Clinical trial results:
A clinical trial comparing efficacy and safety of insulin degludec/liraglutide (IDegLira) in subjects with type 2 diabetes mellitus using two different titration algorithms (DUAL™ VI)

Summary

EudraCT number	2012-004625-25
Trial protocol	HU BG AT SK CZ
Global end of trial date	23 December 2015

Results information

Result version number	v1 (current)
This version publication date	07 January 2017
First version publication date	07 January 2017

Trial information

Trial identification

Sponsor protocol code	NN9068-4056

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02298192
WHO universal trial number (UTN)	U1111-1135-6634

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@novnordisk.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	15 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 December 2015
Global end of trial reached?	Yes
Global end of trial date	23 December 2015
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 (IDegLira), using a once weekly titration algorithm, in controlling glycaemia in insulin-naïve subjects with type 2 diabetes (T2DM), inadequately controlled on metformin alone or in combination with pioglitazone. This is done by comparing the difference in change from baseline HbA1c (glycosylated haemoglobin) after 32 weeks of treatment to a non-inferiority limit of 0.30 % for once weekly titration vs. twice weekly titration.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (64th WMA Assembly, October 2013) and ICH Good Clinical Practice (May 1996) and 21 CFR 312.120.

Background therapy: -

Evidence for comparator:

Not applicable

Actual start date of recruitment	21 November 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	Austria: 30
Country: Number of subjects enrolled	Bulgaria: 40
Country: Number of subjects enrolled	Canada: 30
Country: Number of subjects enrolled	Czech Republic: 35
Country: Number of subjects enrolled	Hungary: 42
Country: Number of subjects enrolled	Serbia: 39
Country: Number of subjects enrolled	Russian Federation: 35
Country: Number of subjects enrolled	Slovakia: 60
Country: Number of subjects enrolled	United States: 109
Worldwide total number of subjects	420
EEA total number of subjects	207

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)	328
From 65 to 84 years	92
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 80 sites in 9 countries as follows: Austria: 6 sites; Bulgaria: 5 sites; Canada: 7 sites, Czech Republic: 5 sites; Hungary: 4 sites, Russian Federation: 6 sites; Serbia: 4 sites, Slovakia: 7 sites; United States: 36 sites.

Pre-assignment

Screening details:

Stable daily treatment with metformin (≥1500 mg or max tolerated dose) ± pioglitazone (≥30 mg) for at least 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

Arms

Are arms mutually exclusive?	Yes
Arm title	IDegLira 1WT

Arm description:

Subjects inadequately controlled on metformin either alone or in combination with pioglitazone were randomized in a 1:1 manner to receive IDegLira once daily. The subjects were stratified by their OAD treatment prior to entering the trial. The starting dose of IDegLira was 10 dose steps (10 units IDeg/0.36mg liraglutide), and the maximum dose was 50 dose steps (50 units/1.8mg liraglutide). The daily dose for metformin was ≥ 1500mg or max tolerated dose and ≥ 30mg for pioglitazone. In the IDegLira once weekly titration group (1WT), the dose of IDegLira was adjusted based on the mean of 2 fasting SMPG values measured prebreakfast in the morning of two consecutive days corresponding to one obtained on the day before titration and one obtained on titration day.

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

Dosage and administration details:

IDegLira was supplied in a 3 mL pre-filled PDS290 pen-injector with a fixed insulin degludec/liraglutide ratio of 100 units/3.6 mg per mL solution subcutaneously in the thigh, upper arm(deltoid) or abdomen approximately at the same time everyday.

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:

IDegLira was supplied in a 3 mL pre-filled PDS290 pen-injector with a fixed insulin degludec/liraglutide ratio of 100 units/3.6 mg per mL solution subcutaneously in the thigh, upper arm(deltoid) or abdomen approximately at the same time everyday.

Arm title	IDegLira

Arm description:

Subjects inadequately controlled on metformin either alone or in combination with pioglitazone were randomized in a 1:1 manner to receive IDegLira once daily. The subjects were stratified by their OAD treatment prior to entering the trial. The starting dose of IDegLira was 10 dose steps (10 units IDeg/0.36mg liraglutide), and the maximum dose was 50 dose steps (50units/1.8mg liraglutide) The daily dose for metformin was ≥ 1500mg or max tolerated dose and ≥ 30mg for pioglitazone. In the

weekly titration group, the dose of IDegLira was adjusted based on the mean of 3 fasting SMPG values measured prebreakfast in the morning of three consecutive days corresponding to one obtained on each of two days before titration and one obtained on titration day.

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

Dosage and administration details:

IDegLira was supplied in a 3 mL pre-filled PDS290 pen-injector with a fixed insulin degludec/liraglutide ratio of 100 units/3.6 mg per mL solution subcutaneously in the thigh, upper arm(deltoid) or abdomen approximately at the same time everyday.

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:

IDegLira was supplied in a 3 mL pre-filled PDS290 pen-injector with a fixed insulin degludec/liraglutide ratio of 100 units/3.6 mg per mL solution subcutaneously in the thigh, upper arm(deltoid) or abdomen approximately at the same time everyday.

Number of subjects in period 1	IDegLira 1WT	IDegLira
Started	210	210
Completed	191	204
Not completed	19	6
Consent withdrawn by subject	6	1
unclassifed	3	2
Adverse event, non-fatal	6	2
withdrawal critera	2	-
Lost to follow-up	2	1

Baseline characteristics

Reporting groups	
Reporting group title	IDegLira 1WT
Reporting group description:	
Subjects inadequately controlled on metformin either alone or in combination with pioglitazone were randomized in a 1:1 manner to receive IDegLira once daily. The subjects were stratified by their OAD treatment prior to entering the trial. The starting dose of IDegLira was 10 dose steps (10 units IDeg/0.36mg liraglutide), and the maximum dose was 50 dose steps (50 units/1.8mg liraglutide). The daily dose for metformin was ≥ 1500mg or max tolerated dose and ≥ 30mg for pioglitazone. In the IDegLira once weekly titration group (1WT), the dose of IDegLira was adjusted based on the mean of 2 fasting SMPG values measured prebreakfast in the morning of two consecutive days corresponding to one obtained on the day before titration and one obtained on titration day.	
Reporting group title	IDegLira
Reporting group description:	
Subjects inadequately controlled on metformin either alone or in combination with pioglitazone were randomized in a 1:1 manner to receive IDegLira once daily. The subjects were stratified by their OAD treatment prior to entering the trial. The starting dose of IDegLira was 10 dose steps (10 units IDeg/0.36mg liraglutide), and the maximum dose was 50 dose steps (50units/1.8mg liraglutide) The daily dose for metformin was ≥ 1500mg or max tolerated dose and ≥ 30mg for pioglitazone. In the IDegLira twice weekly titration group, the dose of IDegLira was adjusted based on the mean of 3 fasting SMPG values measured prebreakfast in the morning of three consecutive days corresponding to one obtained on each of two days before titration and one obtained on titration day.	

Reporting group values	IDegLira 1WT	IDegLira	Total
Number of subjects	210	210	420
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)			

End points

End points reporting groups

Reporting group title	IDegLira 1WT

Reporting group description:

Subjects inadequately controlled on metformin either alone or in combination with pioglitazone were randomized in a 1:1 manner to receive IDegLira once daily. The subjects were stratified by their OAD treatment prior to entering the trial. The starting dose of IDegLira was 10 dose steps (10 units IDeg/0.36mg liraglutide), and the maximum dose was 50 dose steps (50 units/1.8mg liraglutide). The daily dose for metformin was ≥ 1500mg or max tolerated dose and ≥ 30mg for pioglitazone. In the IDegLira once weekly titration group (1WT), the dose of IDegLira was adjusted based on the mean of 2 fasting SMPG values measured prebreakfast in the morning of two consecutive days corresponding to one obtained on the day before titration and one obtained on titration day.

Reporting group title	IDegLira

Reporting group description:

Subjects inadequately controlled on metformin either alone or in combination with pioglitazone were randomized in a 1:1 manner to receive IDegLira once daily. The subjects were stratified by their OAD treatment prior to entering the trial. The starting dose of IDegLira was 10 dose steps (10 units IDeg/0.36mg liraglutide), and the maximum dose was 50 dose steps (50units/1.8mg liraglutide) The daily dose for metformin was ≥ 1500mg or max tolerated dose and ≥ 30mg for pioglitazone. In the IDegLira twice weekly titration group, the dose of IDegLira was adjusted based on the mean of 3 fasting SMPG values measured prebreakfast in the morning of three consecutive days corresponding to one obtained on each of two days before titration and one obtained on titration day.

Primary: Change from baseline in HbA1c

End point title	Change from baseline in HbA1c

End point description:

Change in glycosylated haemoglobin A1c (HbA1c) (%) from baseline after 32 weeks of treatment. Full analysis set (FAS) included all randomised subjects. 20 subjects in the IDegLira (1WT) and 10 subjects in the IDegLira arm did not contribute to the analysis for this endpoint.

End point type	Primary

End point timeframe:

Week 0, week 32

End point values	IDegLira 1WT	IDegLira		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	200		
Units: percentage				
arithmetic mean (standard deviation)	-2.01 (± 1.09)	-2.02 (± 0.98)		

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

A standard MMRM model was applied for primary endpoint. The model included treatment, visit, region and previous OAD treatment as fixed factors and the corresponding baseline value as a covariate with an unstructured covariance structure. Interactions between visit and all factors and covariates were also included in the model. In the following, this model will be referred to as the standard MMRM model.

Comparison groups	IDegLira v IDegLira 1WT
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.012
Method	Mixed models analysis
Parameter estimate	Treatment-Contrast
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.28

Secondary: HbA1c below 7.0%

End point title	HbA1c below 7.0%

End point description:

Responders to HbA1c below 7% after 32 weeks of treatment. Full analysis set (FAS) included all randomised subjects. 20 subjects in the IDegLira (1WT) and 10 subjects in the IDegLira arm did not contribute to the analysis for this endpoint.

End point type	Secondary

End point timeframe:

Week 0, week 32

End point values	IDegLira 1WT	IDegLira		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	200		
Units: Participants				
number (not applicable)				
Yes	170	179		
No	19	21		

Statistical analyses

No statistical analyses for this end point

Secondary: HbA1c below or equal to 6.5%

End point title	HbA1c below or equal to 6.5%

End point description:

Responders to HbA1c below or equal to 6.5% after 32 weeks of treatment. Full analysis set (FAS) included all randomised subjects. 20 subjects in the IDegLira (1WT) and 10 subjects in the IDegLira arm did not contribute to the analysis for this endpoint.

End point type	Secondary

End point timeframe:
Week 0, week 32

End point values	IDegLira 1WT	IDegLira		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	200		
Units: Participants				
number (not applicable)				
Yes	158	170		
No	31	30		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Defined as an event that has onset date on or after the first day of exposure to randomised treatment and no later than seven days after the last day of randomised treatment. (Visit 1- Visit 36)

Adverse event reporting additional description:

Safety Analysis Set (SAS): Included all subjects receiving at least one dose of trial product. Subjects contributed to the evaluation "as treated".

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	IDegLira

Reporting group description:

Subjects inadequately controlled on metformin either alone or in combination with pioglitazone were randomized in a 1:1 manner to receive IDegLira once daily. The subjects were stratified by their OAD treatment prior to entering the trial. The starting dose of IDegLira was 10 dose steps (10 units IDeg/0.36mg liraglutide), and the maximum dose was 50 dose steps (50units/1.8mg liraglutide) The daily dose for metformin was ≥ 1500mg or max tolerated dose and ≥ 30mg for pioglitazone. In the IDegLira twice weekly titration group, the dose of IDegLira was adjusted based on the mean of 3 fasting SMPG values measured prebreakfast in the morning of three consecutive days corresponding to one obtained on each of two days before titration and one obtained on titration day.

Reporting group title	IDegLira (1WT)

Reporting group description:

Subjects inadequately controlled on metformin either alone or in combination with pioglitazone were randomized in a 1:1 manner to receive IDegLira once daily. The subjects were stratified by their OAD treatment prior to entering the trial. The starting dose of IDegLira was 10 dose steps (10 units IDeg/0.36mg liraglutide), and the maximum dose was 50 dose steps (50 units/1.8mg liraglutide). The daily dose for metformin was ≥ 1500mg or max tolerated dose and ≥ 30mg for pioglitazone. In the IDegLira once weekly titration group (1WT), the dose of IDegLira was adjusted based on the mean of 2 fasting SMPG values measured prebreakfast in the morning of two consecutive days corresponding to one obtained on the day before titration and one obtained on titration day.

Serious adverse events	IDegLira	IDegLira (1WT)	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 210 (6.67%)	7 / 209 (3.35%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 210 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			

subjects affected / exposed	0 / 210 (0.00%)	1 / 209 (0.48%)	
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			
Meniscus injury			
subjects affected / exposed	1 / 210 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 210 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypotension			
subjects affected / exposed	0 / 210 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 210 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 210 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 210 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Migraine			

subjects affected / exposed	0 / 210 (0.00%)	1 / 209 (0.48%)	
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 / 210 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 210 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 210 (0.00%)	1 / 209 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 210 (0.48%)	0 / 209 (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			
Haematuria			
subjects affected / exposed	1 / 210 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	2 / 210 (0.95%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Spinal pain			

subjects affected / exposed	1 / 210 (0.48%)	0 / 209 (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			
Appendicitis			
subjects affected / exposed	2 / 210 (0.95%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 210 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	1 / 210 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 210 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 210 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 210 (0.48%)	0 / 209 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 210 (0.48%)	0 / 209 (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			

Hyperglycaemia			
subjects affected / exposed	0 / 210 (0.00%)	1 / 209 (0.48%)	
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	IDegLira	IDegLira (1WT)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 210 (9.05%)	24 / 209 (11.48%)	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	11 / 210 (5.24%)	11 / 209 (5.26%)	
occurrences (all)	20	16	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 210 (4.29%)	13 / 209 (6.22%)	
occurrences (all)	13	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported