Clinical trial results:
A trial comparing sequential addition of insulin aspart versus further dose increase with insulin degludec/liraglutide in subjects with type 2 diabetes mellitus, previously treated with insulin degludec/liraglutide and metformin and in need of further intensification

Summary

EudraCT number	2013-002878-47
Trial protocol	ES GR HU SK
Global end of trial date	27 April 2015

Results information

Result version number	v1 (current)
This version publication date	12 May 2016
First version publication date	12 May 2016

Trial information

Trial identification

Sponsor protocol code	NN9068-4119

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02100475
WHO universal trial number (UTN)	U1111-1145-0183

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 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2015
Global end of trial reached?	Yes
Global end of trial date	27 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To explore the efficacy of dose adjustment of insulin degludec/liraglutide to a maximum dose of 80 dose steps as compared to adding insulin aspart to insulin degludec/liraglutide with a maximum dose of 50 dose steps, both arms in combination with metformin, in controlling glycaemia.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Seoul, 2008), ICH Good Clinical Practice and FDA 21 CFR 312.120.

Background therapy:

As a background therapy, subjects continued metformin treatment at pre-trial dose level (dose as taken at visit 28 in NN9068-3952) throughout the trial period. However, 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	03 April 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	Argentina: 7
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Hungary: 1
Worldwide total number of subjects	31
EEA total number of subjects	10

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	22
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 19 sites in 8 countries as follows: Argentina: 2 sites; Greece: 2 sites, Hungary: 1 site; Russian Federation: 5 sites; Slovakia: 4 sites, South Africa: 1 site; Spain: 1 site, United States: 3 sites.

Pre-assignment

Screening details:

Subjects with type 2 diabetes mellitus who were inadequately controlled (HbA1c level ≥ 7% [53 mmol/mol]) on treatment with IDegLira after 26 weeks of treatment in the NN9068-3952 trial were screened for this trial. Eligible subjects were randomised in a 1:1 manner to one of the two parallel treatment groups (IDegLira or IDegLira + IAsp).

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	IDegLira

Arm description:

Insulin degludec/liraglutide (IDegLira) was given subcutaneously (s.c., under the skin) once daily in combination with metformin. Treatment intensification with IDegLira was done by increasing the dose up to a maximum of 80 dose steps (80 units IDeg/2.9 mg Lira). All subjects continued with metformin at pre-trial doses (≥ 1500 mg or the maximum tolerated dose).

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

Dosage and administration details:

Subjects started on the same treatment dose of IDegLira as used in the NN9068-3952 trial at visit 28 (end of 26 weeks of treatment). IDegLira was given subcutaneously (s.c., under the skin), once daily. Treatment intensification with IDegLira was done by increasing the dose up to a maximum of 80 dose steps (80 units IDeg/2.9 mg Lira).

Arm title	IDegLira + IAsp

Arm description:

IDegLira was given subcutaneously (s.c., under the skin) once daily in combination with metformin. IDegLira titrated up to a maximum dose of 50 steps (50 units IDeg/1.8 mg Lira) with the sequential add-on of bolus IAsp. Dose titration of insulin aspart was based on the respective pre-meal(s) and bedtime self-measured plasma glucose (SMPG) measured daily. All subjects continued with metformin at pre-trial doses (≥ 1500 mg or the maximum tolerated dose).

Arm type	Active comparator

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

Dosage and administration details:

IAsp was given subcutaneously (s.c., under the skin), 1, 2 or 3 times per day. The starting dose of IAsp for subjects intensified with IDegLira + IAsp was 4 units of IAsp. Dose titration of insulin aspart was based on the respective pre-meal(s) and bedtime self-measured plasma glucose measured daily. No maximum dose of IAsp was specified. An
extra IAsp dose was allowed at the investigator's discretion.

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

Dosage and administration details:

Subjects started on the same treatment dose of IDegLira as used in the NN9068-3952 trial at visit 28 (end of 26 weeks of treatment). IDegLira was given subcutaneously (s.c., under the skin) once daily. IDegLira titrated up to a maximum dose of 50 steps (50 units IDeg/1.8 mg Lira).

Number of subjects in period 1	IDegLira	IDegLira + IAsp
Started	16	15
Completed	14	13
Not completed	2	2
unclassified	1	2
withdrawal criteria	1	-

Baseline characteristics

Reporting groups	
Reporting group title	IDegLira

Reporting group description:

Insulin degludec/liraglutide (IDegLira) was given subcutaneously (s.c., under the skin) once daily in combination with metformin. Treatment intensification with IDegLira was done by increasing the dose up to a maximum of 80 dose steps (80 units IDeg/2.9 mg Lira). All subjects continued with metformin at pre-trial doses (≥ 1500 mg or the maximum tolerated dose).

Reporting group title	IDegLira + IAsp

Reporting group description:

IDegLira was given subcutaneously (s.c., under the skin) once daily in combination with metformin. IDegLira titrated up to a maximum dose of 50 steps (50 units IDeg/1.8 mg Lira) with the sequential add-on of bolus IAsp. Dose titration of insulin aspart was based on the respective pre-meal(s) and bedtime self-measured plasma glucose (SMPG) measured daily. All subjects continued with metformin at pre-trial doses (≥ 1500 mg or the maximum tolerated dose).

Reporting group values	IDegLira	IDegLira + IAsp	Total
Number of subjects	16	15	31
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	57.3	57.4	
standard deviation	± 11.7	± 11.2	-
Gender categorical Units: Subjects			
Female	9	8	17
Male	7	7	14
HbA1c Units: Percentage			
arithmetic mean	7.6	7.7	
standard deviation	± 0.9	± 0.7	-

End points

End points reporting groups

Reporting group title	IDegLira

Reporting group description:

Insulin degludec/liraglutide (IDegLira) was given subcutaneously (s.c., under the skin) once daily in combination with metformin. Treatment intensification with IDegLira was done by increasing the dose up to a maximum of 80 dose steps (80 units IDeg/2.9 mg Lira). All subjects continued with metformin at pre-trial doses (≥ 1500 mg or the maximum tolerated dose).

Reporting group title	IDegLira + IAsp

Reporting group description:

IDegLira was given subcutaneously (s.c., under the skin) once daily in combination with metformin. IDegLira titrated up to a maximum dose of 50 steps (50 units IDeg/1.8 mg Lira) with the sequential add-on of bolus IAsp. Dose titration of insulin aspart was based on the respective pre-meal(s) and bedtime self-measured plasma glucose (SMPG) measured daily. All subjects continued with metformin at pre-trial doses (≥ 1500 mg or the maximum tolerated dose).

Primary: Change from baseline in HbA1c

End point title	Change from baseline in HbA1c

End point description:

Change from baseline in HbA1c after 26 weeks of treatment.
Full analysis set (FAS) included all randomised subjects (31 subjects). Data were presented based on last observation carried forward (LOCF) method.

End point type	Primary

End point timeframe:

After 26 weeks of treatment

End point values	IDegLira	IDegLira + IAsp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: percent				
arithmetic mean (standard deviation)	-0.43 (± 0.94)	-0.14 (± 1.09)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The response and change from baseline in the response after 26 weeks of treatment was analysed using an analysis of covariance (ANCOVA) method with treatment and baseline IDegLira dose strata as fixed factors and baseline response as a covariate. Missing data were imputed using LOCF.

Comparison groups	IDegLira v IDegLira + IAsp

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.427
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	0.46
Variability estimate	Standard error of the mean

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. FAS included all randomised subjects (31 subjects). Data were presented based on LOCF method.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	IDegLira	IDegLira + IAsp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: kilogram(s)				
arithmetic mean (standard deviation)	0.9 (± 2.1)	1.5 (± 3.2)		

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:

Safety analysis set (SAS) included all subjects receiving at least one dose of the investigational product or comparator (31 subjects). Treatment-emergent Hypoglycaemic episodes: if the onset of the episode occurred on or after the first day of investigational medicinal product administration, and no later than 7 days after the last day on investigational medicinal product. Confirmed hypoglycaemia: Subject unable to treat himself/herself and/or have a recorded plasma glucose < 3.1 mmol/L (56 mg/dL).

End point type	Secondary

End point timeframe:
During 26 weeks of treatment

End point values	IDegLira	IDegLira + IAsp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: number of episodes	34	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first day of exposure to randomised treatment to 7 days after the last day of randomised treatment.

Adverse event reporting additional description:

SAS included all subjects receiving at least one dose of the investigational product or comparator, (SAS = 31 subjects). A treatment-emergent adverse event (TEAE) was defined as an event that had an 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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	IDegLira + IAsp

Reporting group description:

IDegLira was given subcutaneously (s.c., under the skin) once daily in combination with metformin. IDegLira titrated up to a maximum dose of 50 steps (50 units IDeg/1.8 mg Lira) with the sequential add-on of bolus IAsp. Dose titration of insulin aspart was based on the respective pre-meal(s) and bedtime SMPG measured daily. All subjects continued with metformin at pre-trial doses (≥ 1500 mg or the maximum tolerated dose).

Reporting group title	IDegLira

Reporting group description:

IDegLira was given subcutaneously (s.c., under the skin) once daily in combination with metformin. Treatment intensification with IDegLira was done by increasing the dose up to a maximum of 80 dose steps (80 units IDeg/2.9 mg Lira). All subjects continued with metformin at pre-trial doses (≥ 1500 mg or the maximum tolerated dose).

Serious adverse events	IDegLira + IAsp	IDegLira	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)	1 / 16 (6.25%)	
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)			
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (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 coronary syndrome			

subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
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 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 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	IDegLira + IAsp	IDegLira	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)	11 / 16 (68.75%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Investigations			

Amylase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Blood calcitonin increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Cardiac murmur			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Lipase increased			
subjects affected / exposed	1 / 15 (6.67%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Eye disorders			
Macular degeneration			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	

Tooth disorder			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Renal cyst			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 15 (6.67%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Hyperkalaemia			

subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 16 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

Due to the small number of subjects in this trial, the data should be interpreted with caution.

Notes: