Clinical trial results:
Efficacy and safety of FIAsp in a basal-bolus regimen versus basal insulin therapy, both in combination with metformin in adult Subjects with type 2 diabetes

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-005583-10
Trial protocol	SI
Global end of trial date	17 November 2014

Results information

Result version number	v1 (current)
This version publication date	27 July 2016
First version publication date	27 July 2016

Trial information

Trial identification

Sponsor protocol code	NN1218-4049

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01850615
WHO universal trial number (UTN)	U1111-1137-6242

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	09 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 November 2014
Global end of trial reached?	Yes
Global end of trial date	17 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm superiority of meal-time faster-acting insulin aspart (FIAsp)/faster aspart in a full basal-bolus regimen versus basal insulin therapy, both in combination with metformin, in terms of glycaemic control after 18-weeks of randomised treatment.

Protection of trial subjects:

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

Background therapy:

Metformin (≥1000 mg) was used as background therapy. At the start of the 8-week run-in (pre-assignment) period, subjects continued on the once daily (OD) basal insulin (insulin detemir or insulin glargine or Neutral Protamine Hagedorn (NPH) insulin) and metformin at the same dose level as before the trial. Subjects were instructed to discontinue all other OADs at the start of the run in period (visit 2). During the run-in period, basal insulin dose was adjusted weekly.

Evidence for comparator:

Not applicable

Actual start date of recruitment	23 September 2013
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: 44
Country: Number of subjects enrolled	India: 61
Country: Number of subjects enrolled	Mexico: 31
Country: Number of subjects enrolled	Romania: 28
Country: Number of subjects enrolled	Slovenia: 32
Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	236
EEA total number of subjects	60

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)	177
From 65 to 84 years	59
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 51 sites in 6 countries as follows: Argentina: 4 sites; India: 8 sites; Mexico: 3 sites; Romania: 5 sites; Slovenia: 4 sites; United States: 27 sites.

Pre-assignment

Screening details:

Included subjects were with type 2 diabetes mellitus, who were being treated with once daily (OD) insulin detemir or insulin glargine or NPH insulin, in addition to metformin (≥1000 mg) ± other OADs. A total of 555 subjects were screened, of which 232 subjects were screening failures and 323 subjects entered the run-in (pre-assignment) period.

Pre-assignment period milestones

Number of subjects started	323[1]
Number of subjects completed	236

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Failure to meet randomization criteria: 62
Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Protocol deviation: 12
Reason: Number of subjects	Lack of efficacy: 1
Reason: Number of subjects	Lost to follow-up: 1
Reason: Number of subjects	Consent withdrawn by subject: 8
Reason: Number of subjects	Unclassified: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 323 subjects entered the run-in (pre-assignment) period of the trial; of which, 87 subjects were run-in failures. Hence, 236 subjects were enrolled to the 18 weeks of treatment period.

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	Faster aspart + Basal

Arm description:

During the 18-week treatment period, subjects received subcutaneous (s.c., under the skin) injection of faster aspart (bolus insulin) along with s.c. basal insulin (insulin detemir or insulin glargine or NPH insulin) and metformin. Treatment recommendations were developed for the different trial products specifying the recommended dose adjustments at different plasma glucose (PG) levels. Trial products were titrated according to the insulin dosing recommendations provided during the study. No maximum dose of insulin was specified as doses were titrated individually.

Arm type	Experimental

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

Dosage and administration details:

Faster aspart was used for bolus insulin administration at each main meal (i.e., breakfast, lunch and main evening meal) and was to be injected subcutaneously into the abdomen. Injection sites were to be rotated within the same area. The bolus insulin injection was to be given 0–2 minutes before each main meal.

Investigational medicinal product name	Insulin detemir
Investigational medicinal product code	
Other name	Levemir®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin detemir was used for basal insulin administration and was to be injected subcutaneously into the thigh or upper arm (deltoid area). The basal insulin injection was to be given OD, in the evening, at approximately the same time each day. Changing the frequency (e.g., from OD to twice daily [BID]) of basal insulin dosing during the trial was not allowed.

Investigational medicinal product name	NPH insulin
Investigational medicinal product code	
Other name	Insulatard®, Protaphane®, Novolin N™
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

NPH insulin was used for basal insulin administration and was to be injected subcutaneously into the thigh or upper arm (deltoid area). The basal insulin injection was to be given OD, in the evening, at approximately the same time each day. Changing the frequency (e.g., from OD to BID) of basal insulin dosing during the trial was not allowed.

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:

Insulin glargine was used for basal insulin administration and was to be injected subcutaneously into the thigh or upper arm (deltoid area). The basal insulin injection was to be given OD, in the evening, at approximately the same time each day. Changing the frequency (e.g., from OD to BID) of basal insulin dosing during the trial was not allowed.

Arm title	Basal

Arm description:

During the 18-week treatment period, subjects received s.c. injection of basal insulin (insulin detemir or insulin glargine or NPH insulin) and metformin. Treatment recommendations were developed for the different trial products specifying the recommended dose adjustments at different plasma glucose (PG) levels. Trial products were titrated according to the insulin dosing recommendations provided during the study. No maximum dose of insulin was specified as doses were titrated individually.

Arm type	Active comparator
Investigational medicinal product name	Insulin detemir
Investigational medicinal product code	
Other name	Levemir®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin detemir was used for basal insulin administration and was to be injected subcutaneously into the thigh or upper arm (deltoid area). The basal insulin injection was to be given OD, in the evening, at

approximately the same time each day. Changing the frequency (e.g., from OD to BID) of basal insulin dosing during the trial was not allowed.

Investigational medicinal product name	NPH insulin
Investigational medicinal product code	
Other name	Insulatard®, Protaphane®, Novolin N™
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

NPH insulin was used for basal insulin administration and was to be injected subcutaneously into the thigh or upper arm (deltoid area). The basal insulin injection was to be given OD, in the evening, at approximately the same time each day. Changing the frequency (e.g., from OD to BID) of basal insulin dosing during the trial was not allowed.

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:

Insulin glargine was used for basal insulin administration and was to be injected subcutaneously into the thigh or upper arm (deltoid area). The basal insulin injection was to be given OD, in the evening, at approximately the same time each day. Changing the frequency (e.g., from OD to BID) of basal insulin dosing during the trial was not allowed.

Number of subjects in period 1	Faster aspart + Basal	Basal
Started	116	120
Exposed	115	120
Completed	107	115
Not completed	9	5
Consent withdrawn by subject	3	1
Adverse event, non-fatal	2	1
Unclassified	-	1
Lost to follow-up	-	1
Protocol deviation	4	1

Baseline characteristics

Reporting groups	
Reporting group title	Faster aspart + Basal
Reporting group description:	
During the 18-week treatment period, subjects received subcutaneous (s.c., under the skin) injection of faster aspart (bolus insulin) along with s.c. basal insulin (insulin detemir or insulin glargine or NPH insulin) and metformin. Treatment recommendations were developed for the different trial products specifying the recommended dose adjustments at different plasma glucose (PG) levels. Trial products were titrated according to the insulin dosing recommendations provided during the study. No maximum dose of insulin was specified as doses were titrated individually.	
Reporting group title	Basal
Reporting group description:	
During the 18-week treatment period, subjects received s.c. injection of basal insulin (insulin detemir or insulin glargine or NPH insulin) and metformin. Treatment recommendations were developed for the different trial products specifying the recommended dose adjustments at different plasma glucose (PG) levels. Trial products were titrated according to the insulin dosing recommendations provided during the study. No maximum dose of insulin was specified as doses were titrated individually.	

Reporting group values	Faster aspart + Basal	Basal	Total
Number of subjects	116	120	236
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	57.5	57.4	
standard deviation	± 9.9	± 8.5	-
Gender categorical Units: Subjects			
Female	61	61	122
Male	55	59	114
Glycosylated haemoglobin (HbA1c) Units: Percentage of glycosylated haemoglobin			
arithmetic mean	7.93	7.92	
standard deviation	± 0.69	± 0.68	-
Body weight Units: Kg			
arithmetic mean	82.2	85.1	
standard deviation	± 16.2	± 17.3	-

End points

End points reporting groups

Reporting group title	Faster aspart + Basal

Reporting group description:

During the 18-week treatment period, subjects received subcutaneous (s.c., under the skin) injection of faster aspart (bolus insulin) along with s.c. basal insulin (insulin detemir or insulin glargine or NPH insulin) and metformin. Treatment recommendations were developed for the different trial products specifying the recommended dose adjustments at different plasma glucose (PG) levels. Trial products were titrated according to the insulin dosing recommendations provided during the study. No maximum dose of insulin was specified as doses were titrated individually.

Reporting group title	Basal

Reporting group description:

During the 18-week treatment period, subjects received s.c. injection of basal insulin (insulin detemir or insulin glargine or NPH insulin) and metformin. Treatment recommendations were developed for the different trial products specifying the recommended dose adjustments at different plasma glucose (PG) levels. Trial products were titrated according to the insulin dosing recommendations provided during the study. No maximum dose of insulin was specified as doses were titrated individually.

Primary: Change from baseline in HbA1c

End point title	Change from baseline in HbA1c

End point description:

For this endpoint, baseline (week 0) and week 18 have been presented, where week 18 data are the "end of trial" data containing last available measurements. Analysis population: Full analysis set (FAS); the FAS included all randomised subjects. n = treatment wise number of subjects analysed for individual time-point.

End point type	Primary

End point timeframe:

After 18 weeks of randomised treatment

End point values	Faster aspart + Basal	Basal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	120		
Units: Percentage of glycosylated haemoglobin				
arithmetic mean (standard deviation)				
Baseline (n=116, 120)	7.93 (± 0.69)	7.92 (± 0.68)		
Week 18 (n=116, 120)	6.78 (± 0.92)	7.7 (± 0.93)		

Statistical analyses

Statistical analysis title	"Faster aspart + Basal" versus "Basal"

Statistical analysis description:

Change from baseline in HbA1c after 18 weeks of treatment was analysed using a mixed-effect model for repeated measurements (MMRM) where all calculated changes in HbA1c from baseline at visits 16, 22 and 28 were included in the analysis. This model included treatment, region and strata as fixed factors, subject as random effect, baseline HbA1c as covariate and interaction between all fixed effects

and visit, and between the covariate and visit.

Comparison groups	Faster aspart + Basal v Basal
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	Treatment difference
Point estimate	-0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	-0.72

Notes:

[1] - Superiority was considered confirmed if the upper bound of the two-sided 95% confidence interval (CI) for the estimated treatment difference (faster aspart+basal minus basal only), which was calculated using the FAS, was below 0%.

Secondary: Self-measured plasma glucose (SMPG) 7- point profile: Post prandial plasma glucose (PPG), overall 2-hour mean (of breakfast, lunch, main evening meal)

End point title	Self-measured plasma glucose (SMPG) 7- point profile: Post prandial plasma glucose (PPG), overall 2-hour mean (of breakfast, lunch, main evening meal)

End point description:

For this endpoint the "end of trial" data containing last available measurements are presented. PPG measurements were recorded by the subjects at 2 hours after each meal (breakfast, lunch and main evening meal) as part of three 7-point profiles (SMPG) prior to the visits. Individual mean meal PPG (post-breakfast, post-lunch, post-main evening meal) was derived from the three measurements. Overall mean PPG was derived from the individual derived meal time mean PPG values. Analysis population: FAS; the FAS included all randomised subjects. n = treatment wise number of subjects analysed for individual time-point.

End point type	Secondary

End point timeframe:

After 18 weeks of randomised treatment

End point values	Faster aspart + Basal	Basal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	120		
Units: mmol/L				
arithmetic mean (standard deviation)				
PPG breakfast; SMPG (n=114, 120)	7.2 (± 1.8)	9 (± 2.4)		
PPG lunch; SMPG (n=114, 120)	7.1 (± 1.9)	9.7 (± 2.6)		
PPG main evening meal; SMPG (n=116, 120)	7.4 (± 1.9)	10.1 (± 2.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Self-measured plasma glucose (SMPG) 7- point profile: Prandial plasma glucose (PG) increment, overall 2-hour mean (of breakfast, lunch, main evening meal)

End point title	Self-measured plasma glucose (SMPG) 7- point profile: Prandial plasma glucose (PG) increment, overall 2-hour mean (of breakfast, lunch, main evening meal)

End point description:

For this endpoint the "end of trial" data containing last available measurements are presented. Prandial PG increment for each meal (breakfast, lunch, main evening meal) was derived from the 7-point profiles (SMPG) as the difference between the PPG value 2 hours after each meal and the PG value before each meal. Individual mean meal PPG (post-breakfast, post-lunch, post-main evening meal) was derived from the three measurements. Overall mean PPG was derived from the individual derived meal time mean PPG values. Analysis population: FAS; the FAS included all randomised subjects. n = treatment wise number of subjects analysed for individual time-point.

End point type	Secondary

End point timeframe:

After 18 weeks of randomised treatment

End point values	Faster aspart + Basal	Basal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	120		
Units: mmol/L				
arithmetic mean (standard deviation)				
Breakfast increment; SMPG (n=114, 120)	1.2 (± 1.8)	2.9 (± 2.4)		
Lunch increment; SMPG (n=114, 120)	0.9 (± 2)	1.8 (± 2.2)		
Main evening meal increment; SMPG (n=115, 120)	0.7 (± 1.7)	1.4 (± 1.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in body weight

End point title	Change from baseline in body weight

End point description:

For this endpoint, baseline (week 0) and week 18 have been presented, where week 18 data are the "end of trial" data containing last available measurements. Analysis population: FAS; the FAS included all randomised subjects. n = treatment wise number of subjects analysed for individual time-point.

End point type	Secondary

End point timeframe:

After 18 weeks of randomised treatment

End point values	Faster aspart + Basal	Basal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	120		
Units: Kg				
arithmetic mean (standard deviation)				
Baseline (n=116, 120)	82.2 (± 16.2)	85.1 (± 17.3)		
Week 18 (n=116, 120)	83.9 (± 16.9)	85.4 (± 17.5)		

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:

Plasma glucose (PG) was always to be measured and recorded when a hypoglycaemic episode was suspected. All PG values ≤3.9 mmol/L (70 mg/dL) or >3.9 mmol/L (70 mg/dL) when they occurred in conjunction with hypoglycaemic symptoms were to be recorded by the subject. Numbers of treatment emergent hypoglycaemic episodes were recorded during 18 weeks of treatment. Analysis population: Safety Analysis Set (SAS); the SAS included all subjects receiving at least one dose of the investigational product or its comparator.

End point type	Secondary

End point timeframe:

During 18 weeks of randomised treatment

End point values	Faster aspart + Basal	Basal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	120		
Units: Number of episodes	1908	347		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events

End point title	Number of adverse events

End point description:

All adverse events (AEs) described here refer to treatment emergent adverse events (TEAE). A TEAE was defined as an event that had onset date on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment, week 18. Analysis population: SAS; the SAS included all subjects receiving at least one dose of the investigational product or its comparator.

End point type	Secondary

End point timeframe:

During 18 weeks of randomised treatment period.

End point values	Faster aspart + Basal	Basal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	120		
Units: Number of events	123	121		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During 18 weeks of randomised treatment period + 7 days of follow-up period.

Adverse event reporting additional description:

All AEs described here refer to TEAE. Analysis population: SAS - included all subjects receiving at least one dose of the investigational product or its comparator. Number of deaths causally related to treatment is the data considered to present under "total number of deaths resulting from adverse events".

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Faster aspart + Basal

Reporting group description:

During the 18-week treatment period, subjects received subcutaneous (s.c., under the skin) injection of faster aspart (bolus insulin) along with s.c. basal insulin (insulin detemir or insulin glargine or NPH insulin) and metformin. Treatment recommendations were developed for the different trial products specifying the recommended dose adjustments at different plasma glucose (PG) levels. Trial products were titrated according to the insulin dosing recommendations provided during the study. No maximum dose of insulin was specified as doses were titrated individually.

Reporting group title	Basal

Reporting group description:

During the 18-week treatment period, subjects received s.c. injection of basal insulin (insulin detemir or insulin glargine or NPH insulin) and metformin. Treatment recommendations were developed for the different trial products specifying the recommended dose adjustments at different plasma glucose (PG) levels. Trial products were titrated according to the insulin dosing recommendations provided during the study. No maximum dose of insulin was specified as doses were titrated individually.

Serious adverse events	Faster aspart + Basal	Basal	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 115 (5.22%)	5 / 120 (4.17%)	
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)			
Breast cancer			
subjects affected / exposed	0 / 115 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant respiratory tract neoplasm			

subjects affected / exposed	0 / 115 (0.00%)	1 / 120 (0.83%)	
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			
Carbon monoxide poisoning			
subjects affected / exposed	0 / 115 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 115 (1.74%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrong drug administered			
subjects affected / exposed	1 / 115 (0.87%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 115 (0.87%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	1 / 115 (0.87%)	0 / 120 (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 unconsciousness			
subjects affected / exposed	0 / 115 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	0 / 115 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung infiltration			
subjects affected / exposed	0 / 115 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	1 / 115 (0.87%)	0 / 120 (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			
Hypoglycaemia			
subjects affected / exposed	2 / 115 (1.74%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	1 / 2	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	Faster aspart + Basal	Basal	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 115 (1.74%)	6 / 120 (5.00%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 115 (1.74%)	6 / 120 (5.00%)	
occurrences (all)	4	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2013	1) Addition of a 30-day follow-up period to collect major adverse cardiovascular event (MACE) information. 2) Collection of smoking history and post-trial diabetes treatment. 3) Statement added to specify that subjects without post-randomisation HbA1c data were not to be included in analysis of the primary endpoint. 4) Section added on handling of missing data. 5) Update of hypoglycaemia classification and adverse event outcome definitions. 6) Correction of minor inconsistencies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported