Clinical trial results:
A 26-week open label, randomised, 2-armed, parallel group, multi-centre trial investigating efficacy and safety of insulin detemir versus insulin Neutral Protamine Hagedorn in combination with the maximum tolerated dose of metformin and diet/exercise on glycaemic control in children and adolescents with type 2 diabetes insufficiently controlled on the maximum tolerated dose of metformin ± other oral antidiabetic drug(s) ± basal insulin

Summary

EudraCT number	2013-005500-33
Trial protocol	HU IT DE HR GR ES PT
Global end of trial date	14 June 2016

Results information

Result version number	v1 (current)
This version publication date	29 December 2016
First version publication date	29 December 2016

Trial information

Trial identification

Sponsor protocol code	NN304-4093

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02131272
WHO universal trial number (UTN)	U1111-1151-4056

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 June 2016
Global end of trial reached?	Yes
Global end of trial date	14 June 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of insulin detemir in combination with metformin and diet/exercise versus insulin neutral protamine hagedorn (NPH) in combination with the maximum tolerated dose (MTD) of metformin and diet/exercise in controlling glycaemia, after 26 weeks of treatment, in children and adolescents (aged 10–17 years) with type 2 diabetes, who are insufficiently treated with the MTD of metformin ± other OAD(s) ± basal insulin.

Protection of trial subjects:

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

Background therapy:

Subjects continued treatment with metformin on their pre-study dose(s) throughout the trial.

Evidence for comparator:

Not applicable

Actual start date of recruitment	11 June 2014
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	Brazil: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	India: 4
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	42
EEA total number of subjects	1

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)	3
Adolescents (12-17 years)	39
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The following 12 countries screened subjects (no. of sites that randomised subjects within parentheses): Brazil (1), Germany (1), India (3), Israel (1), South Korea (1), Malaysia (3), Mexico (1), Russian Federation (1) Taiwan (3), Turkey (3), United States (6), Hungary (0). A total of 24 sites in 11 countries randomised subjects to treatment.

Pre-assignment

Screening details:

Subjects continued their treatment with metformin during the trial.

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	Insulin detemir + metformin + diet/exercise

Arm description:

Subjects were treated with insulin detemir 100 U/mL administered subcutaneously in the thigh region once or twice daily for a period of 26 weeks. All subjects continued treatment with metformin on their pre-study dose(s) throughout the trial. The diet/exercise intervention was performed through changes in eating and activity behaviours.

Arm type	Experimental
Investigational medicinal product name	Insulin detemir
Investigational medicinal product code	
Other name	Insulin detemir
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

For insulin naïve subjects, insulin detemir was initiated at a dose of 0.1−0.2 U/kg with a maximum dose of 10 U at the investigators discretion. Subjects who were already on basal insulin were switched to insulin detemir unit-to-unit once or twice daily, depending on previous injection frequency. Subjects were dosed according to individual requirements during the trial period.

Arm title	Insulin NPH + metformin + diet/exercise

Arm description:

Subjects were treated with insulin NPH 100 IU/mL administered subcutaneously in the thigh region once or twice daily for a period of 26 weeks. All subjects continued treatment with metformin on their pre-study dose(s) throughout the trial. The diet/exercise intervention was performed through changes in eating and activity behaviours.

Arm type	Active comparator
Investigational medicinal product name	Insulin neutral protamine hagedorn (NPH)
Investigational medicinal product code	
Other name	Insulin human
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

For insulin naïve subjects, insulin NPH was initiated at a dose of 0.1−0.2 U/kg with a maximum dose of 10 U at the investigators discretion. Subjects who were already on basal insulin were switched to insulin NPH unit-to-unit once or twice daily, depending on previous injection frequency. Subjects were dosed according to individual requirements during the trial period.

Number of subjects in period 1	Insulin detemir + metformin + diet/exercise	Insulin NPH + metformin + diet/exercise
Started	20	22
Completed	19	20
Not completed	1	2
Withdrawal Criteria	1	-
Consent withdrawn by subject	-	1
Consent withdrawn by parent	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Insulin detemir + metformin + diet/exercise
Reporting group description:	
Subjects were treated with insulin detemir 100 U/mL administered subcutaneously in the thigh region once or twice daily for a period of 26 weeks. All subjects continued treatment with metformin on their pre-study dose(s) throughout the trial. The diet/exercise intervention was performed through changes in eating and activity behaviours.	
Reporting group title	Insulin NPH + metformin + diet/exercise
Reporting group description:	
Subjects were treated with insulin NPH 100 IU/mL administered subcutaneously in the thigh region once or twice daily for a period of 26 weeks. All subjects continued treatment with metformin on their pre-study dose(s) throughout the trial. The diet/exercise intervention was performed through changes in eating and activity behaviours.	

Reporting group values	Insulin detemir + metformin + diet/exercise	Insulin NPH + metformin + diet/exercise	Total
Number of subjects	20	22	42
Age Categorical			
Units: Subjects			
Adolescents (10-14 years)	9	11	20
Adults (15-17 years)	11	11	22
Age Continuous			
Units: years			
arithmetic mean	15	15	
standard deviation	± 2.1	± 2.2	-
Gender Categorical			
Units: Subjects			
Female	12	15	27
Male	8	7	15
Glycosylated haemoglobin (HbA1c)			
Units: pecentage of glycosylated HbA1c			
arithmetic mean	8.72	8.95	
standard deviation	± 0.86	± 1.05	-
Body weight standard deviation score (SDS)			
The body weight SD scores were derived from the age and sex of the subjects and the body weight together with growth curves defined for the reference population (US population).			
Units: standard deviation score			
arithmetic mean	1.532	1.26	
standard deviation	± 0.685	± 0.835	-

End points

End points reporting groups

Reporting group title	Insulin detemir + metformin + diet/exercise

Reporting group description:

Subjects were treated with insulin detemir 100 U/mL administered subcutaneously in the thigh region once or twice daily for a period of 26 weeks. All subjects continued treatment with metformin on their pre-study dose(s) throughout the trial. The diet/exercise intervention was performed through changes in eating and activity behaviours.

Reporting group title	Insulin NPH + metformin + diet/exercise

Reporting group description:

Subjects were treated with insulin NPH 100 IU/mL administered subcutaneously in the thigh region once or twice daily for a period of 26 weeks. All subjects continued treatment with metformin on their pre-study dose(s) throughout the trial. The diet/exercise intervention was performed through changes in eating and activity behaviours.

Primary: Change in HbA1c

End point title	Change in HbA1c

End point description:

Estimated mean change in glycosylated haemoglobin from baseline to week 26.

End point type	Primary

End point timeframe:

From baseline to week 26

End point values	Insulin detemir + metformin + diet/exercise	Insulin NPH + metformin + diet/exercise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: Pecentage of glycosylated haemoglobin				
least squares mean (standard error)	-0.64 (± 0.32)	-0.81 (± 0.31)		

Statistical analyses

Statistical analysis title	Mixed model for repeated measurements (MMRM)

Statistical analysis description:

HbA1c measurements were analysed using MMRM with an unstructured covariance matrix. The model included treatment, visit, age group, prior antidiabetic therapy and interaction between prior antidiabetic therapy and age group as fixed factors and the HbA1c baseline value as covariate. Interactions between visit and all factors and covariates were also included in the model.

Comparison groups	Insulin detemir + metformin + diet/exercise v Insulin NPH + metformin + diet/exercise

Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.3075 [2]
Method	Mixed models analysis
Parameter estimate	Treatment contrast
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	1.09

Notes:

[1] - Efficacy conclusions cannot be drawn from the analysis due to low number of subjects included in the trial.
[2] - P value is reported for one-sided test.

Secondary: Change in body weight standard deviation score (SDS)

End point title	Change in body weight standard deviation score (SDS)

End point description:

Change in body weight standard deviation score (SDS) from baseline to week 26. The SD scores were derived from the age and sex of the subjects and the body weight together with growth curves defined for the reference population (US population).

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Insulin detemir + metformin + diet/exercise	Insulin NPH + metformin + diet/exercise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: standard deviation score				
arithmetic mean (standard deviation)	0.006 (± 0.192)	0.098 (± 0.139)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects achieving HbA1c <7.0%, who have not experienced any treatment emergent severe hypoglycaemic episodes within the last 14 weeks of treatment

End point title	Proportion of subjects achieving HbA1c <7.0%, who have not experienced any treatment emergent severe hypoglycaemic episodes within the last 14 weeks of treatment

End point description:

Percentage of subjects achieving HbA1c <7.0%, who have not experienced any treatment emergent severe hypoglycaemic episodes (an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions) within the last 14 weeks of treatment.

End point type	Secondary

End point timeframe:

At week 26

End point values	Insulin detemir + metformin + diet/exercise	Insulin NPH + metformin + diet/exercise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21[3]		
Units: Percentage of subjects				
number (not applicable)	25	33.3		

Notes:

[3] - Subjects who have been exposed for a minimum of 14 weeks are included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects achieving HbA1c <7.5%, who have not experienced any treatment emergent severe hypoglycaemic episodes within the last 14 weeks of treatment

End point title	Proportion of subjects achieving HbA1c <7.5%, who have not experienced any treatment emergent severe hypoglycaemic episodes within the last 14 weeks of treatment

End point description:

Percentage of subjects achieving HbA1c <7.5%, who have not experienced any treatment emergent severe hypoglycaemic episodes (an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions) within the last 14 weeks of treatment.

End point type	Secondary

End point timeframe:

At Week 26

End point values	Insulin detemir + metformin + diet/exercise	Insulin NPH + metformin + diet/exercise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21[4]		
Units: Percentage of subjects				
number (not applicable)	30	38.1		

Notes:

[4] - Subjects who have been exposed for a minimum of 14 weeks contributed to the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Total number of treatment emergent nocturnal (23:00-06:59) severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes

End point title	Total number of treatment emergent nocturnal (23:00-06:59) severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes

End point description:

The total number of blood glucose confirmed symptomatic nocturnal (time of onset between 23:00 and 06.59 both inclusive) severe (an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions) or blood glucose confirmed symptomatic hypoglycaemic episodes (plasma glucose value <3.1 mmol/L [56 mg/dL] with symptoms consistent with hypoglycaemia) experienced by the subjects during the trial.

End point type	Secondary

End point timeframe:

During 26 weeks of treatment

End point values	Insulin detemir + metformin + diet/exercise	Insulin NPH + metformin + diet/exercise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: Number of episodes				
Severe	0	0		
Blood glucose confirmed symptomatic	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Total number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes

End point title	Total number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes

End point description:

Total number of treatment emergent severe (an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions) or blood glucose confirmed symptomatic hypoglycaemic episodes (plasma glucose value <3.1 mmol/L [56 mg/dL] with symptoms consistent with hypoglycaemia) experienced by the subjects during the trial.

End point type	Secondary

End point timeframe:

During 26 weeks of treatment

End point values	Insulin detemir + metformin + diet/exercise	Insulin NPH + metformin + diet/exercise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[5]	22[6]		
Units: Number of episodes				
Severe	0	0		
BG confirmed symptomatic	4	12		

Notes:

[5] - One subject contributed to the events reported in this arm.

[6] - 5 subjects contributed to the events reported in this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of adverse events (AEs)

End point title	Incidence of adverse events (AEs)

End point description:

The total number of treatment emergent adverse events (the onset of the adverse event is on or after the first day of trial product administration, and no later than 7 days after the last day of trial product administration) reported during the 26 weeks of treatment.

End point type	Secondary

End point timeframe:

During the 26 weeks of treatment

End point values	Insulin detemir + metformin + diet/exercise	Insulin NPH + metformin + diet/exercise		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[7]	22[8]		
Units: Number of events	30	41		

Notes:

[7] - AEs were reported by 8 subjects in this arm.

[8] - AEs were reported by 13 subjects in this arm.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events from the first trial-related activity (week -2) after the subject and/or his/her legally acceptable representative has signed the informed consent until the end of the trial (week 26).

Adverse event reporting additional description:

Safety analysis set included all subjects receiving at least one dose of randomised treatment. A treatment emergent adverse event was defined as an event that had the onset date on or after the first day of trial product administration, and no later than 7 days after the last day of trial product administration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Insulin NPH + metformin + diet/exercise

Reporting group description:

Subjects were treated with NPH 100 IU/mL administered subcutaneously in the thigh region once or twice daily for a period of 26 weeks. All subjects continued treatment with metformin on their pre-study dose(s) throughout the trial. The diet/exercise intervention was performed through changes in eating and activity behaviours.

Reporting group title	Insulin detemir + metformin + diet/exercise

Reporting group description:

Subjects were treated with insulin detemir 100 U/mL administered subcutaneously in the thigh region once or twice daily for a period of 26 weeks. All subjects continued treatment with metformin on their pre-study dose(s) throughout the trial. The diet/exercise intervention was performed through changes in eating and activity behaviours.

Serious adverse events	Insulin NPH + metformin + diet/exercise	Insulin detemir + metformin + diet/exercise	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Migraine			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (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	Insulin NPH + metformin + diet/exercise	Insulin detemir + metformin + diet/exercise	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 22 (40.91%)	8 / 20 (40.00%)	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Soft tissue injury			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 22 (4.55%)	3 / 20 (15.00%)	
occurrences (all)	4	4	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Lip dry			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	2 / 22 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Vomiting			

subjects affected / exposed	0 / 22 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	3 / 22 (13.64%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Rhinitis allergic			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	4	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 22 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Gastroenteritis viral			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Impetigo			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	2 / 22 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Nasopharyngitis			
subjects affected / exposed	2 / 22 (9.09%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Viral infection			

subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 20 (5.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2015	• Reduced the number of fasting visits, blood samples and assessments. • Clinic visit 3 had been changed to a phone contact.• The trial population was updated to include subjects who were treated with a maximum tolerated dose of metformin or who had documented complete metformin intolerance.• An additional exclusion criterion had been added.• Additional text regarding the informed consent process had been added.

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.

The trial was terminated earlier than planned. Based on the low number of subjects, the conclusions should be interpreted with caution.

Notes: