Clinical trial results:
A trial investigating the efficacy and safety of insulin degludec/insulin aspart (IDegAsp) once daily plus insulin aspart (IAsp) for the remaining meals versus insulin detemir (IDet) once or twice daily plus meal time insulin aspart in children and adolescents with type 1 diabetes mellitus

Summary

EudraCT number	2012-003566-41
Trial protocol	CZ SI ES BE HR
Global end of trial date	07 November 2014

Results information

Result version number	v2 (current)
This version publication date	16 March 2016
First version publication date	21 May 2015
Version creation reason	• Correction of full data set AE data to be updated

Trial information

Trial identification

Sponsor protocol code	NN5401-3816

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01835431
WHO universal trial number (UTN)	U1111-1133-0958

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Soeborg, 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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000479-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 November 2014
Global end of trial reached?	Yes
Global end of trial date	07 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/insulin aspart administered once daily plus meal-time insulin aspart for the remaining meals in controlling glycaemia with respect to change from baseline in HbA1c after 16 weeks of treatment. This is done by comparing the difference in change from baseline in HbA1c between insulin degludec/insulin aspart + meal-time insulin aspart for the remaining meals and insulin detemir + meal-time insulin aspart to a non-inferiority limit of 0.4%, and if non-inferiority is confirmed, to a superiority limit of 0%.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. World Medical Association. 20 A.D) and International Conference on Harmonisation (ICH) Good Clinical Practice (ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice. J Postgrad Med 2001; 47(3):199-203) and 21 Code of Federal Regulations (CFR) 312.120.

Background therapy:

Not Applicable

Evidence for comparator:

Not Applicable

Actual start date of recruitment	17 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Israel: 34
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 20
Country: Number of subjects enrolled	Russian Federation: 46
Country: Number of subjects enrolled	Serbia: 27
Country: Number of subjects enrolled	South Africa: 12
Country: Number of subjects enrolled	United States: 114
Country: Number of subjects enrolled	Brazil: 7
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Slovenia: 4
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Croatia: 12
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Czech Republic: 19

Worldwide total number of subjects	362
EEA total number of subjects	91

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)	1
Children (2-11 years)	203
Adolescents (12-17 years)	158
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 63 sites in 14 countries as follows: Belgium: 3 sites; Brazil: 1 sites; Canada: 3 sites; Czech Republic 3 sites; Croatia: 2 sites; Israel: 6 sites; Macedonia: 2 sites; Poland: 3 sites; Russia: 5 sites; Serbia: 4 sites; Slovenia: 1 sites; South Africa: 2 sites; Spain: 5 sites; and United States: 23 sites.

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	Not blinded

Blinding implementation details:

Open label trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	IDegAsp OD +IAsp

Arm description:

IDegAsp OD with a main meal + IAsp for the remaining meals

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

Dosage and administration details:

IDegAsp was to be administered subcutaneously in the thigh, upper arm (deltoid area) or abdomen OD in connection with a main meal. The dosing time could be moved to a different main meal at any time during the trial.

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

Dosage and administration details:

IAsp was to be administered subcutaneously according to local labelling as mealtime insulin.

Arm title	IDet+IAsp

Arm description:

IDet once or twice daily + mealtime IAsp.

Arm type	Active comparator

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

Dosage and administration details:

IDet was to be administered subcutaneously according to local labelling. Subjects randomised into the IDet treatment group continued with their pre-trial dosing scheme (OD or BID) and were allowed to switch from OD to BID dosing.

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

Dosage and administration details:

IAsp was to be administered subcutaneously as mealtime insulin.

Number of subjects in period 1	IDegAsp OD +IAsp	IDet+IAsp
Started	182	180
Completed	174	168
Not completed	8	12
Adverse event, non-fatal	1	-
Other	-	2
Withdrawal criteria	6	10
Non Compliance with protocol	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	362	362	
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)	1	1	
Children (2-11 years)	203	203	
Adolescents (12-17 years)	158	158	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	10.6		
standard deviation	± 4.5	-	
Gender categorical Units: Subjects			
Female	187	187	
Male	175	175	

End points

End points reporting groups	
Reporting group title	IDegAsp OD +IAsp
Reporting group description: IDegAsp OD with a main meal + IAsp for the remaining meals	

Reporting group title	IDet+IAsp
Reporting group description: IDet once or twice daily + mealtime IAsp.	

Primary: Change from baseline in HbA1c (%-point)	
End point title	Change from baseline in HbA1c (%-point)
End point description: Percentage point change in glycosylated haemoglobin A1c (HbA1c) from baseline (week 0) to 16 Weeks.	
End point type	Primary
End point timeframe: After 16 weeks of treatment	

End point values	IDegAsp OD +IAsp	IDet+IAsp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	165		
Units: percentage-point				
arithmetic mean (standard deviation)	-0.3 (± 1)	-0.3 (± 0.9)		

Statistical analyses

Statistical analysis title	Change from baseline in HbA1c (%-point)
Comparison groups	IDegAsp OD +IAsp v IDet+IAsp
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.15

Notes:

[1] - If non-inferiority was confirmed, superiority of IDegAsp over IDet was investigated for the FAS. Non-inferiority will be considered confirmed if the upper bound of the two-sided 95% confidence interval is below or equal to 0.4% corresponding to one-sided test at the 2.5% level. The subjects in this analysis is 350/362 from FAS who had baseline and atleast one post-baseline assessment.

Secondary: Change from baseline in fasting plasma glucose

End point title	Change from baseline in fasting plasma glucose

End point description:

FPG was analysed on blood samples from fasting subjects which were analysed centrally.

End point type	Secondary

End point timeframe:

After 16 weeks of treatment

End point values	IDegAsp OD +IAsp	IDet+IAsp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	148		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.3 (± 6.4)	-0.1 (± 4.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Treatment Emergent Adverse Events (TEAEs)

End point title	Incidence of Treatment Emergent Adverse Events (TEAEs)

End point description:

A Treatment Emergent Adverse Event (TEAE) was defined as an event with 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

End point timeframe:

After 16 weeks of treatment.

End point values	IDegAsp OD +IAsp	IDet+IAsp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	179		
Units: Number of events	501	460		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment emergent confirmed hypoglycaemic episodes

End point title	Treatment emergent confirmed hypoglycaemic episodes

End point description:

Treatment emergent hypoglycaemic episodes (PG < 3.1 mmol/L (56 mg/dL) or severe hypoglycaemia). Confirmed hypoglycaemic episodes were defined as episodes that were either:
1. Severe (i.e. the child is having altered mental status and cannot assist in their care, is semiconscious or unconscious or in coma with or without convulsions and may require parenteral therapy (glucagon or i.v. glucose), or
2. An episode biochemically confirmed by PG value of <3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycaemia.

End point type	Secondary

End point timeframe:

After 16 weeks of treatment

End point values	IDegAsp OD +IAsp	IDet+IAsp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	179		
Units: Number of treatment emergent episodes				
Confirmed	2532	2672		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment emergent nocturnal confirmed hypoglycaemic episodes

End point title	Treatment emergent nocturnal confirmed hypoglycaemic episodes

End point description:

The confirmed hypoglycaemic episodes occurring between 23:00 and 07:00 were considered for this endpoint.

End point type	Secondary

End point timeframe:

After 16 weeks of treatment

End point values	IDegAsp OD +IAsp	IDet+IAsp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	179		
Units: Number of treatment emergent episodes				
Confirmed	316	291		

Statistical analyses

No statistical analyses for this end point

Secondary: Hyperglycaemic episodes

End point title	Hyperglycaemic episodes

End point description:

Number of hyperglycaemic episodes (PG > 14.0 mmol/L (250 mg/dL) where subject looks/feels ill.

End point type	Secondary

End point timeframe:

After 16 weeks of treatment

End point values	IDegAsp OD +IAsp	IDet+IAsp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	179		
Units: Number of hyperglycaemic episodes	599	449		

Statistical analyses

No statistical analyses for this end point

Secondary: Hyperglycaemic episodes with ketosis

End point title	Hyperglycaemic episodes with ketosis

End point description:

Number of hyperglycaemic episodes (PG > 14.0 mmol/L (250 mg/dL) where subject looks/feels ill with ketosis (blood ketones > 1.5 mmol/L)

End point type	Secondary

End point timeframe:

After 16 weeks of treatment

End point values	IDegAsp OD +IAsp	IDet+IAsp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	179		
Units: Number of hyperglycaemic episodes				
Hyperglycaemic episodes with ketones(.1.5mmol/L)	6	12		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	IDegAsp OD + IAsp

Reporting group description:

IDegAsp OD with a main meal + IAsp for the remaining meals

Reporting group title	IDet +IAsp

Reporting group description:

IDet once or twice daily + mealtime IAsp.

Serious adverse events	IDegAsp OD + IAsp	IDet +IAsp	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 181 (6.08%)	7 / 179 (3.91%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula Fracture			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia Fracture			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			

Developmental glaucoma			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (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			
Hypoglycaemic seizure			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Compartment syndrome			
subjects affected / exposed	1 / 181 (0.55%)	0 / 179 (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			
Laryngitis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	1 / 181 (0.55%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 181 (0.55%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	5 / 181 (2.76%)	1 / 179 (0.56%)	
occurrences causally related to treatment / all	4 / 5	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	IDegAsp OD + IAsp	IDet +IAsp	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 181 (53.04%)	97 / 179 (54.19%)	
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 181 (12.71%)	32 / 179 (17.88%)	
occurrences (all)	47	64	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	17 / 181 (9.39%)	10 / 179 (5.59%)	
occurrences (all)	26	15	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 181 (5.52%)	7 / 179 (3.91%)	
occurrences (all)	13	13	
Abdominal pain upper			

subjects affected / exposed	14 / 181 (7.73%)	17 / 179 (9.50%)	
occurrences (all)	22	26	
Vomiting			
subjects affected / exposed	22 / 181 (12.15%)	12 / 179 (6.70%)	
occurrences (all)	25	13	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 181 (7.18%)	9 / 179 (5.03%)	
occurrences (all)	16	9	
Oropharyngeal pain			
subjects affected / exposed	9 / 181 (4.97%)	13 / 179 (7.26%)	
occurrences (all)	13	14	
Infections and infestations			
Influenza			
subjects affected / exposed	9 / 181 (4.97%)	10 / 179 (5.59%)	
occurrences (all)	10	12	
Nasopharyngitis			
subjects affected / exposed	36 / 181 (19.89%)	32 / 179 (17.88%)	
occurrences (all)	43	42	
Pharyngitis			
subjects affected / exposed	3 / 181 (1.66%)	10 / 179 (5.59%)	
occurrences (all)	3	13	
Upper respiratory tract infection			
subjects affected / exposed	11 / 181 (6.08%)	17 / 179 (9.50%)	
occurrences (all)	12	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2013	The protocol was updated upon request from FDA; the use of Last observation carried forward (LOCF) in the statistical analyses was discarded in favour of mixed effect model repeat measurement (MMRM). Furthermore, the blood volume needed for blood sampling in the age group below 6 years was updated to a smaller volume due to a miscalculation. Furthermore, the text in the master subject information related to the use of Lantus® was updated. In addition, a few typing errors in Section 17 (Statistical considerations) were discovered and corrected.
22 April 2014	Error corrected regarding definition of the Full Analysis Set (FAS).

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: