Clinical trial results:
A 52-Week, Multinational, Multi-Centre, Open-Labelled, Randomised, Parallel, Efficacy and Safety Comparison of Insulin Detemir and NPH Insulin in Children and Adolescents 2-16 years with Type 1 Diabetes on a Basal-Bolus Regimen with Insulin Aspart as Bolus Insulin

Summary

EudraCT number	2006-000051-18
Trial protocol	HU FI CZ DK BG FR
Global end of trial date	03 September 2008

Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	NN304-1689

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00435019
WHO universal trial number (UTN)	-

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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000412-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	09 October 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 September 2008
Global end of trial reached?	Yes
Global end of trial date	03 September 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the glycaemic control, measured as HbA1c, of insulin detemir administered once or twice daily plus mealtime insulin aspart with NPH insulin administered once or twice daily plus mealtime insulin aspart in children and adolescents with type 1 diabetes.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (October 2000, amended 2002 and 2004) and ICH Good Clinical Practice (01-May-1996).

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	12 February 2007
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	Denmark: 19
Country: Number of subjects enrolled	Finland: 18
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Czech Republic: 38
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Bulgaria: 38
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 24
Country: Number of subjects enrolled	Poland: 50
Country: Number of subjects enrolled	Russian Federation: 82
Country: Number of subjects enrolled	Turkey: 31
Country: Number of subjects enrolled	United Kingdom: 13
Worldwide total number of subjects	347
EEA total number of subjects	210

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)	221
Adolescents (12-17 years)	126
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 35 centres in 11 countries: 3 in Bulgaria, 3 in the Czech Republic, 3 in Denmark, 5 in Finland, 2 in France, 2 in Hungary, 1 in Macedonia, 4 in Poland, 4 in the Russian Federation, 4 in Turkey and 4 in the UK.

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:

Not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Insulin detemir

Arm description:

Individually adjusted insulin detemir dose injected subcutaneously once daily (evening) or twice daily (morning and evening) + insulin aspart with larger meals

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

Dosage and administration details:

s.c. injection, once or twice daily

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

Dosage and administration details:

s.c. injection, at main meals

Arm title	NPH Insulin

Arm description:

Individually adjusted NPH insulin dose injected subcutaneously once daily (evening) or twice daily (morning and evening) + insulin aspart with larger meals

Arm type	Experimental
Investigational medicinal product name	NPH insulin
Investigational medicinal product code	
Other name	insulin human
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

s.c. injection, once or twice daily

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

Dosage and administration details:

s.c. injection, at main meals

Number of subjects in period 1	Insulin detemir	NPH Insulin
Started	177	170
Exposed to Study Drug	177	170
Completed	164	161
Not completed	13	9
Adverse event, non-fatal	1	-
Unclassified	8	6
Protocol deviation	3	1
Lack of efficacy	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Insulin detemir
Reporting group description:	
Individually adjusted insulin detemir dose injected subcutaneously once daily (evening) or twice daily (morning and evening) + insulin aspart with larger meals	
Reporting group title	NPH Insulin
Reporting group description:	
Individually adjusted NPH insulin dose injected subcutaneously once daily (evening) or twice daily (morning and evening) + insulin aspart with larger meals	

Reporting group values	Insulin detemir	NPH Insulin	Total
Number of subjects	177	170	347
Age categorical			
Units: Subjects			
<=18 years	177	170	347
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Age continuous			
Units: years			
arithmetic mean	10	9.8	
standard deviation	± 4.09	± 3.9	-
Gender categorical			
Units: Subjects			
Female	94	73	167
Male	83	97	180
Body weight			
Units: Kg			
arithmetic mean	37.1	36.2	
standard deviation	± 16.4	± 16.1	-
Body mass index (BMI)			
Units: Kg/m2			
arithmetic mean	18	17.99	
standard deviation	± 2.74	± 2.65	-
HbA1c			
Units: Percentage			
arithmetic mean	8.41	8.4	
standard deviation	± 1.11	± 1.1	-
Fasting plasma glucose (FPG)			
Units: mmol/L			
arithmetic mean	8.36	8.7	
standard deviation	± 4.38	± 4.59	-
Serum ALAT			
Units: U/L			
arithmetic mean	19.15	20.24	
standard deviation	± 8.37	± 9.88	-
Serum Lactate dehydrogenase			
Units: U/L			

arithmetic mean	204	204.5	
standard deviation	± 48.12	± 39.32	-
Serum albumin			
Units: g/dL			
arithmetic mean	4.32	4.32	
standard deviation	± 0.22	± 0.23	-
Serum alkaline phosphatase			
Units: U/L			
arithmetic mean	243.5	257.7	
standard deviation	± 84.96	± 84.09	-
Serum creatinine			
Units: umol/L			
arithmetic mean	44.82	44.55	
standard deviation	± 11.38	± 11.38	-
Serum potassium			
Units: mmol/L			
arithmetic mean	4.35	4.37	
standard deviation	± 0.37	± 0.37	-
Serum sodium			
Units: mmol/L			
arithmetic mean	138.4	138.2	
standard deviation	± 2.06	± 2.47	-
Serum total proteins			
Units: g/dL			
arithmetic mean	7.05	7.06	
standard deviation	± 0.42	± 0.45	-
Blood haemoglobin			
Units: mmol/L			
arithmetic mean	8.39	8.33	
standard deviation	± 0.57	± 0.67	-
Blood leukocytes			
Units: 10^9/L			
arithmetic mean	6.22	6.58	
standard deviation	± 1.7	± 2.09	-
Blood thrombocytes			
Units: 10^9/L			
arithmetic mean	304.8	312.4	
standard deviation	± 70.51	± 82.51	-
Diastolic Blood Pressure, Sitting			
Units: mmHg			
arithmetic mean	65.5	65.4	
standard deviation	± 9.6	± 10.8	-
Systolic Blood Pressure, Sitting			
Units: mmHg			
arithmetic mean	104	104	
standard deviation	± 11.7	± 13.8	-
Pulse, Sitting			
Units: beats/min			
arithmetic mean	85.6	86.1	
standard deviation	± 13.1	± 12.5	-

End points

End points reporting groups

Reporting group title	Insulin detemir
Reporting group description:	
Individually adjusted insulin detemir dose injected subcutaneously once daily (evening) or twice daily (morning and evening) + insulin aspart with larger meals	
Reporting group title	NPH Insulin
Reporting group description:	
Individually adjusted NPH insulin dose injected subcutaneously once daily (evening) or twice daily (morning and evening) + insulin aspart with larger meals	

Primary: Glycosylated haemoglobin A1c (HbA1c), at the end of trial.

End point title	Glycosylated haemoglobin A1c (HbA1c), at the end of trial.
End point description:	
Glycosylated haemoglobin A1c (HbA1c) measured after 52 weeks of treatment and analysed by central laboratory. N = number of subject participated; N (detemir) = 171 and N (NPH) = 168	
End point type	Primary
End point timeframe:	
After 52 weeks of treatment	

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[1]	170[2]		
Units: Percent (%) glycosylated haemoglobin				
least squares mean (standard error)	8.75 (± 0.11)	8.64 (± 0.11)		

Notes:

[1] - Full analysis set for Insulin detemir arm has 177 subjects.

[2] - Full analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Insulin detemir v NPH Insulin
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.36

Notes:

[3] - The null hypothesis for the non-inferiority test was that the mean HbA1c with insulin detemir was greater than or equal to the mean HbA1c with NPH insulin plus 0.4%.

Secondary: Insulin detemir specific, insulin aspart specific and insulin detemir/aspart cross-reacting antibodies during treatment.

End point title	Insulin detemir specific, insulin aspart specific and insulin detemir/aspart cross-reacting antibodies during treatment.

End point description:

Insulin detemir specific antibodies, insulin aspart specific antibodies and insulin detemir/insulin aspart cross-reacting antibodies during 52 weeks of treatment.
N = number of subject participated.
1. Insulin detemir specific, week 0 , N (detemir) = 127, N (NPH) = 112 and week 52, N (detemir) =125, N (NPH)=128. 2. Cross-reacting insulin, week 0, N (detemir) = 130, N (NPH) = 113 and week 52, N (detemir) =132, N (NPH)=135.
3. Insulin aspart specific, week 0 N (detemir) = 126, N (NPH) = 111 and week 52, N (detemir) = 128, N (NPH) =133.

End point type	Secondary

End point timeframe:

During 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[4]	170[5]		
Units: Percent bound of total				
arithmetic mean (standard deviation)				
Insulin detemir specific, week 0	3.23 (± 1.03)	2.95 (± 1.23)		
Insulin detemir specific, week 52	5.15 (± 3.3)	3.01 (± 1.66)		
Cross-reacting insulin, week 0	27.06 (± 19.1)	27.26 (± 18.6)		
Cross-reacting insulin, week 52	43.7 (± 15.6)	30.19 (± 17.3)		
Insulin aspart specific, week 0	2.26 (± 2.32)	2.24 (± 2.99)		
Insulin aspart specific, week 52	4.2 (± 4.35)	2.68 (± 3.6)		

Notes:

[4] - Safety analysis set for Insulin detemir arm has 177 subjects.

[5] - safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Fasting plasma glucose (FPGlab), end of trial

End point title	Fasting plasma glucose (FPGlab), end of trial

End point description:

Fasting plasma glucose (FPGlab), measured after 52 weeks of treatment and analysed by central laboratory.
N = number of subject participated. N (detemir) = 171, N (NPH) = 168.

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[6]	170[7]		
Units: mmol/L				
least squares mean (standard error)	7.99 (± 0.42)	8.61 (± 0.43)		

Notes:

[6] - Full analysis set for Insulin detemir arm has 177 subjects.

[7] - Full analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: 9-points plasma glucose (PG) profile, end of trial

End point title	9-points plasma glucose (PG) profile, end of trial

End point description:

9-points plasma glucose (PG) profile, after 52 weeks of treatment

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[8]	170[9]		
Units: mmol/L				
least squares mean (standard error)				
Before Breakfast	8.24 (± 0.35)	8.44 (± 0.34)		
90 min after start of breakfast	9.74 (± 0.4)	9.66 (± 0.39)		
Before Lunch	8.75 (± 0.37)	8.75 (± 0.36)		
90 min after start of lunch	8.73 (± 0.36)	8.61 (± 0.35)		
Before dinner	9.53 (± 0.4)	8.91 (± 0.39)		
90 min after start of dinner	9.19 (± 0.35)	8.23 (± 0.34)		
Bedtime	10.4 (± 0.4)	9.45 (± 0.39)		
At 3.00 am	9.51 (± 0.39)	9.05 (± 0.38)		
Before breakfast the next day	8.39 (± 0.36)	9.27 (± 0.35)		

Notes:

[8] - Full analysis set for Insulin detemir arm has 177 subjects.

[9] - Full analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Nocturnal plasma glucose, end of trial

End point title	Nocturnal plasma glucose, end of trial

End point description:

Nocturnal plasma glucose after 52 weeks of treatment.
N = number of subject participated. N (detemir) = 125, N (NPH) = 132

End point type	Secondary

End point timeframe:

After 52 weeks of treatment.

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[10]	170[11]		
Units: mmol/L				
arithmetic mean (standard deviation)	9.07 (± 3.83)	8.65 (± 4.28)		

Notes:

[10] - Full analysis set for Insulin detemir arm has 177 subjects.

[11] - Full analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Body weight (kg), end of trial.

End point title	Body weight (kg), end of trial.

End point description:

Body weight (kg) after 52 weeks of treatment.
N = number of subject participated
N (detemir) = 172, N (NPH) = 166

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[12]	170[13]		
Units: kilogram(s)				
arithmetic mean (standard deviation)	40.43 (± 17.2)	40.82 (± 17.3)		

Notes:

[12] - Safety analysis set for Insulin detemir arm has 177 subjects.

[13] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Body mass index (BMI), end of trial

End point title	Body mass index (BMI), end of trial

End point description:

Body mass index (BMI), after 52 weeks of treatment.
N = number of subject participated.
N (detemir) = 172, N (NPH) = 166

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[14]	170[15]		
Units: kg/m2				
arithmetic mean (standard deviation)	18.3 (± 3)	18.8 (± 3.1)		

Notes:

[14] - Safety analysis set for Insulin detemir arm has 177 subjects.

[15] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: SD-score (Z-score) for body weight, end of trial

End point title	SD-score (Z-score) for body weight, end of trial

End point description:

SD-score (Z-score) for body weight, after 52 weeks of treatment.
N = number of subject participated.
N (detemir) = 172, N (NPH) = 166

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[16]	170[17]		
Units: Number				
arithmetic mean (standard deviation)	0.16 (± 0.97)	0.42 (± 1)		

Notes:

[16] - Safety analysis set for Insulin detemir arm has 177 subjects.

[17] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety laboratory parameters haematology, end of trial

End point title	Safety laboratory parameters haematology, end of trial

End point description:

Safety laboratory parameters haematology, after 52 weeks of treatment.
N = number of subject participated.
N (detemir): Blood leukocytes, N = 168; Blood thrombocytes, N = 169
N (NHP): Blood leukocytes, N = 163; Blood thrombocytes, N = 160

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[18]	170[19]		
Units: 10^9/L				
arithmetic mean (standard deviation)				
Blood leukocytes	6.59 (± 1.93)	6.94 (± 1.79)		
Blood thrombocytes	287.1 (± 67.08)	310.9 (± 79.5)		

Notes:

[18] - Safety analysis set for Insulin detemir arm has 177 subjects.

[19] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety laboratory parameters haematology and biochemistry, end of trial

End point title	Safety laboratory parameters haematology and biochemistry, end of trial

End point description:

Safety laboratory parameters haematology and biochemistry, after 52 weeks of treatment
N = number of subject participated.
N (detemir): Blood haemoglobin, serum sodium and serum potassium, N = 169
N (NPH): Blood haemoglobin, N = 163; serum sodium, N = 166; serum potassium, N = 166

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[20]	170[21]		
Units: mmol/L				
arithmetic mean (standard deviation)				
Blood haemoglobin	8.22 (± 0.58)	8.07 (± 0.69)		
Serum sodium	140.5 (± 3.2)	140.6 (± 2.86)		
Serum potassium	4.35 (± 0.48)	4.38 (± 0.42)		

Notes:

[20] - Safety analysis set for Insulin detemir arm has 177 subjects.

[21] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety laboratory parameters biochemistry, end of trial

End point title	Safety laboratory parameters biochemistry, end of trial

End point description:

Safety laboratory parameters biochemistry, after 52 weeks of treatment.
N = number of subject participated.
N (detemir) = 169 and N (NPH) = 166

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[22]	170[23]		
Units: g/dL				
arithmetic mean (standard deviation)				
Serum albumin	4.38 (± 0.2)	4.33 (± 0.22)		
Serum total proteins	7.13 (± 0.4)	7.07 (± 0.46)		

Notes:

[22] - Safety analysis set for Insulin detemir arm has 177 subjects.

[23] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety laboratory parameters biochemistry, end of trial

End point title	Safety laboratory parameters biochemistry, end of trial

End point description:

Safety laboratory parameters biochemistry, after 52 weeks of treatment.
N = number of subject participated.
N (detemir) = 169 and N (NPH) = 166

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[24]	170[25]		
Units: U/L				
arithmetic mean (standard deviation)				
Serum alkaline phosphatase	252.4 (± 106.5)	266.7 (± 99.1)		
Serum ALAT	19.89 (± 9.64)	21.95 (± 24.74)		
Serum Lactate dehydrogenase	195.8 (± 42.47)	203.1 (± 42.85)		

Notes:

[24] - Safety analysis set for Insulin detemir arm has 177 subjects.

[25] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of ketoacidosis requiring hospitalisation during treatment

End point title	Occurrence of ketoacidosis requiring hospitalisation during treatment

End point description:

Occurrence of ketoacidosis requiring hospitalisation during 52 weeks of treatment

End point type	Secondary

End point timeframe:

During 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[26]	170[27]		
Units: Number of events	3	4		

Notes:

[26] - Safety analysis set for Insulin detemir arm has 177 subjects.

[27] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin detemir dose, at end of trial

End point title	Insulin detemir dose, at end of trial[28]

End point description:

Insulin detemir dose after 52 weeks of treatment.
N = number of subject participated; N (detemir) = 134

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only insulin detemir arm is presented here as the unit of measurement for it is U/kg. The other arm has different unit of measurement so it could not be possible to present both arms together.

End point values	Insulin detemir			
Subject group type	Reporting group			
Number of subjects analysed	177[29]			
Units: U/kg				
arithmetic mean (standard deviation)				
Basal dose	0.6 (± 0.26)			
Bolus dose	0.48 (± 0.18)			

Notes:

[29] - Safety analysis set for Insulin detemir arm has 177 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Injection pain assessment using a facial visual analogue scale (VAS), at end-of-trial.

End point title	Injection pain assessment using a facial visual analogue scale (VAS), at end-of-trial.

End point description:

Injection pain assessment using a facial visual analogue scale (VAS), during 52 weeks of treatment.
Visual Analogue Scale (VAS) range = 0 to 100; from no pain (0) to the worst possible pain (100).
N = number of subject participated; N (detemir) = 133 and N (NPH) = 138

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[30]	170[31]		
Units: VAS score				
arithmetic mean (standard deviation)	39.6 (± 19.5)	33.9 (± 18.1)		

Notes:

[30] - Safety analysis set for Insulin detemir arm has 177 subjects.

[31] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs, end of trial

End point title	Vital signs, end of trial

End point description:

Vital signs after 52 weeks of treatment.

N = number of subject participated. Mean blood pressure-systolic, N (detemir) = 171 and N (NPH) = 163. Mean blood pressure-diastolic, N (detemir) = 171 and N (NPH) = 163. Mean pulse, N (detemir) = 170 and N (NPH) = 164

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[32]	170[33]		
Units: Number				
Mean blood pressure (mmHg, systolic)	107	106		
Mean blood pressure (mmHg, diastolic)	65	65		
Mean pulse (beats/min)	84	84		

Notes:

[32] - Safety analysis set for Insulin detemir arm has 177 subjects.

[33] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of all 24 hours hypoglycaemia (mild, moderate or severe) episodes during treatment

End point title	Incidence of all 24 hours hypoglycaemia (mild, moderate or severe) episodes during treatment

End point description:

Incidence of all 24 hours hypoglycaemia (mild, moderate or severe) episodes during 52 weeks of treatment.
Detemir: 3 severe episodes were reported by 3 subjects; 370 moderate episodes were reported by 30 subjects; 5956 mild episodes were reported by 148 subjects.
NPH: 15 severe episodes were reported by 12 subjects; 947 moderate episodes were reported by 28 subjects; 7189 mild episodes were reported by 151 subjects.

End point type	Secondary

End point timeframe:

During 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[34]	170[35]		
Units: Number of episodes				
Severe	3	15		
Moderate	370	947		
Mild	5956	7189		

Notes:

[34] - Safety analysis set for Insulin detemir arm has 177 subjects.

[35] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of daytime hypoglycaemia (mild, moderate or severe) episodes during treatment

End point title	Incidence of daytime hypoglycaemia (mild, moderate or severe) episodes during treatment

End point description:

Incidence of daytime hypoglycaemia (mild, moderate or severe) episodes during treatment.
Detemir: 3 severe episodes were reported by 3 subjects; 311 moderate episodes were reported by 27 subjects; 5244 mild episodes were reported by146 subjects.
NPH: 9 severe episodes were reported by 8 subjects; 835 moderate episodes were reported by 27 subjects; 6050 mild episodes were reported by150 subjects.

End point type	Secondary

End point timeframe:

During 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[36]	170[37]		
Units: Number				
Severe	3	9		
Moderate	311	835		
Mild	5244	6050		

Notes:

[36] - Safety analysis set for Insulin detemir arm has 177 subjects.

[37] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of nocturnal hypoglycaemia (mild, moderate or severe) episodes during treatment

End point title	Incidence of nocturnal hypoglycaemia (mild, moderate or severe) episodes during treatment

End point description:

Incidence of nocturnal hypoglycaemia (mild, moderate or severe) episodes during 52 weeks of treatment.
Detemir: No severe episodes were reported; 59 moderate episodes were reported by 15 subjects; 712 mild episodes were reported by100 subjects.
NPH: 6 severe episodes were reported by 5 subjects; 112 moderate episodes were reported by 14 subjects; 1139 mild episodes were reported by111 subjects.

End point type	Secondary

End point timeframe:

During 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[38]	170[39]		
Units: Number				
Severe	0	6		
Moderate	59	112		
Mild	712	1139		

Notes:

[38] - Safety analysis set for Insulin detemir arm has 177 subjects.

[39] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety laboratory parameter biochemistry, end of trial

End point title	Safety laboratory parameter biochemistry, end of trial

End point description:

Safety laboratory parameter biochemistry, after 52 weeks of treatment.
N = number of subject participated; N (detemir) = 169 and N (NPH) = 166

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[40]	170[41]		
Units: umol/L				
arithmetic mean (standard deviation)				
Serum creatinine	47.8 (± 13.21)	48.77 (± 13.51)		

Notes:

[40] - Safety analysis set for Insulin detemir arm has 177 subjects.

[41] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin NPH dose at the end of trial

End point title	Insulin NPH dose at the end of trial[42]

End point description:

Insulin NPH dose after 52 weeks of treatment.
N = number of subject participated; N (NPH) = 140

End point type	Secondary

End point timeframe:

After 52 weeks of treatment

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only NPH insulin arm is presented here as the unit of measurement for it is IU/kg. The other arm has different unit of measurement so it could not be possible to present both arms together.

End point values	NPH Insulin			
Subject group type	Reporting group			
Number of subjects analysed	170[43]			
Units: IU/kg				
arithmetic mean (standard deviation)				
Basal dose	0.58 (± 0.22)			
Bolus dose	0.45 (± 0.17)			

Notes:

[43] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events during treatment

End point title	Adverse events during treatment

End point description:

Adverse events reported during 52 weeks of treatment.
Detemir: 537 adverse events were reported by 132 subjects
NPH: 554 adverse events were reported by 135 subjects

End point type	Secondary

End point timeframe:

During 52 weeks of treatment.

End point values	Insulin detemir	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[44]	170[45]		
Units: Number of events	537	554		

Notes:

[44] - Safety analysis set for Insulin detemir arm has 177 subjects.

[45] - Safety analysis set for NPH Insulin arm has 170 subjects.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from week 0 to week 52.	
Adverse event reporting additional description:	
Safety analysis set (SAS): all randomised subjects exposed to at least one dose of trial product, classified according to actual treatment	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups	
Reporting group title	Insulin detemir
Reporting group description:	
Individually adjusted insulin detemir dose injected subcutaneously once daily (evening) or twice daily (morning and evening) + insulin aspart with larger meals	
Reporting group title	NPH Insulin
Reporting group description:	
Individually adjusted NPH insulin dose injected subcutaneously once daily (evening) or twice daily (morning and evening) + insulin aspart with larger meals	

Serious adverse events	Insulin detemir	NPH Insulin	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 177 (7.91%)	20 / 170 (11.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Burns second degree			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medication error			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
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 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 177 (0.56%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 177 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (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			
Adenoidal Hypertrophy			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephropathy			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			

subjects affected / exposed	4 / 177 (2.26%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 177 (0.56%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis shigella			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Viral			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis Media Acute			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 170 (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			
Diabetic ketoacidosis			
subjects affected / exposed	3 / 177 (1.69%)	4 / 170 (2.35%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	1 / 177 (0.56%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	1 / 177 (0.56%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic Unconsciousness			
subjects affected / exposed	0 / 177 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
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	NPH Insulin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	131 / 177 (74.01%)	134 / 170 (78.82%)	
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 177 (14.69%)	23 / 170 (13.53%)	
occurrences (all)	65	44	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 177 (5.08%)	7 / 170 (4.12%)	
occurrences (all)	10	7	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	75 / 177 (42.37%)	81 / 170 (47.65%)	
occurrences (all)	147	179	
Pharyngitis			
subjects affected / exposed	19 / 177 (10.73%)	15 / 170 (8.82%)	
occurrences (all)	29	16	
Upper respiratory tract infection			
subjects affected / exposed	18 / 177 (10.17%)	16 / 170 (9.41%)	
occurrences (all)	32	32	
Gastroenteritis			

subjects affected / exposed	15 / 177 (8.47%)	12 / 170 (7.06%)	
occurrences (all)	20	13	
Influenza			
subjects affected / exposed	10 / 177 (5.65%)	18 / 170 (10.59%)	
occurrences (all)	14	25	
Viral infection			
subjects affected / exposed	12 / 177 (6.78%)	14 / 170 (8.24%)	
occurrences (all)	14	17	
Bronchitis			
subjects affected / exposed	9 / 177 (5.08%)	12 / 170 (7.06%)	
occurrences (all)	11	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 September 2006	Global substantial amendment 1: The NN304-1689 trial was planned as a post approval commitment trial requested by the EU Authorities to follow the insulin antibody formation in children between 6 and 16 years. Since then, the protocol has developed to include a trial population down to 2 years. As insulin detemir is not yet approved for children below 6 years, the phase of the trial should be changed to phase 3b.
12 December 2006	Global substantial amendment 2: 1.1 Insulin Antibodies. To determine insulin detemir specific antibodies, insulin aspart specific antibodies and insulin detemir/aspart cross-reacting antibodies, a blood sample will be obtained at baseline (Visit 2) and at Visits 8, 9, 10. To minimise assay interference from excess insulin detemir, NPH insulin, aspart insulin, blood should be collected, when the blood levels of these drugs are the lowest. The most optimal time would be immediately before dinner and before injecting pre-dinner insulin aspart. For practical purposes, blood sampling should take place in the afternoon at least 3 hours after the pre-lunch insulin aspart injection and the following data should be recorded: • Date, time and dose of last basal insulin dose prior to blood sampling • Date, time and dose of last bolus insulin dose prior to blood sampling • Date and time of blood sample 1.2 Clinical Supplies IV/WRS Management Due to the introduction of Clinical Supplies IV/WRS (Interactive Voice/Web Response System) Management (CSIM) the protocol has been updated to be in accordance with the CSIM procedures. In addition the Trial Materials section has been updated to correspond with new standards of wording. Finally, the text has been updated and it is now correctly stated, that NPH insulin can be kept for 6 weeks, after the seal has been broken. There will be no changes with regards to trial design, subject treatment or methods/assessments.

Notes:

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/21418455