Clinical trial results:
A randomised, double-blind, cross-over trial comparing the safety and efficacy of insulin degludec and insulin glargine, both with insulin aspart as mealtime insulin in subjects with type 1 diabetes

Summary

EudraCT number	2012-001930-32
Trial protocol	PL
Global end of trial date	12 January 2016

Results information

Result version number	v1 (current)
This version publication date	27 January 2017
First version publication date	27 January 2017

Trial information

Trial identification

Sponsor protocol code	NN1250-3995

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02034513
WHO universal trial number (UTN)	U1111-1129-9668

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?	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	03 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2016
Global end of trial reached?	Yes
Global end of trial date	12 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the rates of severe or BG (blood glucose) confirmed symptomatic hypoglycaemia of IDeg once daily (OD) + IAsp to IGlar OD + IAsp, by demonstrating that the upper limit of the 95% confidence interval of the rate ratio is below or equal to a non-inferiority margin of 1.10, and if confirmed, to a superiority limit of 1.00.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice, and 21 CFR 312.120.

Background therapy:

Insulin aspart (IAsp; bolus insulin) was titrated individually based on either carbohydrate counting or by using sliding scale based on the lowest of three pre-meal or bedtime self-measured plasma glucose (SMPG) values.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	06 January 2014
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: 43
Country: Number of subjects enrolled	United States: 458
Worldwide total number of subjects	501
EEA total number of subjects	43

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)	448
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 90 sites in 2 countries, as follows: the United States (US): 84 sites, Poland: 6 sites.

Pre-assignment

Screening details:

Not applicable.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Insulin degludec/insulin glargine (IDeg/IGlar)

Arm description:

Subjects received insulin degludec (IDeg) in treatment period 1 and insulin glargine (IGlar) in treatment period 2. Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period).

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

Dosage and administration details:

Subjects received IGlar for a total of 32 weeks (16-week titration period and a 16-week maintenance period). IGlar was administered s.c. in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and were to be taken OD at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IGlar were reduced by 20% at the start of both the treatment periods. Doses of IGlar were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast SMPG values measured on 3 consecutive days immediately prior to titration (fasting glycaemic target of 4.0-5.0 mmol/L).

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

Dosage and administration details:

Subjects received IDeg for a total of 32 weeks (16-week titration period and a 16-week maintenance period). IDeg was administered subcutaneously (s.c.; under the skin) in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and was to be taken once daily (OD) at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IDeg were reduced by 20% at the start of both the treatment periods. Doses of IDeg were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast self measured plasma glucose (SMPG) values measured on 3 consecutive days immediately prior to titration (fasting glycaemic target of 4.0-5.0 mmol/L).

Arm title	Insulin glargine/insulin degludec (IGlar/IDeg)

Arm description:

Subjects received IGlar in treatment period 1 and IDeg in treatment period 2. Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period).

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

Dosage and administration details:

Subjects received IGlar for a total of 32 weeks (16-week titration period and a 16-week maintenance period). IGlar was administered s.c. in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and were to be taken OD at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IGlar were reduced by 20% at the start of both the treatment periods. Doses of IGlar were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast SMPG values measured on 3 consecutive days immediately prior to titration (fasting glycaemic target of 4.0-5.0 mmol/L).

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

Dosage and administration details:

Subjects received IDeg for a total of 32 weeks (16-week titration period and a 16-week maintenance period). IDeg was administered s.c. in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and was to be taken OD at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IDeg were reduced by 20% at the start of both the treatment periods. Doses of IDeg were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast SMPG values measured on 3 consecutive days immediately prior to titration (fasting glycaemic target of 4.0-5.0 mmol/L).

Number of subjects in period 1	Insulin degludec/insulin glargine (IDeg/IGlar)	Insulin glargine/insulin degludec (IGlar/IDeg)
Started	249	252
Exposed	249	251
Completed	200	195
Not completed	49	57
Consent withdrawn by subject	25	25
Adverse event, non-fatal	11	10
Pregnancy	-	3
Unclassified	-	1
Lost to follow-up	6	7
Protocol deviation	7	10
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Insulin degludec/insulin glargine (IDeg/IGlar)
Reporting group description:	
Subjects received insulin degludec (IDeg) in treatment period 1 and insulin glargine (IGlar) in treatment period 2. Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period).	
Reporting group title	Insulin glargine/insulin degludec (IGlar/IDeg)
Reporting group description:	
Subjects received IGlar in treatment period 1 and IDeg in treatment period 2. Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period).	

Reporting group values	Insulin degludec/insulin glargine (IDeg/IGlar)	Insulin glargine/insulin degludec (IGlar/IDeg)	Total
Number of subjects	249	252	501
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	223	225	448
From 65-84 years	26	27	53
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	45.4	46.4	
standard deviation	± 13.7	± 14.6	-
Gender, Male/Female			
Units: Subjects			
Female	123	109	232
Male	126	143	269
Study Specific Characteristic | Glycosylated hemoglobin (HbA1c)			
Number of subjects analyzed=248 for IDeg/IGlar arm, 252 for IGlar/IDeg arm.			
Units: Percentage of HbA1c			
arithmetic mean	7.7	7.5	
standard deviation	± 1	± 1	-
Study Specific Characteristic | Fasting plasma glucose (FPG)			
Number of subjects analyzed=248 for IDeg/IGlar arm, 252 for IGlar/IDeg arm.			
Units: mg/dL			
arithmetic mean	165.1	174.4	
standard deviation	± 77.3	± 81.7	-

End points

End points reporting groups

Reporting group title	Insulin degludec/insulin glargine (IDeg/IGlar)

Reporting group description:

Subjects received insulin degludec (IDeg) in treatment period 1 and insulin glargine (IGlar) in treatment period 2. Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period).

Reporting group title	Insulin glargine/insulin degludec (IGlar/IDeg)

Reporting group description:

Subjects received IGlar in treatment period 1 and IDeg in treatment period 2. Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period).

Subject analysis set title	Insulin degludec (IDeg)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received IDeg in treatment period 1 (from treatment sequence IDeg/IGlar) and in treatment period 2 (from treatment sequence IGlar/IDeg). Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period). IDeg was administered s.c. in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and was to be taken OD at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IDeg were reduced by 20% at the start of both the treatment periods. Doses of IDeg were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast SMPG values measured on 3 consecutive days immediately prior to titration.

Subject analysis set title	Insulin glargine (IGlar)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received IGlar in treatment period 1 (from treatment sequence IGlar/IDeg) and in treatment period 2 (from treatment sequence IDeg/IGlar). Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period). IGlar was administered s.c. in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and was to be taken OD at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IGlar were reduced by 20% at the start of both the treatment periods. Doses of IGlar were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast SMPG values measured on 3 consecutive days immediately prior to titration.

Subject analysis set title	Insulin degludec (IDeg)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received IDeg in treatment period 1 (from treatment sequence IDeg/IGlar) and in treatment period 2 (from treatment sequence IGlar/IDeg). Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period). IDeg was administered s.c. in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and was to be taken OD at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IDeg were reduced by 20% at the start of both the treatment periods. Doses of IDeg were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast SMPG values measured on 3 consecutive days immediately prior to titration.

Subject analysis set title	Insulin glargine (IGlar)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received IGlar in treatment period 1 (from treatment sequence IGlar/IDeg) and in treatment period 2 (from treatment sequence IDeg/IGlar). Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period). IGlar was administered s.c. in the morning (from waking up to breakfast) or in the evening (from main evening meal to bedtime), as per randomisation and was to be taken OD at the same time of day throughout the trial. To prevent an increased risk of hypoglycaemia in the first treatment month, the overall daily doses of IGlar were reduced by 20% at the start of both the treatment periods. Doses of IGlar were titrated individually. Titration of the dose was performed once weekly based on the lowest of 3 pre-breakfast

SMPG values measured on 3 consecutive days immediately prior to titration.

Primary: Number of treatment emergent severe or BG (blood glucose) confirmed symptomatic hypoglycaemic episodes during the maintenance period

End point title	Number of treatment emergent severe or BG (blood glucose) confirmed symptomatic hypoglycaemic episodes during the maintenance period

End point description:

Severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes were defined as episodes that were severe and/or BG confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia. Treatment emergent hypoglycaemic episode was defined as an event with onset date on or after the first day of exposure to randomised treatment and no later than the last day of randomised treatment. The trial followed a cross over design. Descriptive analysis was based on the safety analysis set (SAS: subjects receiving at least 1 dose of the investigational product, IDeg or its comparator, IGlar; number of subjects (N)=500). Number of subjects analysed=subjects with available data for the endpoint as per individual trial product. Statistical analysis was based on the subjects in the full analysis set (FAS: included all randomised subjects (N=501)), who were exposed in at least one maintenance period (i.e., N=437).

End point type	Primary

End point timeframe:

After 16 weeks of treatment, in each treatment period (Week 16-32 and Week 48-64).

End point values	Insulin degludec (IDeg)	Insulin glargine (IGlar)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	418	422		
Units: Event	2772	3126		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stepwise hierarchical testing procedure was applied for confirmatory endpoints: Step 1: Number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during the maintenance period. Due to cross-over design of the study, the following "number of subjects included in analysis" is being erroneously displayed as 840. Actual "number of subjects included in analysis" is 437.

Comparison groups	Insulin degludec (IDeg) v Insulin glargine (IGlar)
Number of subjects included in analysis	840
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001
Method	Poisson
Parameter estimate	Treatment ratio
Point estimate	0.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	0.94

Notes:

[1] - Non-inferiority was considered confirmed if the 95% confidence interval for the rate ratio (IDeg/IGlar) was ≤1.10 or equivalently if the p-value for the 1-sided test of H0: RR >1.10 against HA: RR ≤1.10 was less than 2.5%, where RR is the estimated rate ratio IDeg/IGlar. If non-inferiority was confirmed the superiority of IDeg/IGlar was investigated outside of the test hierarchy. Superiority was considered confirmed if the upper bound of the 2-sided 95% confidence interval was <1.00.

Secondary: Number of treatment emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes during the maintenance period

End point title	Number of treatment emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes during the maintenance period

End point description:

Severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes were defined as episodes that were severe and/or BG confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia and with time of onset between 00:01 and 05.59 a.m., both inclusive. Treatment emergent hypoglycaemic episode was defined as an event with onset date on or after the first day of exposure to randomised treatment and no later than the last day of randomised treatment. The trial followed a cross over design. Descriptive analysis was based on the SAS (N=500). Number of subjects analysed=subjects with available data for the endpoint as per individual trial product. Statistical analysis was based on the subjects in the FAS (N=501), who were exposed in at least one maintenance period (i.e., N=437).

End point type	Secondary

End point timeframe:

After 16 weeks of treatment, in each treatment period (Week 16-32 and Week 48-64)

End point values	Insulin degludec (IDeg)	Insulin glargine (IGlar)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	418	422		
Units: Event	349	544		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stepwise hierarchical testing procedure was applied for confirmatory endpoints: Step 2: Number of treatment-emergent severe or BG confirmed symptomatic nocturnal hypoglycaemic episodes during the maintenance period. Due to cross-over design of the study, the following "number of subjects included in analysis" is being erroneously displayed as 840. Actual "number of subjects included in analysis" is 437.

Comparison groups	Insulin degludec (IDeg) v Insulin glargine (IGlar)

Number of subjects included in analysis	840
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.0001
Method	Poisson
Parameter estimate	Treatment ratio
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.73

Notes:

[2] - Non-inferiority was considered confirmed if the 95% confidence interval for the rate ratio (IDeg/IGlar) was ≤1.10 or equivalently if the p-value for the 1-sided test of H0: RR >1.10 against HA: RR ≤1.10 was less than 2.5%, where RR is the estimated rate ratio IDeg/IGlar. If non-inferiority was confirmed the superiority of IDeg/IGlar was investigated outside of the test hierarchy. Superiority was considered confirmed if the upper bound of the 2-sided 95% confidence interval was <1.00.

Secondary: Proportion of subjects with one or more severe hypoglycaemic episodes during the maintenance period

End point title	Proportion of subjects with one or more severe hypoglycaemic episodes during the maintenance period

End point description:

Percentage of subjects who experienced one or more severe hypoglycaemic episodes during the maintenance period. Severe hypoglycaemia (according to the American Diabetes Association 2013 definition): A hypoglycaemic episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose values may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. The trial followed a cross over design. Descriptive analysis was based on the SAS (N=500). Number of subjects analysed=subjects with available data for the endpoint as per individual trial product. Statistical analysis was based on the subjects in the FAS (N=501) who were exposed in both the maintenance periods (i.e., N=403).

End point type	Secondary

End point timeframe:

After 16 weeks of treatment, in each treatment period (Week 16-32 and Week 48-64)

End point values	Insulin degludec (IDeg)	Insulin glargine (IGlar)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	418	422		
Units: Percentage of subjects				
number (not applicable)	10.3	17.1		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stepwise hierarchical testing procedure was applied for confirmatory endpoints: Step 3: Proportion of subjects with one or more severe hypoglycaemic episodes during the maintenance period. Due to cross-

over design of the study, the following “number of subjects included in analysis” is being erroneously displayed as 840. Actual “number of subjects included in analysis” is 403.

Comparison groups	Insulin degludec (IDeg) v Insulin glargine (IGlar)
Number of subjects included in analysis	840
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0016
Method	Mcnemar

Notes:

[3] - Superiority was confirmed if the p-value was less than 0.025.

Secondary: Incidence of treatment emergent adverse events

End point title	Incidence of treatment emergent adverse events

End point description:

Treatment emergent adverse event was defined as an event with onset date on or after the first day of exposure to randomised treatment and no later than the last day of randomised treatment. The trial followed a cross over design. Results are based on the SAS (N=500). Total "number of subjects analysed" for this endpoint: 500.

End point type	Secondary

End point timeframe:

During 32 weeks of treatment for each treatment period

End point values	Insulin degludec (IDeg)	Insulin glargine (IGlar)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	454	460		
Units: Event	925	937		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in HbA1c (glycosylated haemoglobin)

End point title	Change from baseline in HbA1c (glycosylated haemoglobin)

End point description:

Change from baseline in HbA1c (glycosylated haemoglobin) at week 32 (treatment period 1) and at week 64 (treatment period 2). Week 32 HbA1c absolute values were considered as baseline for calculating change from baseline in HbA1c at week 64. Week 32 HbA1c absolute values: mean (standard deviation) = 6.9% (0.9) and 6.8% (0.8) for IDeg/IGlar and IGlar/IDeg treatment groups, respectively. Both descriptive analysis and statistical analysis were based on the FAS (n=501). Here, 'n' specifies the number of subjects with available data at specified time-point.

End point type	Secondary

End point timeframe:

Week 32, Week 64

End point values	Insulin degludec/insulin glargine (IDeg/IGlar)	Insulin glargine/insulin degludec (IGlar/IDeg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	252		
Units: Percentage of glycosylated haemoglobin				
arithmetic mean (standard deviation)				
week 32 (n=209, 205)	-0.73 (± 0.89)	-0.66 (± 0.76)		
week 64 (n=203, 199)	0.04 (± 0.51)	0.17 (± 0.64)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change from baseline in HbA1c at week 32 (treatment period 1). Before testing the primary endpoint, the secondary supportive efficacy endpoint "Change from baseline in HbA1c after 32 weeks of treatment" was tested for non-inferiority as a prerequisite for testing the primary endpoint. Analysis was based on mixed model for repeated measurement (MMRM); treatment, sex, region, pre-trial insulin treatment regimen, visit and dosing time were fixed effects, and age and baseline HbA1c were covariates.

Comparison groups	Insulin degludec/insulin glargine (IDeg/IGlar) v Insulin glargine/insulin degludec (IGlar/IDeg)
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Treatment contrast
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.15

Notes:

[4] - Non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval was below or equal to 0.40%. The above comparison groups should be read as: "IDeg versus IGlar". Due to cross-over design of the study, the above "number of subjects included in analysis" is being erroneously displayed as 501. Actual "number of subjects included in analysis" is 437 (n=220 for IDeg and n=217 for IGlar).

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Change from baseline in HbA1c at week 64 (treatment period 2). Before the primary endpoint was tested, the secondary supportive efficacy endpoint "Change from baseline in HbA1c after 32 weeks of treatment" was tested for non-inferiority as prerequisite for testing the primary endpoint. Analysis was based on MMRM; treatment, sex, region, pre-trial insulin treatment regimen, visit and dosing time were fixed effects, and age and baseline HbA1c were covariates.

Comparison groups	Insulin degludec/insulin glargine (IDeg/IGlar) v Insulin glargine/insulin degludec (IGlar/IDeg)

Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Treatment contrast
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.23

Notes:

[5] - For this analysis, Week 32 HbA1c absolute values were considered as baseline. Non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval was below or equal to 0.40%. The above comparison groups should be read as: "IDeg versus IGlar". Due to cross-over design of the study, the above "number of subjects included in analysis" is being erroneously displayed as 501. Actual "number of subjects included in analysis" is 410 (n=202 for IDeg and n=208 for IGlar).

Secondary: FPG (Fasting plasma glucose)

End point title	FPG (Fasting plasma glucose)

End point description:

Fasting plasma glucose values at week 32 and week 64. Results are based on the FAS (N=501). Here, 'n' specifies the number of subjects with available data at specified time-point.

End point type	Secondary

End point timeframe:

Week 32, Week 64

End point values	Insulin degludec/insulin glargine (IDeg/IGlar)	Insulin glargine/insulin degludec (IGlar/IDeg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	252		
Units: mmol/L				
arithmetic mean (standard deviation)				
week 32 (n=208, 204)	7.45 (± 3.57)	8.12 (± 3.56)		
week 64 (n=203, 201)	8.62 (± 4.24)	7.54 (± 3.68)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first day of exposure to randomised treatment and no later than the last day of randomised treatment (64 weeks).

Adverse event reporting additional description:

The trial followed a cross over design. Subjects in the SAS (N=500) contributed to the evaluation of adverse events. Treatment emergent adverse event was defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than the last day of randomised treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Insulin glargine (IGlar)

Reporting group description:

Subjects received IGlar in treatment period 1 (from treatment sequence IGlar/IDeg) and in treatment period 2 (from treatment sequence IDeg/IGlar). Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period).

Reporting group title	Insulin degludec (IDeg)

Reporting group description:

Subjects received IDeg in treatment period 1 (from treatment sequence IDeg/IGlar) and in treatment period 2 (from treatment sequence IGlar/IDeg). Each treatment period consisted of a 16-week titration period and a 16-week maintenance period (total 32 weeks for each treatment period).

Serious adverse events	Insulin glargine (IGlar)	Insulin degludec (IDeg)	
Total subjects affected by serious adverse events			
subjects affected / exposed	70 / 460 (15.22%)	58 / 454 (12.78%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer in situ			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			

subjects affected / exposed	0 / 460 (0.00%)	2 / 454 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Pancreas transplant			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			

subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	3 / 460 (0.65%)	2 / 454 (0.44%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 460 (0.00%)	2 / 454 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gun shot wound			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory fume inhalation disorder			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Road traffic accident			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			

subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 460 (0.22%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wolff-Parkinson-White syndrome			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic coma			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic seizure			
subjects affected / exposed	5 / 460 (1.09%)	3 / 454 (0.66%)	
occurrences causally related to treatment / all	3 / 5	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic unconsciousness			
subjects affected / exposed	19 / 460 (4.13%)	18 / 454 (3.96%)	
occurrences causally related to treatment / all	17 / 24	18 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Optic ischaemic neuropathy			

subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 460 (0.22%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			

subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 460 (0.43%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc degeneration			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc displacement			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lumbar spinal stenosis			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 460 (0.00%)	2 / 454 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal skin infection			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 460 (0.22%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	3 / 460 (0.65%)	2 / 454 (0.44%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 460 (0.00%)	1 / 454 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 460 (0.22%)	0 / 454 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	3 / 460 (0.65%)	2 / 454 (0.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	33 / 460 (7.17%)	17 / 454 (3.74%)	
occurrences causally related to treatment / all	34 / 47	23 / 32	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Insulin glargine (IGlar)	Insulin degludec (IDeg)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 460 (21.09%)	97 / 454 (21.37%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	61 / 460 (13.26%)	68 / 454 (14.98%)	
occurrences (all)	73	92	

Upper respiratory tract infection subjects affected / exposed occurrences (all)	39 / 460 (8.48%) 41	29 / 454 (6.39%) 34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2014	Amendment-1: Due to major challenges in recruiting the population described in protocol version 5.0 dated 22-Oct-2013, a broadening of inclusion criteria was needed. This amendment was prepared in order to broaden the inclusion criteria to include subjects using continuous subcutaneous insulin infusion (CSII), to increase the upper limit of HbA1c to ≤10% and to increase the upper limit of BMI to ≤45 kg/m2. Exclusion criterion 4 was altered to allow short-term use of IGlar prior to screening. Short term use (≤2 weeks) before the last 4 weeks prior to inclusion is not believed to bias the study as this would not require subjects to adapt their lifestyle to a specific insulin profile. Finally, a note has been added to exclusion criterion 2, allowing subjects that were screening failures due to inclusion criteria 5, 6 and 7 and exclusion criterion 4 in protocol version 5.0 dated 22-Oct-2013 to be re-screened according to this protocol amendment. A EudraCT number has been added as Poland was added to the trial.
18 September 2014	Amendment-2: This amendment was created to clarify that bolus insulin may include both rapid acting and fast acting insulin. This amendment also clarifies that review of patient reported outcome (PRO) questionnaires for adverse events and/or change in overall health and concomitant medication could be done by any medically qualified site staff delegated by the investigator.
01 December 2015	Amendment-3: The analysis of HbA1c specified in protocol version 7.0 dated 25-Jul-2014 was not in alignment with Novo Nordisk's response to FDA's comments to the Special Protocol Assessment on this study. This protocol amendment was created to reflect the response to the FDA, as the analysis is a prerequisite for performing the primary analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported