IDet specific, IAsp specific and antibodies cross-reacting to human insulin) after 26 weeks and 52 weeks of treatment was added to fulfil the requirement of monitoring the long term immunogenicity. Substantial amendment 3 was not approved in South Africa due to administrative delay and therefore subjects in South Africa could not continue into the extension period of the trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Not Applicable

Notes: