



## Clinical trial results:

**A single-centre, randomised, double-blind, cross-over trial comparing the within-subject variability of the pharmacokinetic profiles of insulin detemir and insulin glargine in children and adolescents with type 1 diabetes**

### Summary

EudraCT number	2004-001692-19
Trial protocol	DE
Global end of trial date	09 October 2005

### 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	NN304-1633
-----------------------	------------

#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01497574
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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes
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	01 April 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 October 2005
Global end of trial reached?	Yes
Global end of trial date	09 October 2005
Was the trial ended prematurely?	No

Notes:

---

**General information about the trial**

Main objective of the trial:

To compare the within-subject variability of the pharmacokinetic profiles of insulin detemir and insulin glargine in children and adolescents (6 to 17 years) with type 1 diabetes.

Protection of trial subjects:

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

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	26 May 2005
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: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	8
Adolescents (12-17 years)	24
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 a single 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:

The trial products could not be blinded due to different colour of the code caps of the cartridges, and double-blinding was assured by permitting a qualified person not otherwise involved in the trial to perform the trial product dose preparation and administration.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	IDet-IGlar

Arm description:

Subjects received insulin detemir (IDet) followed by insulin glargine (IGlar).

Arm type	Cross-over assignment
Investigational medicinal product name	Insulin detemir (IDet)
Investigational medicinal product code	
Other name	Levemir
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One injection of insulin detemir (0.4 U/kg) administered subcutaneously on first dosing visit (visit 2) and another injection on second dosing visit (visit 3).

Investigational medicinal product name	Insulin glargine (IGlar)
Investigational medicinal product code	
Other name	Lantus
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One injection of insulin glargine (0.4 IU/kg) administered subcutaneously on first dosing visit (visit 2) and another injection on second dosing visit (visit 3).

<b>Arm title</b>	IGlar-IDet
------------------	------------

Arm description:

Subjects received insulin glargine (IGlar) followed by insulin detemir (IDet).

Arm type	cross-over assignment
Investigational medicinal product name	Insulin detemir (IDet)
Investigational medicinal product code	
Other name	Levemir
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

---

**Dosage and administration details:**

One injection of insulin detemir (0.4 U/kg) administered subcutaneously on first dosing visit (visit 2) and another injection on second dosing visit (visit 3).

Investigational medicinal product name	Insulin glargine (IGlar)
Investigational medicinal product code	
Other name	Lantus
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

**Dosage and administration details:**

One injection of insulin glargine (0.4 IU/kg) administered subcutaneously on first dosing visit (visit 2) and another injection on second dosing visit (visit 3).

Number of subjects in period 1	IDet-IGlar	IGlar-IDet
Started	17	15
Completed	16	14
Not completed	1	1
Adverse event, non-fatal	1	-
Poor condition of vein	-	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:**

The trial products could not be blinded due to different colour of the code caps of the cartridges, and double-blinding was assured by permitting a qualified person not otherwise involved in the trial to perform the trial product dose preparation and administration.

**Arms**

Are arms mutually exclusive?	Yes
Arm title	IDet-IGlar

**Arm description:**

Subjects received insulin detemir (IDet) followed by insulin glargine (IGlar).

Within a period of 7 to 31 days of completion of visit 2, subject of IGlar-IDet arm (of period 1) were received one injection of IDet on visit 3, day 1 followed by one injection of IGlar after a 24 hours interval (visit 3, day 2).

Arm type	Cross-over assignment
Investigational medicinal product name	Insulin detemir (IDet)
Investigational medicinal product code	
Other name	Levemir
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One injection of insulin detemir (0.4 U/kg) administered subcutaneously on first dosing visit (visit 2) and another injection on second dosing visit (visit 3).

Investigational medicinal product name	Insulin glargine (IGlar)
Investigational medicinal product code	
Other name	Lantus
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One injection of insulin glargine (0.4 IU/kg) administered subcutaneously on first dosing visit (visit 2) and another injection on second dosing visit (visit 3).

<b>Arm title</b>	IGlar-IDet
------------------	------------

Arm description:

Subjects received insulin glargine (IGlar) followed by insulin detemir (IDet).

Within a period of 7 to 31 days of completion of visit 2, subject of IDet-IGlar arm (of period 1) were received one injection of IGlar (0.4 IU/kg) on visit 3, day 1 followed by one injection of IDet (0.4 IU/kg) after a 24 hours interval (visit 3, day 2).

Arm type	Cross-over assignment
Investigational medicinal product name	Insulin detemir (IDet)
Investigational medicinal product code	
Other name	Levemir
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One injection of insulin detemir (0.4 U/kg) administered subcutaneously on first dosing visit (visit 2) and another injection on second dosing visit (visit 3).

Investigational medicinal product name	Insulin glargine (IGlar)
Investigational medicinal product code	
Other name	Lantus
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One injection of insulin glargine (0.4 IU/kg) administered subcutaneously on first dosing visit (visit 2) and another injection on second dosing visit (visit 3).

<b>Number of subjects in period 2</b>	IDet-IGlar	IGlar-IDet
Started	14	16
Completed	14	16

**Period 3**

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

**Blinding implementation details:**

The trial products could not be blinded due to different colour of the code caps of the cartridges, and double-blinding was assured by permitting a qualified person not otherwise involved in the trial to perform the trial product dose preparation and administration.

**Arms**

Are arms mutually exclusive?	No
<b>Arm title</b>	IGlar

**Arm description:**

All the subjects, who had received both the doses of IGlar (first dose on first dosing visit-visit 2 and second dose on second dosing visit-visit 3) were included in this arm.

Arm type	Active comparator
Investigational medicinal product name	Insulin glargine (IGlar)
Investigational medicinal product code	
Other name	Lantus
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

**Dosage and administration details:**

One injection of insulin glargine (0.4 IU/kg) administered subcutaneously on first dosing visit (visit 2) and another injection on second dosing visit (visit 3).

<b>Arm title</b>	IDet
------------------	------

**Arm description:**

All the subjects, who had received both the doses of IDet (first dose on first dosing visit-visit 2 and second dose on second dosing visit-visit 3) were included in this arm.

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

**Dosage and administration details:**

One injection of insulin detemir (0.4 U/kg) administered subcutaneously on first dosing visit (visit 2) and another injection on second dosing visit (visit 3).

<b>Arm title</b>	IGlar: Children (6-12 years)
------------------	------------------------------

**Arm description:**

All the children, who had received both the doses of IGlar (first dose on first dosing visit-visit 2 and second dose on second dosing visit-visit 3) were included in this arm.

Arm type	Experimental
Investigational medicinal product name	Insulin glargine (IGlar)
Investigational medicinal product code	
Other name	Lantus
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

**Dosage and administration details:**

One injection of insulin glargine (0.4 IU/kg) administered subcutaneously on first dosing visit (visit 2) and another injection on second dosing visit (visit 3).

<b>Arm title</b>	IGlar: Adolescents (13-17 years)
------------------	----------------------------------

**Arm description:**

All the adolescents, who had received both the doses of IGLar (first dose on first dosing visit-visit 2 and second dose on second dosing visit-visit 3) were included in this arm.

Arm type	Experimental
Investigational medicinal product name	Insulin glargine (IGlar)
Investigational medicinal product code	
Other name	Lantus
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

**Dosage and administration details:**

One injection of insulin glargine (0.4 IU/kg) administered subcutaneously on first dosing visit (visit 2) and another injection on second dosing visit (visit 3).

<b>Arm title</b>	IDet : Children (6-12 years)
------------------	------------------------------

**Arm description:**

All the children, who had received both the doses of IDet (first dose on first dosing visit-visit 2 and second dose on second dosing visit-visit 3) were included in this arm.

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

**Dosage and administration details:**

One injection of insulin detemir (0.4 U/kg) administered subcutaneously on first dosing visit (visit 2) and another injection on second dosing visit (visit 3).

<b>Arm title</b>	IDet: Adolescents (13-17 years)
------------------	---------------------------------

**Arm description:**

All the adolescents, who had received both the doses of IDet (first dose on first dosing visit-visit 2 and second dose on second dosing visit-visit 3) were included in this arm.

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

**Dosage and administration details:**

One injection of insulin detemir (0.4 U/kg) administered subcutaneously on first dosing visit (visit 2) and another injection on second dosing visit (visit 3).

<b>Number of subjects in period 3</b>	IGlar	IDet	IGlar: Children (6-12 years)
Started	30	30	13
Completed	30	30	13

<b>Number of subjects in period 3</b>	IGlar: Adolescents (13-17 years)	IDet : Children (6-12 years)	IDet: Adolescents (13-17 years)
Started	17	13	17

Completed	17	13	17
-----------	----	----	----



## Baseline characteristics

### Reporting groups

Reporting group title	Period 1
Reporting group description:	
Each subject were randomly allocated to a treatment sequence consisting of 2 dosing visits separated by a wash-out period of 7-31 days.	

Reporting group values	Period 1	Total	
Number of subjects	32	32	
Age categorical			
Units: Subjects			
Children (6-12 years)	13	13	
Adolescents (13-17 years)	19	19	
Age continuous			
Not applicable.			
Units: years			
arithmetic mean	13		
standard deviation	± 2.5	-	
Gender categorical			
Not applicable.			
Units: Subjects			
Female	19	19	
Male	13	13	
Body mass index (BMI)			
Units: kg/m <sup>2</sup>			
arithmetic mean	21.4		
standard deviation	± 2.94	-	
Body weight			
Units: Kg			
arithmetic mean	55		
standard deviation	± 13.1	-	

## End points

### End points reporting groups

Reporting group title	IDet-IGlar
-----------------------	------------

Reporting group description:

Subjects received insulin detemir (IDet) followed by insulin glargine (IGlar).

Reporting group title	IGlar-IDet
-----------------------	------------

Reporting group description:

Subjects received insulin glargine (IGlar) followed by insulin detemir (IDet).

Reporting group title	IDet-IGlar
-----------------------	------------

Reporting group description:

Subjects received insulin detemir (IDet) followed by insulin glargine (IGlar).

Within a period of 7 to 31 days of completion of visit 2, subject of IGlar-IDet arm (of period 1) were received one injection of IDet on visit 3, day 1 followed by one injection of IGlar after a 24 hours interval (visit 3, day 2).

Reporting group title	IGlar-IDet
-----------------------	------------

Reporting group description:

Subjects received insulin glargine (IGlar) followed by insulin detemir (IDet).

Within a period of 7 to 31 days of completion of visit 2, subject of IDet-IGlar arm (of period 1) were received one injection of IGlar (0.4 IU/kg) on visit 3, day 1 followed by one injection of IDet (0.4 IU/kg) after a 24 hours interval (visit 3, day 2).

Reporting group title	IGlar
-----------------------	-------

Reporting group description:

All the subjects, who had received both the doses of IGlar (first dose on first dosing visit-visit 2 and second dose on second dosing visit-visit 3) were included in this arm.

Reporting group title	IDet
-----------------------	------

Reporting group description:

All the subjects, who had received both the doses of IDet (first dose on first dosing visit-visit 2 and second dose on second dosing visit-visit 3) were included in this arm.

Reporting group title	IGlar: Children (6-12 years)
-----------------------	------------------------------

Reporting group description:

All the children, who had received both the doses of IGlar (first dose on first dosing visit-visit 2 and second dose on second dosing visit-visit 3) were included in this arm.

Reporting group title	IGlar: Adolescents (13-17 years)
-----------------------	----------------------------------

Reporting group description:

All the adolescents, who had received both the doses of IGlar (first dose on first dosing visit-visit 2 and second dose on second dosing visit-visit 3) were included in this arm.

Reporting group title	IDet : Children (6-12 years)
-----------------------	------------------------------

Reporting group description:

All the children, who had received both the doses of IDet (first dose on first dosing visit-visit 2 and second dose on second dosing visit-visit 3) were included in this arm.

Reporting group title	IDet: Adolescents (13-17 years)
-----------------------	---------------------------------

Reporting group description:

All the adolescents, who had received both the doses of IDet (first dose on first dosing visit-visit 2 and second dose on second dosing visit-visit 3) were included in this arm.

**Primary: AUC 0-16h, area under the insulin concentration-time curve from 0 to 16 hours**

End point title	AUC 0-16h, area under the insulin concentration-time curve from 0 to 16 hours
End point description: The area under the insulin concentration-time curve (AUC) from 0 to 16 hours was measured. Within-subject variability for AUC 0-16h was estimated for all subject, for children and for adolescents, separately.	
End point type	Primary
End point timeframe: 0-16 hours	

End point values	IGlar	IDet	IGlar: Children (6-12 years)	IGlar: Adolescents (13-17 years)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	30	13	17
Units: pmol/L*h				
least squares mean (confidence interval 95%)	900 (753 to 1075)	29839 (26073 to 34149)	830 (605 to 1138)	978 (793 to 1208)

End point values	IDet : Children (6-12 years)	IDet: Adolescents (13-17 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	17		
Units: pmol/L*h				
least squares mean (confidence interval 95%)	31005 (22904 to 41970)	28958 (25950 to 32315)		

**Statistical analyses**

<b>Statistical analysis title</b>	Within-subject variability, all subjects
Comparison groups	IGlar v IDet
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	< 0.0001
Method	F test
Parameter estimate	Ratio between within-subject variances

Notes:

[1] - Test of no difference between the two insulin types with respect to within-subject variation

<b>Statistical analysis title</b>	Within-subject variability, in children
Comparison groups	IGlar: Children (6-12 years) v IDet : Children (6-12 years)

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other <sup>[2]</sup>
P-value	= 0.0026
Method	F test
Parameter estimate	Ratio between within-subject variances

Notes:

[2] - Test of no difference between the two insulin types with respect to within-subject variation.

<b>Statistical analysis title</b>	Within-subject variability, in adolescents
Comparison groups	IGlar: Adolescents (13-17 years) v IDet: Adolescents (13-17 years)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
P-value	< 0.0001
Method	F test
Parameter estimate	Ratio between within-subject variances

Notes:

[3] - Test of no difference between the two insulin types with respect to within-subject variation

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected and reported from the first trial-related activity after the subject has signed the informed consent and until the end of the post-treatment follow-up period.

Adverse event reporting additional description:

Treatment emergent adverse event is defined as the adverse event that occurs after first dose and within 7 days after last dose.

Assessment type	Non-systematic
-----------------	----------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	10
--------------------	----

### Reporting groups

Reporting group title	IDet
-----------------------	------

Reporting group description:

All the subjects who had received at least one dose of IDet during the treatment period.

Reporting group title	IGlar
-----------------------	-------

Reporting group description:

All the subjects who had received at least one dose of IGlar during the treatment period.

Serious adverse events	IDet	IGlar	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	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	IDet	IGlar	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 31 (38.71%)	7 / 31 (22.58%)	
Investigations			
Body temperature increased			

subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3	0 / 31 (0.00%) 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 31 (6.45%)	4 / 31 (12.90%)	
occurrences (all)	2	4	
Headache			
subjects affected / exposed	4 / 31 (12.90%)	3 / 31 (9.68%)	
occurrences (all)	6	5	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Infections and infestations			
Rhinitis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2004	<p>One substantial protocol amendment was issued, implementing the following changes:</p> <ul style="list-style-type: none"><li>• The upper BMI limit (inclusion criteria No. 4) was increased from 20 to 24 kg/m<sup>2</sup> in children and from 25 to 29 kg/m<sup>2</sup> in adolescents.</li><li>• Children and adolescents with thyroiditis (treated or no treatment necessary) were allowed to be included in the trial.</li><li>• Children and adolescents treated with Semilente® prior to trial initiation were to take their last insulin injection 12 hours before trial product administration instead of being transferred to NPH insulin, 48 hours before trial product administration.</li></ul>

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/18761644>