Clinical trial results:
The effect of insulin degludec in combination with liraglutide and metformin in subjects with type 2 diabetes qualifying for treatment intensification

Summary

EudraCT number	2011-004665-32
Trial protocol	DE GB IT
Global end of trial date	31 December 2013

Results information

Result version number	v1
This version publication date	16 March 2016
First version publication date	28 July 2015

Trial information

Trial identification

Sponsor protocol code	NN1250-3944

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01664247
WHO universal trial number (UTN)	U1111-1124-6612

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	12 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2013
Global end of trial reached?	Yes
Global end of trial date	31 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the efficacy of IDeg compared to placebo, both in combination with liraglutide and metformin, in controlling glycaemia

Protection of trial subjects:

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

Background therapy:

Metformin in combination with sulphonylurea, glinides, dipeptidyl peptidase IV inhibitors or exenatide were the background medications and were therefore treated as non-investigational medicinal product.

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 October 2012
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	Italy: 24
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Serbia: 52
Country: Number of subjects enrolled	South Africa: 16
Country: Number of subjects enrolled	Ukraine: 29
Country: Number of subjects enrolled	United Arab Emirates: 7
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	United States: 124
Worldwide total number of subjects	346
EEA total number of subjects	94

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)	281
From 65 to 84 years	65
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The following sites in each country screened/randomised/assigned subjects in the trial: Canada:7, France: 10, Germany: 8, Israel: 6, Italy: 7, Serbia: 7, South Africa: 6, Ukraine: 4, United Arab Emirates: 3, United Kingdom: 6, and United States: 65.

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	IDeg + liraglutide

Arm description:

Liraglutide treatment was initiated on 0.6 mg daily for one week and increased further after the second week in the run-in period. In the randomized period, IDeg treatment was recommended to be initiated with 10 units. After that it was titrated once weekly. If one or more of the pre-breakfast plasma glucose values were below a certain range, the subjects were to reduce the insulin dose.

Arm type	Active comparator
Investigational medicinal product name	IDeg PDS290
Investigational medicinal product code	SUB25238
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Drug: insulin degludec administered subcutaneously (under the skin) once daily. Dose individually adjusted.

Arm title	Placebo + liraglutide

Arm description:

Placebo treatment was recommended to be initiated with 10 units. After that it was titrated once weekly. If one or more of the pre-breakfast plasma glucose values were below a certain range, the subjects were to reduce the insulin dose.

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	SUB25238
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Drug: Placebo administered subcutaneously (under the skin) once daily.

Number of subjects in period 1	IDeg + liraglutide	Placebo + liraglutide
Started	174	172
Completed	160	131
Not completed	14	41
Withdrawal Criteria	1	4
Adverse event, non-fatal	5	3
Unclassified	5	29
Protocol deviation	3	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description:

IDeg treatment was recommended to be initiated with 10 units. After that it was titrated once weekly. If one or more of the pre-breakfast plasma glucose values were below a certain range, the subjects were to reduce the insulin dose. Liraglutide treatment was initiated on 0.6 mg daily for one week and increased further after the second week in the run-in period. Metformin was the background medications and was therefore treated as non-investigational medicinal product (non-IMP).

Reporting group values	Overall Study	Total	
Number of subjects	346	346	
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)	281	281	
From 65-84 years	65	65	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	57.2		
standard deviation	± 9.7	-	
Gender categorical			
Units: Subjects			
Female	144	144	
Male	202	202	

End points

End points reporting groups

Reporting group title	IDeg + liraglutide

Reporting group description:

Liraglutide treatment was initiated on 0.6 mg daily for one week and increased further after the second week in the run-in period. In the randomized period, IDeg treatment was recommended to be initiated with 10 units. After that it was titrated once weekly. If one or more of the pre-breakfast plasma glucose values were below a certain range, the subjects were to reduce the insulin dose.

Reporting group title	Placebo + liraglutide

Reporting group description:

Placebo treatment was recommended to be initiated with 10 units. After that it was titrated once weekly. If one or more of the pre-breakfast plasma glucose values were below a certain range, the subjects were to reduce the insulin dose.

Primary: Change from baseline in glycosylated haemoglobin (HbA1c) (%) after 26 weeks of randomised treatment

End point title	Change from baseline in glycosylated haemoglobin (HbA1c) (%) after 26 weeks of randomised treatment

End point description:

End point type	Primary

End point timeframe:

Week 0-Week 26

End point values	IDeg + liraglutide	Placebo + liraglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	172		
Units: %				
least squares mean (standard error)	-0.99 (± 0.08)	-0.07 (± 0.08)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change from baseline in HbA1c after 26 weeks of randomised treatment was analysed using an analysis of variance (ANOVA) method with treatment, sex and region as fixed factors, and age and baseline HbA1c as covariates.

Comparison groups	IDeg + liraglutide v Placebo + liraglutide

Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANOVA
Parameter estimate	Mean treatment difference
Point estimate	-0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.75

Secondary: Change from baseline in fasting plasma glucose (FPG) after 26 weeks of randomised treatment

End point title	Change from baseline in fasting plasma glucose (FPG) after 26 weeks of randomised treatment

End point description:

End point type	Secondary

End point timeframe:

Week 0-Week 26

End point values	IDeg + liraglutide	Placebo + liraglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	168		
Units: mmol/L				
arithmetic mean (standard deviation)	-2.6 (± 2.91)	-0.28 (± 2.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of responders for HbA1c (below 7.0 %) after 26 weeks of randomised treatment

End point title	Number of responders for HbA1c (below 7.0 %) after 26 weeks of randomised treatment

End point description:

The end point values reflect percentage of subjects

End point type	Secondary

End point timeframe:

After 26 weeks of randomised treatment

End point values	IDeg + liraglutide	Placebo + liraglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	172		
Units: % of subjects				
number (not applicable)	77.6	35.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean pre-breakfast measurements used for titration after 26 weeks of randomised treatment

End point title	Change from baseline in mean pre-breakfast measurements used for titration after 26 weeks of randomised treatment

End point description:

The endpoint values reflects mean pre-breakfast measurements used for titration after 26 weeks of randomised treatment

End point type	Secondary

End point timeframe:

Week 0-Week 26

End point values	IDeg + liraglutide	Placebo + liraglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	169		
Units: mmol/L				
arithmetic mean (standard deviation)	5.7 (± 1.2)	8.4 (± 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in 8-point profile after 26 weeks of randomised treatment

End point title	Change from baseline in 8-point profile after 26 weeks of randomised treatment

End point description:

The endpoint values reflects 8-point profile after 26 weeks of randomised treatment

End point type	Secondary

End point timeframe:

Week 0-Week 26

End point values	IDeg + liraglutide	Placebo + liraglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171[1]	168[2]		
Units: mmol/L				
arithmetic mean (standard deviation)				
Before breakfast	5.6 (± 1.3)	8.4 (± 2.1)		
90 minutes after start of breakfast	8 (± 2.6)	10.2 (± 3.2)		
Before lunch	6 (± 1.5)	8 (± 2.5)		
90 minutes after start of lunch	7.8 (± 2)	9.8 (± 2.9)		
Before main evening meal	6.5 (± 1.8)	8.3 (± 2.8)		
90 min after main evening meal	8 (± 2.1)	9.9 (± 2.9)		
Before bedtime	7.1 (± 2)	8.9 (± 2.7)		
Before breakfast the following day	5.8 (± 1.9)	8.4 (± 2.2)		

Notes:

[1] - The number of subjects contributing to data varied.

[2] - The number of subjects contributing to data varied.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean of the 8-point profile after 26 weeks of randomised treatment

End point title	Change from baseline in mean of the 8-point profile after 26 weeks of randomised treatment

End point description:

End point type	Secondary

End point timeframe:

Week 0-Week 26

End point values	IDeg + liraglutide	Placebo + liraglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	166		
Units: mmol/L				
arithmetic mean (standard deviation)	-2.3 (± 1.8)	-0.5 (± 1.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of hypoglycaemic episodes (confirmed) during 26 weeks of

randomised treatment	
End point title	Number of hypoglycaemic episodes (confirmed) during 26 weeks of randomised treatment

End point description:

End point type	Secondary

End point timeframe:

Week 0-Week 26

End point values	IDeg + liraglutide	Placebo + liraglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	170		
Units: Event rate/100 patient years of exposure	57	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events during 26 weeks of randomised treatment

End point title	Number of adverse events during 26 weeks of randomised treatment

End point description:

End point type	Secondary

End point timeframe:

Time Frame: Weeks 0-Week 26

End point values	IDeg + liraglutide	Placebo + liraglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	170		
Units: Event rate/100 patient years of exposure	344	335		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in patient reported health-related quality of life using the Short-Form 36 Health Survey version 2 after 26 weeks of randomised treatment

End point title	Change from baseline in patient reported health-related quality of life using the Short-Form 36 Health Survey version 2 after 26 weeks of randomised treatment

End point description:

End point type	Secondary

End point timeframe:

Week 0-Week 26

End point values	IDeg + liraglutide	Placebo + liraglutide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	169		
Units: Not applicable				
arithmetic mean (standard deviation)				
Physical health	0.5 (± 6.3)	0 (± 6.2)		
Mental health	0.6 (± 8.1)	-0.7 (± 8.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event with an onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	IDeg + liraglutide

Reporting group description:

IDeg treatment was recommended to be initiated with 10 units. After that it was titrated once weekly. Liraglutide treatment was initiated on 0.6 mg daily for one week.

Reporting group title	Placebo + liraglutide

Reporting group description:

The placebo treatment was recommended to be initiated with 10 units. Liraglutide treatment was initiated on 0.6 mg daily for one week.

Serious adverse events	IDeg + liraglutide	Placebo + liraglutide	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 173 (3.47%)	9 / 170 (5.29%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lentigo maligna stage II			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
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			

Humerus fracture			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery occlusion			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device removal			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus management			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 173 (0.58%)	0 / 170 (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			
Pleural effusion			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 173 (0.00%)	1 / 170 (0.59%)	
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	IDeg + liraglutide	Placebo + liraglutide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 173 (19.08%)	32 / 170 (18.82%)	
Investigations			
Lipase increased			
subjects affected / exposed	10 / 173 (5.78%)	13 / 170 (7.65%)	
occurrences (all)	11	15	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 173 (5.78%)	13 / 170 (7.65%)	
occurrences (all)	10	17	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 173 (8.09%)	11 / 170 (6.47%)	
occurrences (all)	15	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2013	• Update of the trial flow chart and phone table to question subjects about technical complaints. • Update of trial schedule with updated LPLV date. • Update of Event adjudication section. • Clarification that the PP analysis set consisted of subjects that have not violated any inclusion or randomisation criteria • Update minor editorial and formatting issues.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported