



Clinical trial results:

The efficacy of insulin degludec/liraglutide as add-on therapy in controlling glycaemia in adults with type 2 diabetes inadequately controlled on sulphonylurea with or without metformin therapy

Summary

EudraCT number	2012-000140-97
Trial protocol	DE BG
Global end of trial date	23 October 2013

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	NN9068-3951
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01618162
WHO universal trial number (UTN)	U1111-1126-9776

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	08 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 October 2013
Global end of trial reached?	Yes
Global end of trial date	23 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm superiority of insulin degludec/liraglutide compared to insulin degludec/liraglutide placebo in controlling glycaemia as add-on treatment in insulin naïve subjects with Type 2 Diabetes Mellitus (T2DM) inadequately controlled on sulphonylurea (SU) with or without metformin therapy after 26 weeks of treatment.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, (59th WMA Assembly, Oct 2008), ICH Good Clinical Practice (May 1996) and 21 CFR 312.120.

Background therapy:

Sulphonylurea and metformin were the background medications.

Evidence for comparator:

Not applicable

Actual start date of recruitment	29 August 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	Bulgaria: 110
Country: Number of subjects enrolled	Germany: 46
Country: Number of subjects enrolled	Canada: 38
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	India: 64
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	United States: 150
Worldwide total number of subjects	435
EEA total number of subjects	156

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)	310
From 65 to 84 years	124
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

77 sites in 7 countries randomised subjects: Bulgaria (7), Canada (9), Germany (6), India (6), Israel (7), Turkey (3), United States (39)

Pre-assignment

Screening details:

The trial included a 2 week screening period to assess subject eligibility

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	IDegLira

Arm description:

In this arm, subjects were subcutaneously (s.c.) injected with IDegLira.

Arm type	Experimental
Investigational medicinal product name	IDegLira
Investigational medicinal product code	
Other name	Insulin degludec/liraglutide
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

IDegLira was to be injected s.c. in the thigh, upper arm (deltoid region) or abdomen once daily preferably at the same time every day. The injection area chosen was to remain unchanged throughout the trial, but rotation within the area was to be recommended. Treatment with IDegLira was initiated at 10 dose steps containing 10 units IDeg and 0.36 mg liraglutide. Adjustment of the IDegLira dose was to be performed twice weekly based on the mean of 3 preceding daily fasting SMPG values on 3 consecutive days.

Arm title	Placebo
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Arm description:

In this arm, subjects were subcutaneously (s.c.) injected with placebo solution for IDegLira.

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

Dosage and administration details:

The placebo treatment was to be initiated and titrated as described for IDegLira.

Number of subjects in period 1	IDegLira	Placebo
Started	289	146
Exposed	288	146
Completed	251	111
Not completed	38	35
Withdrawal Criteria	2	10
Adverse event, non-fatal	9	2
Unclassified	14	13
Protocol deviation	13	10

Baseline characteristics

Reporting groups

Reporting group title	IDegLira
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Reporting group description:

In this arm, subjects were subcutaneously (s.c.) injected with IDegLira.

Reporting group title	Placebo
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Reporting group description:

In this arm, subjects were subcutaneously (s.c.) injected with placebo solution for IDegLira.

Reporting group values	IDegLira	Placebo	Total
Number of subjects	289	146	435
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	60 ± 9.6	59.4 ± 10.8	-
Gender categorical Units: Subjects			
Female	135	73	208
Male	154	73	227
Glycosylated haemoglobin Units: Percentage (%) arithmetic mean standard deviation	7.9 ± 0.6	7.9 ± 0.6	-
Fasting plasma glucose Units: mmol/L arithmetic mean standard deviation	9.1 ± 2.2	9.1 ± 2.1	-

End points

End points reporting groups

Reporting group title	IDegLira
Reporting group description:	
In this arm, subjects were subcutaneously (s.c.) injected with IDegLira.	
Reporting group title	Placebo
Reporting group description:	
In this arm, subjects were subcutaneously (s.c.) injected with placebo solution for IDegLira.	

Primary: Change in glycosylated haemoglobin (HbA1c) from baseline

End point title	Change in glycosylated haemoglobin (HbA1c) from baseline
End point description:	
Change in HbA1c from baseline to 26 weeks of treatment	
End point type	Primary
End point timeframe:	
After 26 weeks of treatment.	

End point values	IDegLira	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	146		
Units: Percentage (%)				
arithmetic mean (standard deviation)	-1.45 (± 0.84)	-0.46 (± 0.83)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	IDegLira v Placebo
Number of subjects included in analysis	435
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Estimated treatment difference
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	-0.87

Notes:

[1] - Superiority of IDegLira versus placebo therapy would be concluded if the 95% CI for the treatment differences for change in HbA1c lied entirely below 0%; implying that the two-sided p-value calculated by the ANCOVA model for testing the hypothesis of no difference between treatments was less than 5%.

Secondary: Responders achieving pre-defined target for HbA1c. i.e., HbA1c <7.0% (53 mmol/mol)

End point title	Responders achieving pre-defined target for HbA1c. i.e., HbA1c <7.0% (53 mmol/mol)
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End point description:

Responders achieving pre-defined target for HbA1c

End point type	Secondary
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End point timeframe:

After 26 weeks of treatment

End point values	IDegLira	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	146		
Units: Percentage (%)				
number (not applicable)	79.2	28.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Responders achieving pre-defined target for HbA1c. i.e., HbA1c ≤6.5% (48 mmol/mol).

End point title	Responders achieving pre-defined target for HbA1c. i.e., HbA1c ≤6.5% (48 mmol/mol).
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End point description:

Responders achieving pre-defined target for HbA1c

End point type	Secondary
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End point timeframe:

After 26 weeks of treatment

End point values	IDegLira	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	146		
Units: Percentage (%)				
number (not applicable)	64	12.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in fasting plasma glucose (FPG).

End point title	Change from baseline in fasting plasma glucose (FPG).
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End point description:

Change from baseline in fasting plasma glucose

End point type	Secondary
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End point timeframe:

After 26 weeks of treatment

End point values	IDegLira	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	286	144		
Units: mmol/L				
arithmetic mean (standard deviation)	-2.6 (± 2.61)	-0.31 (± 2.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in body weight

End point title	Change from baseline in body weight
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End point description:

Change from baseline in body weight

End point type	Secondary
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End point timeframe:

After 26 weeks of treatment.

End point values	IDegLira	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	146		
Units: Kg				
arithmetic mean (standard deviation)	0.5 (± 3.1)	-1 (± 2.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent (confirmed) hypoglycaemic episodes

End point title	Number of treatment emergent (confirmed) hypoglycaemic
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episodes

End point description:

Number of treatment emergent (confirmed) hypoglycaemic episodes

End point type	Secondary
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End point timeframe:

During 26 weeks of treatment.

End point values	IDegLira	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	146		
Units: Event rate per 100 PYE				
number (not applicable)	351.7	135.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent adverse events (AEs)

End point title	Number of treatment emergent adverse events (AEs)
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End point description:

Number of treatment emergent adverse events (AEs). A treatment-emergent AE (TEAE) was defined as an event that had onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day on randomised treatment.

End point type	Secondary
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End point timeframe:

During 26 weeks of treatment.

End point values	IDegLira	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	146		
Units: Event rate per 100 PYE				
number (not applicable)	401.4	367		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from treatment period to follow up period (26 weeks + 1 week).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

All 146 subjects receiving at least one dose of placebo were evaluated for AE.

Reporting group title	IDegLira
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Reporting group description:

All 288 subjects receiving at least one dose of IDegLira were evaluated for AE.

Serious adverse events	Placebo	IDegLira	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 146 (3.42%)	14 / 288 (4.86%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pleural mesothelioma malignant			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary revascularisation			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
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			

Pyrexia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Amylase increased			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 146 (0.00%)	2 / 288 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stab wound			
subjects affected / exposed	1 / 146 (0.68%)	0 / 288 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 146 (0.68%)	0 / 288 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
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 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoglycaemic unconsciousness			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vertigo positional			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Normal tension glaucoma			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 146 (0.68%)	0 / 288 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			

subjects affected / exposed	1 / 146 (0.68%)	0 / 288 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 146 (0.68%)	0 / 288 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis haemophilus			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 146 (0.00%)	1 / 288 (0.35%)	
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	Placebo	IDegLira	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 146 (26.03%)	83 / 288 (28.82%)	
Investigations			
Lipase increased			
subjects affected / exposed	6 / 146 (4.11%)	27 / 288 (9.38%)	
occurrences (all)	8	29	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 146 (5.48%)	15 / 288 (5.21%)	
occurrences (all)	11	18	
Infections and infestations			

Influenza			
subjects affected / exposed	8 / 146 (5.48%)	8 / 288 (2.78%)	
occurrences (all)	9	8	
Nasopharyngitis			
subjects affected / exposed	12 / 146 (8.22%)	25 / 288 (8.68%)	
occurrences (all)	15	29	
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	6 / 146 (4.11%)	19 / 288 (6.60%)	
occurrences (all)	7	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 February 2013	Hypoglycaemic and adverse events definitions were updated. Informed consent was updated for blood volume drawn and for increased heart rate as per liraglutide Investigator's brochure. List of participating countries, recruitment timelines, blood volume to be drawn and list of adverse events of special interest was updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not Applicable

Notes: