Clinical trial results:
DUALTM V – basal insulin switch: A trial comparing the efficacy and safety of insulin degludec/liraglutide versus insulin glargine in subjects with type 2 diabetes mellitus.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-004413-14
Trial protocol	HU SK ES GR
Global end of trial date	04 November 2014

Results information

Result version number	v1 (current)
This version publication date	27 July 2016
First version publication date	27 July 2016

Trial information

Trial identification

Sponsor protocol code	NN9068-3952

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01952145
WHO universal trial number (UTN)	U1111-1135-1003

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	16 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 November 2014
Global end of trial reached?	Yes
Global end of trial date	04 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the efficacy of insulin degludec/liraglutide in controlling glycaemia in subjects with type 2 diabetes mellitus (T2DM) on previous treatment with insulin glargine.

This is done by comparing the difference in change in glycosylated haemoglobin (HbA1c) from baseline after 26 weeks of treatment to a non-inferiority limit of 0.30% for insulin degludec/liraglutide versus insulin glargine.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (59th World Medical Association [WMA] Assembly, October 2008) and International Conference on Harmonisation (ICH) Good Clinical Practice (May 1996) and 21 Code of Federal Regulations (CFR) 312.120.

Background therapy:

Subjects were on a stable daily dose of metformin (≥1500 mg or maximum tolerated dose) for at least 90 days prior to screening. Metformin treatment was to be continued at pre-trial dose level throughout the trial period, but reduction in dose of metformin treatment was allowed for safety reasons based on the investigator's judgement.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	20 September 2013
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	Argentina: 80
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Mexico: 83
Country: Number of subjects enrolled	Russian Federation: 95
Country: Number of subjects enrolled	South Africa: 28
Country: Number of subjects enrolled	United States: 39
Country: Number of subjects enrolled	Slovakia: 75
Country: Number of subjects enrolled	Spain: 74
Country: Number of subjects enrolled	Greece: 35
Country: Number of subjects enrolled	Hungary: 40
Worldwide total number of subjects	557
EEA total number of subjects	224

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)	412
From 65 to 84 years	145
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 75 sites in 10 countries, as follows: Argentina: 5 sites; Australia: 4 sites; Greece: 6 sites, Hungary: 4 sites; Mexico: 5 sites, Russian Federation: 11 sites; Slovakia: 11 sites, South Africa: 4 sites; Spain: 6 sites, United States: 19 sites.

Pre-assignment

Screening details:

Screened subjects were diagnosed with T2DM and with a:
1) current treatment with insulin glargine (IGlar) >=90 days prior to screening.
2) stable daily dose of IGlar between 20 units and 50 units (both inclusive) >=56 days prior to screening.
3) stable daily dose of metformin (≥1500 mg or max tolerated dose) >=90 days prior to screening.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Insulin Degludec/Liraglutide (IDegLira)

Arm description:

Eligible subjects received IDegLira once daily (OD) for a duration of 26-week. The total duration of the trial was approximately 29-week, consisting of a 2-week screening period, a 26-week treatment period and a follow-up visit 1-week after end of treatment.

Arm type	Experimental
Investigational medicinal product name	Insulin degludec liraglutide PDS290
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects randomised to treatment with IDegLira discontinued the pre-trial IGlar treatment prior to initiating IDegLira treatment with a start dose of 16 dose steps, equivalent to 16 units IDeg and 0.6 mg liraglutide. The maximum allowed dose was 50 dose steps (50 units IDeg/1.8 mg liraglutide). IDegLira was supplied in a 3 mL pre-filled PDS290 pen-injector with a fixed insulin degludec (IDeg)/liraglutide (lira) ratio of 100 units/3.6 mg per mL solution. IDegLira was to be injected subcutaneous (s.c., under the skin) in the thigh, upper arm (deltoid region) or abdomen (OD) approximately at the same time every day. The chosen injection area was to remain unchanged throughout the trial, but rotation within the area was recommended.

Arm title	Insulin Glargine (IGlar)

Arm description:

Eligible subjects received IGlar OD for a duration of 26-week. The total duration of the trial was approximately 29-week, consisting of a 2-week screening period, a 26-week treatment period and a follow-up visit 1-week after end of treatment.

Arm type	Active comparator

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 randomised for treatment with IGlar discontinued the pre-trial IGlar and initiated Novo Nordisk provided IGlar treatment with a starting dose equal to the pre-trial daily dose (dose-to-dose switch). No predefined maximum dose was specified for IGlar treatment. IGlar 100 units/mL solution was supplied in a 3 mL pre-filled Lantus® SoloStar® pen-injector. IGlar was to be injected s.c., OD according to the approved label and using the pre-trial dosing time and injection site throughout the trial.

Number of subjects in period 1	Insulin Degludec/Liraglutide (IDegLira)	Insulin Glargine (IGlar)
Started	278	279
Completed	250	265
Not completed	28	14
Adverse event, serious fatal	-	1
Adverse event, non-fatal	9	-
Withdrawal criteria	16	11
Unclassified	1	1
Protocol deviation	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Insulin Degludec/Liraglutide (IDegLira)
Reporting group description:	
Eligible subjects received IDegLira once daily (OD) for a duration of 26-week. The total duration of the trial was approximately 29-week, consisting of a 2-week screening period, a 26-week treatment period and a follow-up visit 1-week after end of treatment.	
Reporting group title	Insulin Glargine (IGlar)
Reporting group description:	
Eligible subjects received IGlar OD for a duration of 26-week. The total duration of the trial was approximately 29-week, consisting of a 2-week screening period, a 26-week treatment period and a follow-up visit 1-week after end of treatment.	

Reporting group values	Insulin Degludec/Liraglutide (IDegLira)	Insulin Glargine (IGlar)	Total
Number of subjects	278	279	557
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	58.4	59.1	
standard deviation	± 9.8	± 9.3	-
Gender categorical			
Units: Subjects			
Female	135	142	277
Male	143	137	280
Glycated hemoglobin (HbA1c)			
Units: Percentage (%)			
arithmetic mean	8.4	8.2	
standard deviation	± 0.9	± 0.9	-
Body weight			
Units: kg			
arithmetic mean	88.3	87.3	
standard deviation	± 17.5	± 15.8	-

End points

End points reporting groups

Reporting group title	Insulin Degludec/Liraglutide (IDegLira)

Reporting group description:

Eligible subjects received IDegLira once daily (OD) for a duration of 26-week. The total duration of the trial was approximately 29-week, consisting of a 2-week screening period, a 26-week treatment period and a follow-up visit 1-week after end of treatment.

Reporting group title	Insulin Glargine (IGlar)

Reporting group description:

Eligible subjects received IGlar OD for a duration of 26-week. The total duration of the trial was approximately 29-week, consisting of a 2-week screening period, a 26-week treatment period and a follow-up visit 1-week after end of treatment.

Primary: Change from baseline in HbA1c

End point title	Change from baseline in HbA1c

End point description:

The primary endpoint was change from baseline in HbA1c after 26 weeks of treatment. Analysis population: The Full Analysis Set included all randomised subjects. Missing values (including intermittent missing values) were imputed using the last observation carried forward (LOCF) method.

End point type	Primary

End point timeframe:

After 26 weeks of treatment.

End point values	Insulin Degludec/Liraglutide (IDegLira)	Insulin Glargine (IGlar)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	279		
Units: Percentage (%)				
arithmetic mean (standard deviation)	-1.81 (± 1.08)	-1.13 (± 0.98)		

Statistical analyses

Statistical analysis title	IDegLira versus IGlar

Statistical analysis description:

The change from baseline after 26 weeks of treatment was analysed using analysis of covariance (ANCOVA) model with treatment and region as fixed effects and baseline HbA1c as a covariate. Missing data were imputed using LOCF.

Comparison groups	Insulin Degludec/Liraglutide (IDegLira) v Insulin Glargine (IGlar)

Number of subjects included in analysis	557
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Treatment contrast
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	-0.45

Notes:

[1] - Non-inferiority of IDegLira versus IGlar was considered as confirmed, if the 95% confidence interval (CI) for the mean treatment difference was entirely below 0.30%.

Secondary: Change from baseline in body weight

End point title	Change from baseline in body weight

End point description:

Change from baseline in body weight after 26 weeks of treatment. Analysis population: Full Analysis Set. Missing values (including intermittent missing values) were imputed using the LOCF method.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment.

End point values	Insulin Degludec/Liraglutide (IDegLira)	Insulin Glargine (IGlar)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	279		
Units: Kg				
arithmetic mean (standard deviation)	-1.4 (± 3.5)	1.8 (± 3.6)		

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 episodes

End point description:

Confirmed hypoglycaemic episodes were defined as either: Severe (i.e., an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) or an episode biochemically confirmed by a plasma glucose value of <3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycaemia.
Analysis population: The safety analysis set included all subjects receiving at least one dose of trial product. Subjects contributed to the evaluation "as treated".

End point type	Secondary

End point timeframe:

During 26 weeks of treatment.

End point values	Insulin Degludec/Liraglutide (IDegLira)	Insulin Glargine (IGlar)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	279		
Units: Number of episodes	289	683		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 to week 27 (26-week treatment period and a follow-up visit 1 week after end of treatment).

Adverse event reporting additional description:

All AEs described below are treatment-emergent. 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 of randomised treatment. Analysis population: safety analysis set.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Insulin glargine (IGlar)

Reporting group description:

Eligible subjects received IGlar OD for a duration of 26-week.

Reporting group title	Insulin degludec/liraglutide (IDegLira)

Reporting group description:

Eligible subjects received IDegLira OD for a duration of 26-week.

Serious adverse events	Insulin glargine (IGlar)	Insulin degludec/liraglutide (IDegLira)	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 279 (3.23%)	5 / 278 (1.80%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	0 / 279 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	0 / 279 (0.00%)	1 / 278 (0.36%)	
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 / 279 (0.36%)	0 / 278 (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	1 / 279 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 279 (0.36%)	0 / 278 (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			
Haemorrhagic stroke			
subjects affected / exposed	1 / 279 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 279 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Auricular perichondritis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 279 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			

subjects affected / exposed	1 / 279 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 279 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 279 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 279 (0.36%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
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/liraglutide (IDegLira)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 279 (7.89%)	52 / 278 (18.71%)	
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 279 (5.02%)	11 / 278 (3.96%)	
occurrences (all)	28	12	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	7 / 279 (2.51%)	20 / 278 (7.19%)	
occurrences (all)	10	23	
Nausea			
subjects affected / exposed	3 / 279 (1.08%)	26 / 278 (9.35%)	
occurrences (all)	3	34	
Vomiting			
subjects affected / exposed	5 / 279 (1.79%)	14 / 278 (5.04%)	
occurrences (all)	5	22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2013	Introduction of intensification trial (NN9068-4119), update of subject information/informed consent forms and pregnancy section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26934259