Clinical trial results:
A Trial Investigating the Pharmacokinetic Properties of NN1250 in Children, Adolescents and Adults with Type 1 Diabetes

Summary

EudraCT number	2008-008306-43
Trial protocol	DE
Global end of trial date	03 May 2010

Results information

Result version number	v1
This version publication date	16 March 2016
First version publication date	01 August 2015

Trial information

Trial identification

Sponsor protocol code	NN1250-1995

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01030926
WHO universal trial number (UTN)	U1111-1112-4715

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-000456-PIP01-08, EMEA-000479-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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 December 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 May 2010
Global end of trial reached?	Yes
Global end of trial date	03 May 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the pharmacokinetic total exposure of SIBA (NN1250, IDeg) in children, adolescents and adult subjects with type 1 diabetes

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (59th WMA General Assembly, Seoul 2008. Last amended with Note of Clarification on Paragraph 29 by the WMA General Assembly, Washington 2002, and Note of Clarification on Paragraph 30 by the WMA General assembly, Tokyo 2004) and International Conference on Harmonisation (ICH) Good Clinical Practice (June 1996).

Background therapy:

The following non-investigational medicinal products were used:
NPH insulin: Protaphane®, Novolin® N 100 IU/mL, in 3 mL FlexPen®)
Insulin aspart: NovoRapid®, NovoLog® 100 U/mL, in 3 mL FlexPen®and in 10 mL vials)

Evidence for comparator:

Not applicable

Actual start date of recruitment	08 December 2009
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	Germany: 39
Worldwide total number of subjects	39
EEA total number of subjects	39

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)	13
Adolescents (12-17 years)	13
Adults (18-64 years)	13

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at one site in Germany.

Pre-assignment

Screening details:

Not applicable

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

In order to maintain the blinding, a person not otherwise involved in the conduct of the trial prepared the doses according to the randomisation provided by Novo Nordisk A/S. It was ensured that the cartridge or syringe containing trial product was not revealed to the subject or to the Investigator.

Arms

Are arms mutually exclusive?	Yes
Arm title	IDeg in Period 1

Arm description:

In Period 1, subjects were randomly assigned to receive a single dose of IDeg.

Arm type	Cross-over assignment
Investigational medicinal product name	IDeg
Investigational medicinal product code	
Other name	SIBA, NN1250, insulin degludec
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of IDeg (0.4 U/kg body weight [BW]), administered as a subcutaneous (s.c.) injection into a lifted skin fold on the anterior surface of the thigh.

Arm title	IGlar in Period 1

Arm description:

In Period 1, subjects were randomly assigned to receive a single dose of IGlar.

Arm type	Cross-over assignment
Investigational medicinal product name	IGlar
Investigational medicinal product code	
Other name	Insulin glargine, Lantus
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of IGlar (0.4 U/kg BW), administered as a s.c. injection into a lifted skin fold on the anterior surface of the thigh.

Number of subjects in period 1	IDeg in Period 1	IGlar in Period 1
Started	19	20
Exposed	18	20
Completed	18	20
Not completed	1	0
Consent withdrawn by subject	1	-

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

In order to maintain the blinding, a person not otherwise involved in the conduct of the trial prepared the doses according to the randomisation provided by Novo Nordisk A/S. It was ensured that the cartridge or syringe containing trial product was not revealed to the subject or to the Investigator.

Arms

Are arms mutually exclusive?	Yes
Arm title	IDeg in Period 2

Arm description:

Subjects, who received IGlar in Period 1, were assigned to receive a single dose of IDeg in Period 2. There was a wash-out period of 7-21 days in between Period 1 and Period 2.

Arm type	Cross-over assignment
Investigational medicinal product name	IDeg
Investigational medicinal product code	
Other name	SIBA, NN1250, insulin degludec
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of IDeg (0.4 U/kg BW), administered as a subcutaneous (s.c.) injection into a lifted skin fold on the anterior surface of the thigh.

Arm title	IGlar in Period 2

Arm description:

Subjects, who received IDeg in Period 1, were assigned to receive a single dose of IGlar in Period 2. There was a wash-out period of 7-21 days in between Period 1 and Period 2.

Arm type	Cross-over assignment
Investigational medicinal product name	IGlar
Investigational medicinal product code	
Other name	Insulin glargine, Lantus
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of IGlar (0.4 U/kg BW), administered as a s.c. injection into a lifted skin fold on the anterior surface of the thigh.

Number of subjects in period 2[1]	IDeg in Period 2	IGlar in Period 2
Started	19	18
Exposed	19	18
Completed	19	18

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: One subject was withdrawn after Period 1 due to difficult venous conditions (difficulties of drawing blood).

Period 3

Period 3 title	Period 3 (completers)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

In order to maintain the blinding, a person not otherwise involved in the conduct of the trial prepared the doses according to the randomisation provided by Novo Nordisk A/S. It was ensured that the cartridge or syringe containing trial product was not revealed to the subject or to the Investigator.

Arms

Are arms mutually exclusive?	No
Arm title	IDeg: Children

Arm description:

Subjects (children [6-11 years]) were randomly assigned to receive a single dose of IDeg.

Arm type	Experimental
Investigational medicinal product name	IDeg
Investigational medicinal product code	
Other name	SIBA, NN1250, insulin degludec
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of IDeg (0.4 U/kg BW), administered as a subcutaneous (s.c.) injection into a lifted skin fold on the anterior surface of the thigh.

Arm title	IDeg: Adolescents

Arm description:

Subjects (adolescents [12-17 years]) were randomly assigned to receive a single dose of IDeg.

Arm type	Experimental
Investigational medicinal product name	IDeg
Investigational medicinal product code	
Other name	SIBA, NN1250, insulin degludec
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of IDeg (0.4 U/kg BW), administered as a subcutaneous (s.c.) injection into a lifted skin

fold on the anterior surface of the thigh.

Arm title	IDeg: Adults
Arm description:	
Subjects (adults [18-65 years]) were randomly assigned to receive a single dose of IDeg.	
Arm type	Experimental
Investigational medicinal product name	IDeg
Investigational medicinal product code	
Other name	SIBA, NN1250, insulin degludec
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
A single dose of IDeg (0.4 U/kg BW), administered as a subcutaneous (s.c.) injection into a lifted skin fold on the anterior surface of the thigh.	
Arm title	IGlar: Children
Arm description:	
Subjects (children [6-11 years]) were randomly assigned to receive a single dose of IGlar.	
Arm type	Experimental
Investigational medicinal product name	IGlar
Investigational medicinal product code	
Other name	Insulin glargine, Lantus
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
A single dose of IGlar (0.4 U/kg BW), administered as a s.c. injection into a lifted skin fold on the anterior surface of the thigh.	
Arm title	IGlar: Adolescents
Arm description:	
Subjects (adolescents [12-17 years]) were randomly assigned to receive a single dose of IDeg.	
Arm type	Experimental
Investigational medicinal product name	IGlar
Investigational medicinal product code	
Other name	Insulin glargine, Lantus
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
A single dose of IGlar (0.4 U/kg BW), administered as a s.c. injection into a lifted skin fold on the anterior surface of the thigh.	
Arm title	IGlar: Adults
Arm description:	
Subjects (adults [18-65 years]) were randomly assigned to receive a single dose of IGlar.	
Arm type	Experimental
Investigational medicinal product name	IGlar
Investigational medicinal product code	
Other name	Insulin glargine, Lantus
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of IGlar (0.4 U/kg BW), administered as a s.c. injection into a lifted skin fold on the anterior surface of the thigh.

Number of subjects in period 3	IDeg: Children	IDeg: Adolescents	IDeg: Adults
Started	12	13	12
Exposed	12	13	12
Completed	12	13	12

Number of subjects in period 3	IGlar: Children	IGlar: Adolescents	IGlar: Adults
Started	12	13	12
Exposed	12	13	12
Completed	12	13	12

Baseline characteristics

Reporting groups	
Reporting group title	IDeg in Period 1
Reporting group description:	
In Period 1, subjects were randomly assigned to receive a single dose of IDeg.	
Reporting group title	IGlar in Period 1
Reporting group description:	
In Period 1, subjects were randomly assigned to receive a single dose of IGlar.	

Reporting group values	IDeg in Period 1	IGlar in Period 1	Total
Number of subjects	19	20	39
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	5	8	13
Adolescents (12-17 years)	5	8	13
Adults (18-64 years)	9	4	13
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	10	8	18
Male	9	12	21

End points

End points reporting groups

Reporting group title	IDeg in Period 1
Reporting group description:	
In Period 1, subjects were randomly assigned to receive a single dose of IDeg.	
Reporting group title	IGlar in Period 1
Reporting group description:	
In Period 1, subjects were randomly assigned to receive a single dose of IGlar.	
Reporting group title	IDeg in Period 2
Reporting group description:	
Subjects, who received IGlar in Period 1, were assigned to receive a single dose of IDeg in Period 2. There was a wash-out period of 7-21 days in between Period 1 and Period 2.	
Reporting group title	IGlar in Period 2
Reporting group description:	
Subjects, who received IDeg in Period 1, were assigned to receive a single dose of IGlar in Period 2. There was a wash-out period of 7-21 days in between Period 1 and Period 2.	
Reporting group title	IDeg: Children
Reporting group description:	
Subjects (children [6-11 years]) were randomly assigned to receive a single dose of IDeg.	
Reporting group title	IDeg: Adolescents
Reporting group description:	
Subjects (adolescents [12-17 years]) were randomly assigned to receive a single dose of IDeg.	
Reporting group title	IDeg: Adults
Reporting group description:	
Subjects (adults [18-65 years]) were randomly assigned to receive a single dose of IDeg.	
Reporting group title	IGlar: Children
Reporting group description:	
Subjects (children [6-11 years]) were randomly assigned to receive a single dose of IGlar.	
Reporting group title	IGlar: Adolescents
Reporting group description:	
Subjects (adolescents [12-17 years]) were randomly assigned to receive a single dose of IDeg.	
Reporting group title	IGlar: Adults
Reporting group description:	
Subjects (adults [18-65 years]) were randomly assigned to receive a single dose of IGlar.	

Primary: AUC_IDeg, 0-∞, SD, area under the serum IDeg concentration-time curve from 0 to infinity after single-dose

End point title	AUC_IDeg, 0-∞, SD, area under the serum IDeg concentration-time curve from 0 to infinity after single-dose
End point description:	
End point type	Primary
End point timeframe:	
0 to infinity	

End point values	IDeg: Children	IDeg: Adolescents	IDeg: Adults	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	13	12	
Units: pmol*h/L				
geometric mean (geometric coefficient of variation)	145891 (± 73)	130713 (± 30)	98594 (± 21)	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
The endpoints were log-transformed and analysed using an ANOVA model with age group and period as fixed effects and with different error-terms for each age-group.	
Comparison groups	IDeg: Children v IDeg: Adults
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean ratio
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	2.24

Statistical analysis title	Statistical analysis 2
Comparison groups	IDeg: Adolescents v IDeg: Adults
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean ratio
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	1.64

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the start of first trial product administration to 7 to 21 days after last dosing visit.	
Adverse event reporting additional description:	
Safety Analysis Set included all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety analysis set contributed to the evaluation 'as treated'.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups	
Reporting group title	IDeg: Children (6-11 years)
Reporting group description:	
Subjects (children [6-11 years]), who received at least one dose of IDeg.	
Reporting group title	IDeg: Adolescents (12-17 years)
Reporting group description:	
Subjects (adolescents [12-17 years]), who received at least one dose of IDeg.	
Reporting group title	IDeg: Adults (18-65 years)
Reporting group description:	
Subjects (adults [18-65 years]), who received at least one dose of IDeg.	
Reporting group title	IGlar: Children (6-11 years)
Reporting group description:	
Subjects (children [6-11 years]), who received at least one dose of IGlar.	
Reporting group title	IGlar: Adolescents (12-17 years)
Reporting group description:	
Subjects (adolescents [12-17 years]), who received at least one dose of IGlar.	
Reporting group title	IGlar: Adults (18-65 years)
Reporting group description:	
Subjects (adults [18-65 years]), who received at least one dose of IGlar.	

Serious adverse events	IDeg: Children (6-11 years)	IDeg: Adolescents (12-17 years)	IDeg: Adults (18-65 years)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	IGlar: Children (6-11 years)	IGlar: Adolescents (12-17 years)	IGlar: Adults (18-65 years)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	IDeg: Children (6-11 years)	IDeg: Adolescents (12-17 years)	IDeg: Adults (18-65 years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)	3 / 13 (23.08%)	1 / 12 (8.33%)
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Wrong drug administered			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Catheter site phlebitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Acute sinusitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	IGlar: Children (6-11 years)	IGlar: Adolescents (12-17 years)	IGlar: Adults (18-65 years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)	3 / 13 (23.08%)	1 / 12 (8.33%)
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Wrong drug administered			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Catheter site phlebitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Acute sinusitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2009	The Protocol was amended mainly due to the following reasons: This trial was conducted with the purpose of investigating the pharmacokinetic properties of NN1250 (insulin degludec). To increase convenience for the children it was decided to allow the subjects and the investigator to decide on the injection site for insulin aspart. This had no influence on bioavailability and trial results. To align time windows on blood glucose sampling times with the time windows on the blood sampling for determination of insulin 454 and insulin glargine. For clarity on some of the question asked in relation to a hypoglycaemic episode. The period for when a hypoglycaemic episode is deemed as treatment emergent, had incorrectly been stated as until 5 days after last trial product administration, this should be 7 days. The period for when an adverse event is deemed as treatment emergent, had incorrectly been stated as until the follow up visit, this should be until 7 days after the last trial product administration.

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: