Clinical trial results:
This trial is a randomized, single-centre, double-blind, two-period cross-over glucose clamp trial to test for bioequivalence between two SIBA (IDeg) formulations in healthy subjects.

This trial is part of two PIPs with EMA decision numbers P/44/2010 and P/96/2011

Summary

EudraCT number	2011-002949-35
Trial protocol	Outside EU/EEA
Global end of trial date	02 October 2009

Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	28 July 2015

Trial information

Trial identification

Sponsor protocol code	NN1250-1988

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00966368
WHO universal trial number (UTN)	U1111-1122-2992

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	10 June 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 October 2009
Global end of trial reached?	Yes
Global end of trial date	02 October 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to test for bioequivalence between two formulations of Insulin Degludec (I454) based on AUCI454,0-120h,SD and Cmax,I454,SD.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki 59th WMA General Assembly, Seoul,October 2008, and ICH Good Clinical Practice 01-May-1996.

Background therapy:

Not Applicable

Evidence for comparator:

Not Applicable

Actual start date of recruitment	04 August 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	United States: 26
Worldwide total number of subjects	26
EEA total number of subjects	0

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	26

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

One site in United States.

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, Monitor, Data analyst

Blinding implementation details:

Double - blind, randomised, 2 period cross-over study. Novo Nordisk study staff were also blinded in this study.

Arms

Are arms mutually exclusive?	Yes
Arm title	IDeg (E) in period 1

Arm description:

Subjects received IDeg (E), an insulin degludec formulation used in the phase 2 trials, in period 1

Arm type	Cross over
Investigational medicinal product name	IDeg(E)
Investigational medicinal product code	
Other name	Insulin Degludec, insulin 454, I454, SIBA
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each subject was allocated to a single injection of trial product on 2 occasions (Visits 2 and 3 -Treatment period Day 1-6), and was therefore to receive 1 injection of each IDeg formulation during the trial. The dose level of IDeg was 0.4 U/kg body weight. Trial products were administered as a subcutaneous injection into a lifted skin fold of the anterior surface of the thigh using an appropriate 1 mL syringe.

Arm title	IDeg (M) in period 1

Arm description:

Subjects received IDeg (M), an insulin degludec formulation used in the phase 3 trials, in period 1

Arm type	Cross over
Investigational medicinal product name	IDeg (M)
Investigational medicinal product code	
Other name	Insulin Degludec, insulin 454, I454, SIBA
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each subject was allocated to a single injection of trial product on 2 occasions (Visits 2 and 3-Treatment period Day 1-6), and was therefore to receive 1 injection of each IDeg formulation during the trial. The dose level of IDeg was 0.4 U/kg body weight. Trial products were administered as a subcutaneous injection into a lifted skin fold of the anterior surface of the thigh using an appropriate 1 mL syringe.

Number of subjects in period 1	IDeg (E) in period 1	IDeg (M) in period 1
Started	13	13
Completed	13	13

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, Monitor, Data analyst

Blinding implementation details:

Double blind, 2 period crossover study. Novo Nordisk study staff were also blinded in this study.

Arms

Are arms mutually exclusive?	Yes
Arm title	IDeg (E) in period 2

Arm description:

Subjects received IDeg (E), an insulin degludec formulation used in the phase 2 trials, in period 2

Arm type	Cross over
Investigational medicinal product name	IDeg(E)
Investigational medicinal product code	
Other name	Insulin Degludec, insulin 454, I454, SIBA
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each subject was allocated to a single injection of trial product on 2 occasions (Visits 2 and 3-Treatment period Day 1-6), and was therefore to receive 1 injection of each IDeg formulation during the trial. The dose level of IDeg was 0.4 U/kg body weight. Trial products were administered as a subcutaneous injection into a lifted skin fold of the anterior surface of the thigh using an appropriate 1 mL syringe.

Arm title	IDeg (M) in period 2

Arm description:

Subjects received IDeg (M), an insulin degludec formulation used in the phase 3 trials, in period 2.

Arm type	Cross over
Investigational medicinal product name	IDeg (M)
Investigational medicinal product code	
Other name	Insulin Degludec, insulin 454, I454, SIBA
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each subject was allocated to a single injection of trial product on 2 occasions (Visits 2 and 3-Treatment period Day 1-6), and was therefore to receive 1 injection of each IDeg formulation during the trial. The dose level of IDeg was 0.4 U/kg body weight. Trial products were administered as a subcutaneous injection into a lifted skin fold of the anterior surface of the thigh using an appropriate 1 mL syringe.

Number of subjects in period 2	IDeg (E) in period 2	IDeg (M) in period 2
Started	13	13
Completed	12	13
Not completed	1	0
Non Compliance	1	-

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, Monitor, Data analyst

Blinding implementation details:

Double blind, 2 period crossover study. Novo Nordisk study staff were also blinded in this study.

Arms

Are arms mutually exclusive?	No
Arm title	IDeg (E)

Arm description:

Subjects received IDeg (E), an insulin degludec formulation used in the phase 2 trials.

Arm type	Experimental
Investigational medicinal product name	IDeg(E)
Investigational medicinal product code	
Other name	Insulin Degludec, insulin 454, I454, SIBA
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each subject was allocated to a single injection of trial product on 2 occasions (Visits 2 and 3-Treatment period Day 1-6), and was therefore to receive 1 injection of each IDeg formulation during the trial. The dose level of IDeg was 0.4 U/kg body weight. Trial products were administered as a subcutaneous injection into a lifted skin fold of the anterior surface of the thigh using an appropriate 1 mL syringe.

Arm title	IDeg (M)

Arm description:

Subjects received IDeg (M), an insulin degludec formulation used in the phase 3 trials

Arm type	Experimental
Investigational medicinal product name	IDeg (M)
Investigational medicinal product code	
Other name	Insulin Degludec, insulin 454, I454, SIBA
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Each subject was allocated to a single injection of trial product on 2 occasions (Visits 2 and 3-Treatment period Day 1-6), and was therefore to receive 1 injection of each IDeg formulation during the trial. The dose level of IDeg was 0.4 U/kg body weight. Trial products were administered as a subcutaneous

injection into a lifted skin fold of the anterior surface of the thigh using an appropriate 1 mL syringe.

Number of subjects in period 3	IDeg (E)	IDeg (M)
Started	26	26
Completed	25	26
Not completed	1	0
Non Compliance	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Period 1

Reporting group description: -

Reporting group values	Period 1	Total	
Number of subjects	26	26	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	26	26	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	36.62		
standard deviation	± 9.59	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	19	19	

End points

End points reporting groups	
Reporting group title	IDeg (E) in period 1
Reporting group description:	
Subjects received IDeg (E), an insulin degludec formulation used in the phase 2 trials, in period 1	
Reporting group title	IDeg (M) in period 1
Reporting group description:	
Subjects received IDeg (M), an insulin degludec formulation used in the phase 3 trials, in period 1	
Reporting group title	IDeg (E) in period 2
Reporting group description:	
Subjects received IDeg (E), an insulin degludec formulation used in the phase 2 trials, in period 2	
Reporting group title	IDeg (M) in period 2
Reporting group description:	
Subjects received IDeg (M), an insulin degludec formulation used in the phase 3 trials, in period 2.	
Reporting group title	IDeg (E)
Reporting group description:	
Subjects received IDeg (E), an insulin degludec formulation used in the phase 2 trials.	
Reporting group title	IDeg (M)
Reporting group description:	
Subjects received IDeg (M), an insulin degludec formulation used in the phase 3 trials	

Primary: AUCI454,0-120h,SD -Area under the serum IDeg concentration time curve.	
End point title	AUCI454,0-120h,SD -Area under the serum IDeg concentration time curve.
End point description:	
Area under the serum insulin 454 (IDeg) concentration-time curve	
End point type	Primary
End point timeframe:	
0-120 hours after single dose.	

End point values	IDeg (E)	IDeg (M)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: pmol*h/L				
geometric mean (geometric coefficient of variation)	84346 (± 14.02)	83817 (± 15.89)		

Statistical analyses

Statistical analysis title	AUC IDeg (0-120 h)
Comparison groups	IDeg (M) v IDeg (E)

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Method	ANOVA
Parameter estimate	Treatment ratio
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.94
upper limit	1.05

Notes:

[1] - For AUCI454,0-120h,SD bioequivalence between the 2 IDeg formulations will be claimed if the 90% CI of the treatment ratio for both AUC (0-120h) and Cmax is fully within the interval [80%;125%]. Please note that the analysis type is bioequivalence.
The "Number of subjects included in analysis" is 26, not 51 as stated in the above table (due to EudraCT IT system error).

Primary: Cmax I454,SD-Maximum observed serum IDeg concentration after single-dose

End point title	Cmax I454,SD-Maximum observed serum IDeg concentration after single-dose

End point description:

Maximum observed serum IDeg concentration after single-dose.

End point type	Primary

End point timeframe:

within 0 to 120 hours after dosing

End point values	IDeg (E)	IDeg (M)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: pmol/L				
geometric mean (geometric coefficient of variation)	2345 (± 21.41)	2280 (± 28.87)		

Statistical analyses

Statistical analysis title	Cmax IDeg, SD
Comparison groups	IDeg (M) v IDeg (E)
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Method	ANOVA
Parameter estimate	Treatment ratio
Point estimate	0.97

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.89
upper limit	1.05

Notes:

[2] - For Cmax,I454,SD, bioequivalence between the 2 IDeg formulations will be claimed if the 90% CI of the treatment ratio for both AUC (0-120h) and Cmax is fully within the interval [80%;125%]. Please note the analysis type is bioequivalence.
The "Number of subjects included in analysis" is 26, not 51 as stated in the above table (due to EudraCT IT system error).

Secondary: tmax I454,SD,Time to maximum observed serum IDeg concentration after dosing

End point title	tmax I454,SD,Time to maximum observed serum IDeg concentration after dosing

End point description:

Time to maximum observed serum IDeg concentration after dosing.

End point type	Secondary

End point timeframe:

within 0 to 120 hours after dosing

End point values	IDeg (E)	IDeg (M)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: Hours				
median (full range (min-max))	13 (6 to 22)	13.5 (6 to 36)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUCI454,0-24h,SD-Area under the serum IDeg concentration-time curve after single dose.

End point title	AUCI454,0-24h,SD-Area under the serum IDeg concentration-time curve after single dose.

End point description:

Area under the serum IDeg concentration-time curve after single dose.

End point type	Secondary

End point timeframe:

0-24 hours after single dose

End point values	IDeg (E)	IDeg (M)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: pmol*h/L				
geometric mean (geometric coefficient of variation)	39358 (± 17.78)	37567 (± 28.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: t½,I454-Terminal half-life for IDeg (within 0-120 hours after dosing)

End point title	t½,I454-Terminal half-life for IDeg (within 0-120 hours after dosing)

End point description:

Terminal half-life for IDeg within 0-120 hours after dosing

End point type	Secondary

End point timeframe:

0-120 hours after dosing

End point values	IDeg (E)	IDeg (M)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: hours				
median (full range (min-max))	16.3 (6.5 to 45.5)	18.4 (5.5 to 36.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment to follow-up	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1
Reporting groups	
Reporting group title	IDeg (E)
Reporting group description:	
Subjects received IDeg (E), an insulin degludec formulation used in the phase 2 trials.	
Reporting group title	IDeg (M)
Reporting group description:	
Subjects received IDeg (M), an insulin degludec formulation used in the phase 3 trials.	

Serious adverse events	IDeg (E)	IDeg (M)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 26 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	IDeg (E)	IDeg (M)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 25 (8.00%)	2 / 26 (7.69%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 25 (8.00%)	2 / 26 (7.69%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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: