

**Clinical trial results:****A 52-Week, Multinational, Multi-Centre, Open-Labelled Extension Trial of Insulin Detemir in Children and Adolescents 3-17 years with Type 1 Diabetes on a Basal-Bolus Regimen with Insulin Aspart as Bolus Insulin Trial Phase: 3****Summary**

EudraCT number	2006-002478-23
Trial protocol	GB FI DK HU CZ FR BG
Global end of trial date	07 September 2009

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	NN304-1690
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00623194
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)	EMA-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	17 February 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 September 2009
Global end of trial reached?	Yes
Global end of trial date	07 September 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study the development of insulin detemir-insulin aspart cross-reacting antibodies following a 104 week-period (52 weeks in NN304-1689 and 52 weeks in NN304-1690) of insulin detemir treatment in children and adolescents.

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:

The subjects were treated with insulin detemir and completed 52 weeks of treatment in the NN304-1689 trial.

Evidence for comparator:

Not applicable

Actual start date of recruitment	19 February 2008
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	Poland: 20
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Bulgaria: 19
Country: Number of subjects enrolled	Czech Republic: 18
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 11
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	Turkey: 11
Worldwide total number of subjects	146
EEA total number of subjects	84

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)	88
Adolescents (12-17 years)	58
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial sites included 29 sites in 11 countries: Bulgaria (3 sites), Czech Republic (3 sites), Denmark (2 sites), Finland (4 sites), France (1 site), Hungary (2 sites), Macedonia (1 site), Poland (4 sites), Russian Federation (4 sites), Turkey (4 sites) and United Kingdom (1 site).

Pre-assignment

Screening details:

At entry subjects had finalised 52-weeks treatment with insulin detemir (Trial NN304-1689, NCT00435019). The subjects continued treatment with insulin detemir and insulin aspart doses used in Trial NN304-1689.

Period 1

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

Arms

Arm title	Insulin Detemir
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Arm description:

Subjects received insulin detemir up to twice daily plus insulin aspart at larger meals. Doses were adjusted individually (treatment up to 104 weeks).

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

Dosage and administration details:

Insulin detemir was administered subcutaneously once or twice daily at the same time of the day as in Trial NN304-1689. All subjects also received insulin aspart as bolus insulin immediately before or after main meals. The dose of insulin was continuously and individually adjusted based on plasmaglucoase (PG) measurements according to the NN304-1689 Titration Guideline.

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

Dosage and administration details:

All subjects received insulin aspart as bolus insulin immediately before or after main meals. The dose of insulin was continuously and individually adjusted based on plasmaglucoase (PG) measurements according to the NN304-1689 Titration Guideline.

Number of subjects in period 1	Insulin Detemir
Started	146
Completed	141
Not completed	5
protocol violation	3
unclassified	1
Lack of efficacy	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
Reporting group description:	
Insulin detemir up to twice daily plus insulin aspart at larger meals, doses are adjusted individually (treatment up to 104 weeks)	

Reporting group values	Overall Study	Total	
Number of subjects	146	146	
Age categorical			
Units: Subjects			
2 to 5 years	37	37	
6 to 12 years	59	59	
13 to 16 years	50	50	
Age continuous			
Units: years			
arithmetic mean	10.1		
standard deviation	± 4.2	-	
Gender categorical			
Units: Subjects			
Female	77	77	
Male	69	69	
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	144	144	
More than one race	0	0	
Unknown or Not Reported	2	2	
Pubertal Status			
Units: Subjects			
Tanner grade 1	83	83	
Tanner grade 2+	63	63	
Height			
Units: meters			
arithmetic mean	1.39		
standard deviation	± 0.26	-	
BMI			
Units: kg/m ²			
arithmetic mean	18.14		
standard deviation	± 2.81	-	

End points

End points reporting groups

Reporting group title	Insulin Detemir
Reporting group description: Subjects received insulin detemir up to twice daily plus insulin aspart at larger meals. Doses were adjusted individually (treatment up to 104 weeks).	

Primary: Insulin detemir-insulin aspart cross-reacting antibodies.

End point title	Insulin detemir-insulin aspart cross-reacting antibodies. ^[1]
End point description: Estimated amount of bound antibodies in percent of total antibodies. The primary analysis of cross-reacting antibodies included results from blood samples taken before insulin detemir and less than 3 hours after insulin aspart injection. In addition, an analysis was done including results from samples taken before insulin detemir and less than 2.5 hours after insulin aspart injection. For all subjects the difference between the individual subject's antibody measurements at Visit 10 and Visit 1 extension were calculated. This individual difference was used to adjust the antibody measurements. These corrected values were used for all analyses	
End point type	Primary
End point timeframe: week 0, 52 and 104.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: In order to clarify if the antibody measurements stabilised or decreased the parameter of interest was the estimated slope of the model. No other statistical analysis was provided for Insulin Detemir-insulin Aspart Cross-reacting Antibodies.

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	146			
Units: Percent bound of total				
least squares mean (standard error)				
Week 0 (3 hours)	31.11 (± 1.25)			
Week 52 (3 hours)	43.99 (± 1.02)			
Week 104 (3 hours)	35.96 (± 1.14)			
Week 0 (2.5 hours)	31.22 (± 1.23)			
Week 52 (2.5 hours)	44.09 (± 1.01)			
Week 104 (2.5 hours)	35.92 (± 1.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Development of insulin detemir specific antibodies and insulin aspart specific antibodies

End point title	Development of insulin detemir specific antibodies and insulin aspart specific antibodies
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End point description:

Amount of insulin detemir and insulin aspart specific antibodies in percent of total antibodies after 0, 52 and 104 weeks. The blood samples analysed were taken before insulin detemir and less than 3 hours after insulin aspart injection.

End point type Secondary

End point timeframe:

At 0, 52 and 104 weeks

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	146			
Units: Percent bound of total				
least squares mean (standard error)				
Insulin Detemir specific, week 0	2.81 (\pm 1.28)			
Insulin Detemir specific, week 52	4.4 (\pm 1.27)			
Insulin Detemir specific, week 104	3.05 (\pm 1.27)			
Insulin Aspart specific, week 0	1.32 (\pm 0.67)			
Insulin Aspart specific, week 52	2.79 (\pm 0.64)			
Insulin Aspart specific, week 104	1.99 (\pm 0.65)			

Statistical analyses

No statistical analyses for this end point

Secondary: BMI (Body Mass Index)

End point title BMI (Body Mass Index)

End point description:

BMI (Body Mass Index) after 104 weeks.

End point type Secondary

End point timeframe:

At 104 weeks

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: kg/m ²				
arithmetic mean (standard deviation)	18.88 (\pm 3.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: SD-score (Z-score) for Body Weight

End point title | SD-score (Z-score) for Body Weight

End point description:

Standard deviation-score (SD-score or z-score) after 104 weeks. The SD-score for weight was calculated based on a British reference population from 1990. To estimate the growth of children, standardised mean weight values were calculated for each month of age and for each sex. Thus, a child with a weight equal to the mean value for its age and sex has an SD score of 0, while a child with a weight 2 SDs above the mean value for its age and sex has an SD score of +2.

End point type | Secondary

End point timeframe:

At 104 weeks

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: SD-scores				
arithmetic mean (standard deviation)	0.13 (± 0.97)			

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:

Number of diabetic ketoacidosis events requiring hospitalisation.

End point type | Secondary

End point timeframe:

At 104 weeks

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	146			
Units: Number	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Insulin Dose

End point title	Insulin Dose
End point description:	Daily insulin doses (basal (Insulin Detemir) and bolus (Insulin Aspart)) at week 104.
End point type	Secondary
End point timeframe:	At 104 weeks

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: U/kg				
arithmetic mean (standard deviation)				
Insulin Detemir dose (Basal)	0.66 (± 0.29)			
Insulin Aspart dose (Bolus)	0.51 (± 0.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory safety parameters: Biochemistry - Albumin Serum (g/dL)

End point title	Laboratory safety parameters: Biochemistry - Albumin Serum (g/dL)
End point description:	Albumin Serum after 104 weeks.
End point type	Secondary
End point timeframe:	At 104 weeks

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: g/dL				
arithmetic mean (standard deviation)	4.32 (± 0.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory safety parameters: Biochemistry- Creatinine Serum umol/L

End point title	Laboratory safety parameters: Biochemistry- Creatinine Serum umol/L
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End point description:

Creatine serum after 104 weeks.

End point type	Secondary
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End point timeframe:

At 104 weeks

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: umol/L				
arithmetic mean (standard deviation)	51.08 (\pm 13.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory safety parameters: Biochemistry - Sodium Serum (mmol/L)

End point title	Laboratory safety parameters: Biochemistry - Sodium Serum (mmol/L)
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End point description:

Sodium Serum, Potassium Serum and Haemoglobin after 104 weeks.

End point type	Secondary
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End point timeframe:

At 104 weeks

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: mmol/L				
arithmetic mean (standard deviation)	141.6 (\pm 3.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory safety parameters: Biochemistry- Alkaline Phosphatase Serum (U/L)

End point title	Laboratory safety parameters: Biochemistry- Alkaline Phosphatase Serum (U/L)
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End point description:
Alkaline phosphatase serum after 104 weeks.

End point type	Secondary
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End point timeframe:
At 104 weeks

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: U/L				
arithmetic mean (standard deviation)	226.7 (\pm 197.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory safety parameters: Haematology - Leukocytes

End point title	Laboratory safety parameters: Haematology - Leukocytes
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End point description:
Leukocytes after 104 weeks.

End point type	Secondary
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End point timeframe:
At 104 weeks

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: $10^9/L$				
arithmetic mean (standard deviation)	6.72 (\pm 1.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory safety parameters: Fundoscopy/Fundus Photography

End point title	Laboratory safety parameters: Fundoscopy/Fundus
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End point description:

Fundoscopy after 104 weeks. Abn. CS = Abnormal, clinically significant; Abn. NCS = Abnormal, Not clinically significant; Abn. CS = Abnormal, clinically significant; Abn. NCS = Abnormal, Not clinically significant.

End point type Secondary

End point timeframe:

At 52 weeks and at 104 weeks

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	146			
Units: participants				
Abnormal, clinically significant	1			
Abnormal, not clinically significant	8			
Normal	131			
Missing	6			
Abn CS baseline and 104 weeks	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs: Blood Pressure

End point title Vital Signs: Blood Pressure

End point description:

Blood pressure (Systolic and Diastolic) after 104 weeks.

End point type Secondary

End point timeframe:

At 104 weeks

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	143			
Units: mmHg				
arithmetic mean (standard deviation)				
Systolic Blood Pressure	109.5 (± 13.6)			
Diastolic Blood Pressure	66.6 (± 8.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs: Pulse

End point title	Vital Signs: Pulse
End point description:	Pulse at week 104, measured after resting in a sitting position for 5 minutes.
End point type	Secondary
End point timeframe:	At 104 weeks

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: beats/minute				
arithmetic mean (standard deviation)	82.6 (\pm 9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of hypoglycaemia (mild, moderate, severe and biochemical)

End point title	Incidence of hypoglycaemia (mild, moderate, severe and biochemical)
End point description:	Incidence of hypoglycaemia (mild, moderate, severe and biochemical) – total, daytime and night time during treatment. Mild: signs/symptoms but able to treat him/herself. Moderate: signs/symptoms not able to treat him/herself. Responds to oral treatment. Severe: signs/symptoms and unable to treat him/herself. semiconscious/unconscious/in coma +/- convulsion and may require parenteral treatment. Biochemical: Plasma glucose < 3.6mmol/L with no signs or symptoms.
End point type	Secondary
End point timeframe:	Weeks 0 - 104

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	146			
Units: Episodes				
Total hypoglycaemic episodes	16074			
Total hypoglycaemic episodes, daytime	13605			
Total hypoglycaemic episodes, night-time	2469			
Daytime, Mild	9080			
Daytime, Moderate	396			

Daytime, Severe	3			
Daytime, Biochemical	4122			
Daytime, Unclassified	4			
Night-time, Mild	1450			
Night-time, Moderate	54			
Night-time, Severe	4			
Night-time, Biochemical	958			
Night-time, unclassified	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events during treatment

End point title	Adverse events during treatment
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End point description:

Adverse events during the treatment period expressed as number of events per 100 exposure years.

End point type	Secondary
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End point timeframe:

Adverse events from the first day on trial product (Visit 1 + 1 day) to one week after last day on trial product (Visit 5Ext + 7 days at most).

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	146			
Units: Number of events per 100 exposure years				
number (not applicable)	246.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory safety parameters: Biochemistry - Total protein serum (g/dL)

End point title	Laboratory safety parameters: Biochemistry - Total protein serum (g/dL)
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End point description:

Total protein serum after 104 weeks.

End point type	Secondary
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End point timeframe:

At 104 weeks

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: g/dL				
arithmetic mean (standard deviation)	7.09 (\pm 0.45)			

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory safety parameters: Biochemistry - Pottassium Serum (mmol/L)

End point title	Laboratory safety parameters: Biochemistry - Pottassium Serum (mmol/L)			
End point description:	Potassium Serum after 104 weeks.			
End point type	Secondary			
End point timeframe:	At 104 weeks			

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	137			
Units: mmol/L				
arithmetic mean (standard deviation)	4.38 (\pm 0.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory safety parameters: Haematology - Haemoglobin (mmol/L)

End point title	Laboratory safety parameters: Haematology - Haemoglobin (mmol/L)			
End point description:	Haemoglobin after 104 weeks			
End point type	Secondary			
End point timeframe:	At 104 weeks			

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: mmol/L				
arithmetic mean (standard deviation)	8.28 (\pm 0.65)			

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory safety parameters: Biochemistry -Alanine Aminotransferase Serum (U/L)

End point title	Laboratory safety parameters: Biochemistry -Alanine Aminotransferase Serum (U/L)			
End point description:	Alanine Aminotransferase serum after 104 weeks.			
End point type	Secondary			
End point timeframe:	At 104 weeks			

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: U/L				
arithmetic mean (standard deviation)	19 (\pm 8.26)			

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory safety parameters: Biochemistry - Lactate Dehydrogenase Serum (U/L)

End point title	Laboratory safety parameters: Biochemistry - Lactate Dehydrogenase Serum (U/L)			
End point description:	Lactate Dehydrogenase serum after 104 weeks.			
End point type	Secondary			
End point timeframe:	At 104 weeks			

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	137			
Units: U/L				
arithmetic mean (standard deviation)	199.6 (± 40.34)			

Statistical analyses

No statistical analyses for this end point

Secondary: Laboratory safety parameters: Haematology - Thrombocytes

End point title	Laboratory safety parameters: Haematology - Thrombocytes
End point description:	Thrombocytes after 104 weeks.
End point type	Secondary
End point timeframe:	At 104 weeks

End point values	Insulin Detemir			
Subject group type	Reporting group			
Number of subjects analysed	144			
Units: 10 ⁹ /L				
arithmetic mean (standard deviation)	301.9 (± 76.55)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events were collected over a period of 104 weeks.

Adverse event reporting additional description:

The safety analysis set is all subjects exposed to at least one dose of trial drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.1
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Reporting groups

Reporting group title	Insulin Detemir
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Reporting group description:

Insulin detemir up to twice daily plus insulin aspart at larger meals, doses are adjusted individually (treatment up to 104 weeks)

Serious adverse events	Insulin Detemir		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 146 (8.22%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Burns second degrees			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 146 (1.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abscess limb			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis shigella			

subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis media acute			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	3 / 146 (2.05%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	2 / 146 (1.37%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia unconsciousness			

subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Insulin Detemir		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 146 (72.60%)		
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 146 (17.12%)		
occurrences (all)	84		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	8 / 146 (5.48%)		
occurrences (all)	13		
Abdominal pain			
subjects affected / exposed	9 / 146 (6.16%)		
occurrences (all)	10		
Vomiting			
subjects affected / exposed	10 / 146 (6.85%)		
occurrences (all)	10		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	71 / 146 (48.63%)		
occurrences (all)	164		
Upper Respiratory Tract Infection			
subjects affected / exposed	21 / 146 (14.38%)		
occurrences (all)	44		
Pharyngitis			
subjects affected / exposed	20 / 146 (13.70%)		
occurrences (all)	41		
Influenza			
subjects affected / exposed	17 / 146 (11.64%)		
occurrences (all)	38		

Gastroenteritis			
subjects affected / exposed	15 / 146 (10.27%)		
occurrences (all)	21		
Bronchitis			
subjects affected / exposed	9 / 146 (6.16%)		
occurrences (all)	16		
Viral infection			
subjects affected / exposed	10 / 146 (6.85%)		
occurrences (all)	12		
Rhinitis			
subjects affected / exposed	9 / 146 (6.16%)		
occurrences (all)	11		
Acute Tonsillitis			
subjects affected / exposed	8 / 146 (5.48%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 February 2008	Substantial amendment no. 1, dated 28 January 2008, was prepared to implement the decision to use a paper-based diary in 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: