Clinical trial results:
An 8-week randomised, double-blind, parallel, multiple dose trial comparing NNC0123-0000-0338 in a tablet formulation and insulin glargine in subjects with type 2 diabetes currently treated with oral antidiabetic therapy

Summary

EudraCT number	2014-002716-16
Trial protocol	DE
Global end of trial date	31 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	NN1953-4163

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02470039
WHO universal trial number (UTN)	U1111-1158-3620

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsværd, 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	22 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2015
Global end of trial reached?	Yes
Global end of trial date	31 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the glycaemic control after 8 weeks of treatment with oral insulin 338 in aGIPET® I tablet formulation versus s.c. insulin glargine, when both are administered once daily in combination with metformin ± DPP-4 inhibitor in subjects with T2DM inadequately controlled on oral antidiabetic therapy

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) and ICH Good Clinical Practice (1996). The trial was conducted in accordance with FDA 21 CFR 312.120.

Background therapy:

The non-investigational medicinal products in this trial were metformin and dipeptidyl-peptidase-4 (DPP-4) inhibitor (oral administration). The background treatment was open-label throughout the trial and subjects received their usual medication per prescription from their primary physician.

Evidence for comparator:

Not Applicable

Actual start date of recruitment	01 June 2015
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	Germany: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	33

From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 2 trial sites in Germany.

Pre-assignment

Screening details:

A 2-week run-in period: to avoid carryover effects from discontinued oral anti-diabetic treatment prior to randomisation and to ensure adequate time to achieve stable glycaemic control for evaluation of hypoglycaemia and pharmacodynamics effect. A maximum daily/tolerated dose of metformin±DPP-4 inhibitor was unchanged during the run-in period.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Carer, Data analyst, Assessor, Subject

Blinding implementation details:

A double-blind trial; treatment was blinded by all subjects receiving active and placebo treatment. All tablets and solutions (active or placebo) were visually identical to ensure blinding. The trial drugs were packed blinded at Novo Nordisk A/S. The dumas were blinded within tablet strengths (i.e. a similar package for a duma with 900 nmol oral insulin 338 and a duma with oral placebo, etc.). A vial cover was used to blind the s.c. insulin glargine (Lantus®) and the placebo vial

Arms

Are arms mutually exclusive?	Yes
Arm title	Oral Insulin 338

Arm description:

Insulin 338/placebo (matched to insulin glargine - 10 ml) were taken orally/subcutaneously once daily for 8 weeks. The insulin dose was adjusted once weekly using the same titration algorithm as for the comparator (assuming that 2,700 nmol oral insulin 388 corresponded to 10 units s.c. insulin glargine) and was based on the mean of 3 preceding daily pre-dose self-measured plasma glucose (SMPG) values on 3 consecutive days. The starting dose for oral insulin 338 was 2,700 nmol (a lower starting dose of 900-1,350 nmol could be selected at the discretion of the investigator) and the maximum allowed daily dose was 16,200 nmol. Subjects continued pre-trial metformin with or without DPP-4 inhibitor throughout the entire trial.

Arm type	Experimental
Investigational medicinal product name	NNCO123-0338
Investigational medicinal product code	
Other name	Insulin 338
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral Insulin 338 tablets (strengths of 900, 1350, 2700, 5400, 8100, 10,800 nmol) were taken orally once daily in about 100 ml of water in combination with metformin with or without DPP-4 inhibitor every morning of the 8 week treatment period. A maximum daily dose of 16,200 nmol oral insulin 338 was allowed.

Investigational medicinal product name	Placebo matched to Insulin Glargine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo solution (10 ml) was administered subcutaneously into a lifted skin fold on the anterior surface of the thigh once daily in combination with metformin with or without DPP-4 inhibitor every morning of

the 8 week treatment period

Arm title	Subcutaneous Insulin Glargine

Arm description:

Insulin glargine/placebo (matched to oral insulin 338 - 0 nmol) were taken subcutaneously/orally once daily for 8 weeks. The insulin dose was adjusted once weekly using the same titration algorithm as for the investigational product (assuming that 2,700 nmol oral insulin 388 corresponded to 10 units s.c. insulin glargine) and was based on the mean of 3 preceding daily pre-dose self-measured plasma glucose (SMPG) values on 3 consecutive days. The starting dose for insulin glargine was 10 units (a lower starting dose of 3-5 units could be selected at the discretion of the investigator) and the maximum allowed daily dose was 60 units. Subjects continued pre-trial metformin with or without DPP-4 inhibitor throughout the entire trial.

Arm type	Active comparator
Investigational medicinal product name	Placebo matched to Insulin 338
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral placebo tablets (0 nmol) were taken orally once daily in about 100 ml of water in combination with metformin with or without DPP-4 inhibitor every morning of the 8 week treatment period

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:

Subcutaneous insulin glargine (100U/mL) was administered subcutaneously into a lifted skin fold on the anterior surface of the thigh once daily in combination with metformin with or without DPP-4 inhibitor every morning of the 8 week treatment period. A maximum daily dose of 60 units s.c. insulin glargine was allowed.

Number of subjects in period 1	Oral Insulin 338	Subcutaneous Insulin Glargine
Started	25	25
Completed	24	25
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups

Reporting group title	Oral Insulin 338

Reporting group description:

Insulin 338/placebo (matched to insulin glargine - 10 ml) were taken orally/subcutaneously once daily for 8 weeks. The insulin dose was adjusted once weekly using the same titration algorithm as for the comparator (assuming that 2,700 nmol oral insulin 388 corresponded to 10 units s.c. insulin glargine) and was based on the mean of 3 preceding daily pre-dose self-measured plasma glucose (SMPG) values on 3 consecutive days. The starting dose for oral insulin 338 was 2,700 nmol (a lower starting dose of 900-1,350 nmol could be selected at the discretion of the investigator) and the maximum allowed daily dose was 16,200 nmol. Subjects continued pre-trial metformin with or without DPP-4 inhibitor throughout the entire trial.

Reporting group title	Subcutaneous Insulin Glargine

Reporting group description:

Insulin glargine/placebo (matched to oral insulin 338 - 0 nmol) were taken subcutaneously/orally once daily for 8 weeks. The insulin dose was adjusted once weekly using the same titration algorithm as for the investigational product (assuming that 2,700 nmol oral insulin 388 corresponded to 10 units s.c. insulin glargine) and was based on the mean of 3 preceding daily pre-dose self-measured plasma glucose (SMPG) values on 3 consecutive days. The starting dose for insulin glargine was 10 units (a lower starting dose of 3-5 units could be selected at the discretion of the investigator) and the maximum allowed daily dose was 60 units. Subjects continued pre-trial metformin with or without DPP-4 inhibitor throughout the entire trial.

Reporting group values	Oral Insulin 338	Subcutaneous Insulin Glargine	Total
Number of subjects	25	25	50
Age, Customized Units: participants			
18-64 years	15	18	33
65-84 years	10	7	17
Age Continuous Units: years			
arithmetic mean	60.2	60.8	
standard deviation	± 7.2	± 6.3	-
Gender, Male/Female Units: participants			
Female	2	8	10
Male	23	17	40
Study Specific Characteristic | Fasting Plasma Glucose Units: mmol/L			
arithmetic mean	9.7	9.13	
standard deviation	± 2.8	± 1.71	-

End points

End points reporting groups

Reporting group title	Oral Insulin 338

Reporting group description:

Insulin 338/placebo (matched to insulin glargine - 10 ml) were taken orally/subcutaneously once daily for 8 weeks. The insulin dose was adjusted once weekly using the same titration algorithm as for the comparator (assuming that 2,700 nmol oral insulin 388 corresponded to 10 units s.c. insulin glargine) and was based on the mean of 3 preceding daily pre-dose self-measured plasma glucose (SMPG) values on 3 consecutive days. The starting dose for oral insulin 338 was 2,700 nmol (a lower starting dose of 900-1,350 nmol could be selected at the discretion of the investigator) and the maximum allowed daily dose was 16,200 nmol. Subjects continued pre-trial metformin with or without DPP-4 inhibitor throughout the entire trial.

Reporting group title	Subcutaneous Insulin Glargine

Reporting group description:

Insulin glargine/placebo (matched to oral insulin 338 - 0 nmol) were taken subcutaneously/orally once daily for 8 weeks. The insulin dose was adjusted once weekly using the same titration algorithm as for the investigational product (assuming that 2,700 nmol oral insulin 388 corresponded to 10 units s.c. insulin glargine) and was based on the mean of 3 preceding daily pre-dose self-measured plasma glucose (SMPG) values on 3 consecutive days. The starting dose for insulin glargine was 10 units (a lower starting dose of 3-5 units could be selected at the discretion of the investigator) and the maximum allowed daily dose was 60 units. Subjects continued pre-trial metformin with or without DPP-4 inhibitor throughout the entire trial.

Primary: Fasting plasma glucose (FPG)

End point title	Fasting plasma glucose (FPG)

End point description:

Fasting plasma glucose after 8 weeks of treatment. Full analysis set included all randomised subjects receiving at least one dose of oral insulin 338 or subcutaneous insulin glargine. Number of subjects analyzed=subjects with data available for this endpoint.

End point type	Primary

End point timeframe:

After 8 weeks of treatment

End point values	Oral Insulin 338	Subcutaneous Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	25		
Units: mmol/L				
arithmetic mean (standard deviation)	7.18 (± 1.86)	6.71 (± 0.94)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The results are from MMRM analysis from day 7, 14, 21, 28, 35, 42, 49, 55 and 56 with treatment and strata as factors and baseline FPG as a covariate, all nested within day. An unstructured covariance matrix describes the variability for the repeated measurements for a subject. The residual variance is

depending on treatment. The treatment difference refers to "oral insulin 338 minus subcutaneous insulin glargine. There were 50 subjects, rather than 48 subjects contributing to this analysis.

Comparison groups	Oral Insulin 338 v Subcutaneous Insulin Glargine
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4567
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	1.06

Secondary: 10-points plasma glucose profile

End point title	10-points plasma glucose profile

End point description:

Measurements were performed pre-dose, before and after (90 min after start of the meal) meals (i.e. break-fast, lunch, and main evening meals), at bedtime, at 04:00 in the morning and pre-dose on the following day. Full analysis set was evaluated. Here, 'n' specifies the number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

After 8 weeks of treatment

End point values	Oral Insulin 338	Subcutaneous Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: mmol/L				
arithmetic mean (standard deviation)				
Pre-dose (n=23, 25)	7.18 (± 1.86)	6.71 (± 0.94)		
Before breakfast (n=22, 25)	7.03 (± 1.6)	6.39 (± 0.97)		
90 min after breakfast (n=22, 25)	11.9 (± 3.36)	10.97 (± 2.03)		
Before Lunch (n=22, 25)	8.06 (± 2.06)	6.77 (± 1.83)		
90 min after lunch (n=22, 25)	9.74 (± 3.1)	8.79 (± 1.82)		
Before main evening meal (n=22, 25)	7.14 (± 1.23)	6.51 (± 1.81)		
90 min after main evening meal (n=22, 25)	10.02 (± 2.39)	9.92 (± 1.68)		
Bedtime (n=22, 25)	9.19 (± 2.61)	8.67 (± 2.12)		
At 4 am (n=22, 25)	6.46 (± 1.37)	5.6 (± 0.92)		
Pre-dose on following day (n=22, 25)	6.85 (± 1.73)	6.44 (± 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent hypoglycaemic episodes

End point title	Number of treatment emergent hypoglycaemic episodes

End point description:

Treatment emergent episodes (American Diabetes Association) occurred from first trial product administration on day 1 until end of day 68 (visit 14). Safety analysis set (SAS) included all subjects receiving at least one dose of the investigational product or its comparator. The subjects in the SAS contributed to the evaluation 'as treated'. Number of subjects analyzed=subjects with data available for this endpoint.

End point type	Secondary

End point timeframe:

From start of treatment until Visit 14 (Day 68)

End point values	Oral Insulin 338	Subcutaneous Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: events	7	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the serum insulin concentration-time curve

End point title	Area under the serum insulin concentration-time curve

End point description:

AUCIns,τ,SS: Area under the serum insulin concentration-time curve during one dosing interval (0 to 24-hours) at steady state (days 56). Number of subjects analyzed=subjects with data available for this endpoint.

End point type	Secondary

End point timeframe:

During one dosing interval (0 to 24 hours) at steady state (Day 56)

End point values	Oral Insulin 338	Subcutaneous Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	25		
Units: pmol*h/L				
median (full range (min-max))	666142 (160307 to 3358750)	1988 (227 to 4252)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent AEs occurring after first dose on day 1 (visit 3) to end-of-day 68 (visit 14); end-of-treatment was on day 56 (visit 11).

Adverse event reporting additional description:

Safety analysis set (SAS) included all subjects receiving at least one dose of the investigational product or its comparator. The subjects in the SAS contributed to the evaluation 'as treated'.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Subcutaneous Insulin Glargine

Reporting group description:

Insulin glargine/placebo (matched to oral insulin 338 - 0 nmol) were taken subcutaneously/orally once daily for 8 weeks. The insulin dose was adjusted once weekly using the same titration algorithm as for the investigational product (assuming that 2,700 nmol oral insulin 388 corresponded to 10 units s.c. insulin glargine) and was based on the mean of 3 preceding daily pre-dose self-measured plasma glucose (SMPG) values on 3 consecutive days. The starting dose for insulin glargine was 10 units (a lower starting dose of 3-5 units could be selected at the discretion of the investigator) and the maximum allowed daily dose was 60 units. Subjects continued pre-trial metformin with or without DPP-4 inhibitor throughout the entire trial.

Reporting group title	Oral Insulin 338

Reporting group description:

Insulin 338/placebo (matched to insulin glargine - 10 ml) were taken orally/subcutaneously once daily for 8 weeks. The insulin dose was adjusted once weekly using the same titration algorithm as for the comparator (assuming that 2,700 nmol oral insulin 388 corresponded to 10 units s.c. insulin glargine) and was based on the mean of 3 preceding daily pre-dose self-measured plasma glucose (SMPG) values on 3 consecutive days. The starting dose for oral insulin 338 was 2,700 nmol (a lower starting dose of 900-1,350 nmol could be selected at the discretion of the investigator) and the maximum allowed daily dose was 16,200 nmol. Subjects continued pre-trial metformin with or without DPP-4 inhibitor throughout the entire trial.

Serious adverse events	Subcutaneous Insulin Glargine	Oral Insulin 338	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Renal and urinary disorders			
Urogenital haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (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	Subcutaneous Insulin Glargine	Oral Insulin 338	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 25 (40.00%)	10 / 25 (40.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 25 (4.00%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 25 (12.00%)	3 / 25 (12.00%)	
occurrences (all)	4	4	
Dyspepsia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	4	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 25 (8.00%)	5 / 25 (20.00%)	
occurrences (all)	2	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2015	1. Implementation of additional information in the protocol on local effects of oral insulin 338 in the gastro-intestinal tract. 2. Implementation of severe hypoglycaemic episodes as withdrawal criteria in protocol. 3. Revision of the subject information/informed consent form to include more information on local effects of oral insulin 338 in the gastro-intestinal tract. 4. Revision of the subject information/informed consent form changing the wording from "a large proportion" to "many" subjects with T2DM. 5. Revision of the subject information/informed consent form to include an explanation of the relationship between doses of oral insulin 338 (given in nmol) and s.c.insulin glargine (given in units).

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.

Analysis of pharmacokinetic data: the anti-drug antibody formation influence on the insulin 338 assay performances could not be ruled out. Also, insulin 338 and insulin glargine are different chemical entities and they should not be compared directly

Notes: