Clinical trial results:
The effect of liraglutide versus placebo when added to basal insulin analogues with or without metformin in subjects with type 2 diabetes

Summary

EudraCT number	2011-002696-41
Trial protocol	DE NL FI
Global end of trial date	22 October 2013

Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	21 July 2015

Trial information

Trial identification

Sponsor protocol code	NN2211-3917

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01617434
WHO universal trial number (UTN)	U1111-1121-9874

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	25 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 October 2013
Global end of trial reached?	Yes
Global end of trial date	22 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm superiority on glycaemic control of liraglutide versus liraglutide placebo after 26 weeks of treatment when added to pre-existing basal insulin analogue treatment (with or without concomitant metformin treatment) in subjects with type 2 diabetes.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996) and FDA 21 CFR 312.120.

Background therapy:

All subjects were on pre-trial basal insulin analogue regimen ± metformin. Basal insulin therapy was insulin glargine (100 U/mL, s.c. injection) or insulin detemir (100 U/mL, s.c. injection). Oral antidiabetic drug metformin was administered as a tablet with a total daily dose of ≥1500 mg, divided into one to three doses per day.

Evidence for comparator:

Not applicable

Actual start date of recruitment	10 September 2012
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: 47
Country: Number of subjects enrolled	Canada: 41
Country: Number of subjects enrolled	India: 69
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Serbia: 38
Country: Number of subjects enrolled	United States: 127
Country: Number of subjects enrolled	Netherlands: 23
Country: Number of subjects enrolled	Finland: 34
Country: Number of subjects enrolled	Germany: 61
Worldwide total number of subjects	450
EEA total number of subjects	118

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)	330
From 65 to 84 years	120
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 76 sites in 9 countries as follows: Argentina: 3 sites; Canada: 9 sites; Finland: 5 sites; Germany: 9 sites; India: 9 sites; Mexico: 2 sites; Netherlands: 7 sites; Serbia: 3 sites; United States: 29 sites.

Pre-assignment

Screening details:

All subjects were on pre-trial basal insulin analogue regimen ± metformin. Basal insulin therapy was insulin glargine (100 U/mL, s.c. injection) or insulin detemir (100 U/mL, s.c. injection). Oral antidiabetic drug metformin was administered as a tablet with a total daily dose of ≥1500 mg, divided into one to three doses per day

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	Subject, Investigator

Blinding implementation details:

The subjects were randomised in a 1:1 manner to receive either liraglutide or liraglutide placebo using the interactive voice/web response system (IV/WRS, Visit 2). Liraglutide and liraglutide placebo were considered investigational medicinal products (IMPs), and were blinded throughout the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental: Liraglutide

Arm description:

Liraglutide was administered subcutaneously (s.c. injection, under the skin) once daily (OD) for 26 weeks in combination with pre-trial basal insulin analogue regimen ± metformin.

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

Dosage and administration details:

Liraglutide was administered subcutaneously (s.c. injection, under the skin) once daily (OD) for 26 weeks in combination with pre-trial basal insulin analogue regimen ± metformin. The starting dose of the liraglutide was 0.6 mg/day; dose was escalated to 1.2 mg/day after one week and 1.8 mg/day after 2 weeks; dose was maintained at 1.8 mg day for subsequent weeks until the end of the trial. All subjects continued their pre-trial insulin therapy of insulin glargine (100 U/mL, s.c. injection) or insulin detemir (100 U/mL, s.c. injection). Oral anti diabetic drug metformin was administered as a tablet with a total daily dose of ≥1500 mg, divided into one to three doses per day.

Arm title	Placebo Comparator: Placebo

Arm description:

Liraglutide placebo was administered subcutaneously (s.c. injection, under the skin) once daily (OD) for 26 weeks in combination with pre-trial basal insulin analogue regimen ± metformin.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Liraglutide placebo was administered subcutaneously (s.c. injection, under the skin) once daily (OD) for 26 weeks in combination with pre-trial basal insulin analogue regimen ± metformin. The starting dose of the liraglutide placebo was 0.6 mg/day; dose was escalated to 1.2 mg/day after one week and 1.8 mg/day after 2 weeks; dose was maintained at 1.8 mg day for subsequent weeks until the end of the trial. All subjects continued their pre-trial insulin therapy of insulin glargine (100 U/mL, s.c. injection) or insulin detemir (100 U/mL, s.c. injection). Oral anti diabetic drug metformin was administered as a tablet with a total daily dose of ≥1500 mg, divided into one to three doses per day.

Number of subjects in period 1	Experimental: Liraglutide	Placebo Comparator: Placebo
Started	225	225
Completed	191	174
Not completed	34	51
Adverse event, non-fatal	12	3
Withdrawal criteria	12	37
Unclassified	2	4
Protocol deviation	8	7

Baseline characteristics

Reporting groups	
Reporting group title	Experimental: Liraglutide
Reporting group description:	
Liraglutide was administered subcutaneously (s.c. injection, under the skin) once daily (OD) for 26 weeks in combination with pre-trial basal insulin analogue regimen ± metformin.	
Reporting group title	Placebo Comparator: Placebo
Reporting group description:	
Liraglutide placebo was administered subcutaneously (s.c. injection, under the skin) once daily (OD) for 26 weeks in combination with pre-trial basal insulin analogue regimen ± metformin.	

Reporting group values	Experimental: Liraglutide	Placebo Comparator: Placebo	Total
Number of subjects	225	225	450
Age categorical Units: Subjects			
65-74 years	54	50	104
Adults (18-64 years)	165	165	330
Elderly (≥75 years)	6	10	16
Age continuous Units: years			
arithmetic mean	59.3	57.5	
standard deviation	± 9.2	± 11.1	-
Gender categorical Units: Subjects			
Female	105	89	194
Male	120	136	256
Body Weight Units: kg			
arithmetic mean	90.23	91.85	
standard deviation	± 19.98	± 21.33	-
Fasting Plasma Glucose (FPG) Units: mmol/L			
arithmetic mean	8.32	8.21	
standard deviation	± 2.89	± 2.9	-
Glycosylated Haemoglobin (HbA1c) Units: percentage of glycosylated haemoglobin			
arithmetic mean	8.22	8.28	
standard deviation	± 0.81	± 0.9	-

End points

End points reporting groups

Reporting group title	Experimental: Liraglutide
Reporting group description:	
Liraglutide was administered subcutaneously (s.c. injection, under the skin) once daily (OD) for 26 weeks in combination with pre-trial basal insulin analogue regimen ± metformin.	
Reporting group title	Placebo Comparator: Placebo
Reporting group description:	
Liraglutide placebo was administered subcutaneously (s.c. injection, under the skin) once daily (OD) for 26 weeks in combination with pre-trial basal insulin analogue regimen ± metformin.	

Primary: Change in glycosylated haemoglobin (HbA1c) from baseline to week 26

End point title	Change in glycosylated haemoglobin (HbA1c) from baseline to week 26
End point description:	
The estimated mean change from baseline in HbA1c after 26 weeks of treatment.	
End point type	Primary
End point timeframe:	
Week 0 to week 26	

End point values	Experimental: Liraglutide	Placebo Comparator: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	217		
Units: percentage of glycosylated haemoglobin				
least squares mean (standard deviation)	-1.3 (± 1.015)	-0.11 (± 1.088)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Experimental: Liraglutide v Placebo Comparator: Placebo
Number of subjects included in analysis	432
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.39
upper limit	-0.99

Notes:

[1] - The null hypothesis of no difference between the two treatment arms with regard to changes from baseline in HbA1c (%) after 26 weeks of randomised treatment was analysed using a mixed model repeated measurements (MMRM) analysis with treatment, country, stratification groups as factors and baseline HbA1c as a covariate, all nested within visit.

Secondary: Change in fasting plasma glucose (FPG) from baseline to week 26

End point title	Change in fasting plasma glucose (FPG) from baseline to week 26

End point description:

The estimated mean change from baseline in FPG after 26 weeks of treatment.

End point type	Secondary

End point timeframe:

Week 0 to week 26

End point values	Experimental: Liraglutide	Placebo Comparator: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	217		
Units: mmol/L				
least squares mean (standard deviation)	-1.44 (± 2.494)	-0.16 (± 3.006)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in mean self-measured plasma glucose (SMPG) of 7-point profile from baseline to week 26

End point title	Change in mean self-measured plasma glucose (SMPG) of 7-point profile from baseline to week 26

End point description:

The estimated mean change from baseline in mean SMPG of 7-point profile (7-points were before breakfast, 90 minutes after start of breakfast, before lunch, 90 minutes after start of lunch, before dinner, 90 minutes after start of dinner and at bedtime) after 26 weeks of treatment.

End point type	Secondary

End point timeframe:

Week 0 to week 26

End point values	Experimental: Liraglutide	Placebo Comparator: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	196		
Units: mmol/L				
least squares mean (standard deviation)	-2.61 (± 2.248)	-1.02 (± 3.061)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body weight from baseline to week 26

End point title	Change in body weight from baseline to week 26

End point description:

The estimated mean change in body weight after 26 weeks of treatment.

End point type	Secondary

End point timeframe:

Week 0 to week 26

End point values	Experimental: Liraglutide	Placebo Comparator: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	215	216		
Units: kg				
least squares mean (standard deviation)	-3.54 (± 3.669)	-0.42 (± 3.909)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects achieving HbA1c below 7.0% (American Diabetes Association [ADA] target)

End point title	Number of subjects achieving HbA1c below 7.0% (American Diabetes Association [ADA] target)

End point description:

Number of subjects achieving HbA1c below 7.0% (American Diabetes Association [ADA] target) after 26 weeks of treatment.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Experimental: Liraglutide	Placebo Comparator: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	217		
Units: Percentage of subjects				
number (not applicable)	59.24	14.02		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects achieving HbA1c below or equal to 6.5% (American Association of Clinical Endocrinologists [AACE] Target)

End point title	Number of subjects achieving HbA1c below or equal to 6.5% (American Association of Clinical Endocrinologists [AACE] Target)

End point description:

Number of subjects achieving HbA1c below or equal to 6.5% (American Association of Clinical Endocrinologists [AACE] target) after 26 weeks of treatment.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Experimental: Liraglutide	Placebo Comparator: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	217		
Units: Percentage of subjects				
number (not applicable)	42.91	3.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of minor hypoglycaemic episodes during the randomised treatment period

End point title	Number of minor hypoglycaemic episodes during the randomised treatment period

End point description:

A minor hypoglycaemic episode was defined as either, (a) an episode with symptoms consistent with hypoglycaemia with confirmation by blood glucose <2.8 mmol/L (50 mg/dL) or plasma glucose <3.1

mmol/L (56 mg/dL) that was handled by the subject him/herself or (b) any asymptomatic blood glucose value <2.8 mmol/L (50 mg/dL) or plasma glucose value <3.1 mmol/L (56 mg/dL).

End point type	Secondary

End point timeframe:

Week 0 to week 26 + 7 days follow-up.

End point values	Experimental: Liraglutide	Placebo Comparator: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225	225		
Units: Events/100 years of patient exposure	126	83		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of severe hypoglycaemic episodes during the randomised treatment period

End point title	Number of severe hypoglycaemic episodes during the randomised treatment period

End point description:

Severe hypoglycaemia episode was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.

End point type	Secondary

End point timeframe:

Week 0 to Week 26 + 7 days follow-up

End point values	Experimental: Liraglutide	Placebo Comparator: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225	225		
Units: Events/100 years of patient exposure	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events (AEs) during the randomised treatment period

End point title	Number of adverse events (AEs) during the randomised

	treatment period

End point description:

An AE was defined as treatment emergent if the onset date (or increase in severity) was on or after the first day of exposure to randomised treatment and no later than 7 days after the last day of randomised treatment. The adverse events were categorised as 'serious' and 'non-serious' adverse events. Adverse events were also categorised according to the severity as 'mild', 'moderate' and 'severe' adverse events.

End point type	Secondary

End point timeframe:

Week 0 to Week 26 + 7 days follow-up

End point values	Experimental: Liraglutide	Placebo Comparator: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225	225		
Units: Events/1000 years of patient exposure				
Adverse events	4918	3737		
Serious Adverse Events	149	101		
Severe Adverse Events	169	101		
Moderate Adverse Events	1274	1060		
Mild Adverse Events	3474	2575		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 to week 26 + 7 days follow-up
(From the first trial-related activity after the subject had signed the informed consent through the posttreatment
follow-up period.)

Adverse event reporting additional description:

An adverse event (AE) could be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. Safety analysis set includes all subjects who received at least one dose of the trial product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	Placebo Comparator: Placebo

Reporting group description:

Liraglutide placebo administered s.c. (subcutaneously, under the skin) once daily in addition to the subject's stable pre-trial basal insulin analogue regimen plus/minus metformin.

Reporting group title	Experimental: Liraglutide

Reporting group description:

Max. 1.8 mg administered s.c. (subcutaneously, under the skin) once daily in addition to the subject's stable pre-trial basal insulin analogue regimen plus/minus metformin.

Serious adverse events	Placebo Comparator: Placebo	Experimental: Liraglutide	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 225 (3.11%)	11 / 225 (4.89%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Electrocardiogram change			
subjects affected / exposed	0 / 225 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 225 (0.00%)	1 / 225 (0.44%)	
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			
Fall			
subjects affected / exposed	0 / 225 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 225 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 225 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 225 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 225 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 225 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 225 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 225 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coronary artery disease			
subjects affected / exposed	2 / 225 (0.89%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Percutaneous coronary intervention			
subjects affected / exposed	0 / 225 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Intercostal neuralgia			
subjects affected / exposed	1 / 225 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 225 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Post-traumatic stress disorder			
subjects affected / exposed	0 / 225 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	1 / 225 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	0 / 225 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			

subjects affected / exposed	0 / 225 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 225 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital herpes			
subjects affected / exposed	0 / 225 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 225 (0.44%)	0 / 225 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 225 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 225 (0.00%)	1 / 225 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 225 (0.44%)	0 / 225 (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	Placebo Comparator: Placebo	Experimental: Liraglutide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 225 (26.67%)	110 / 225 (48.89%)	
Investigations			
Lipase increased			
subjects affected / exposed	5 / 225 (2.22%)	16 / 225 (7.11%)	
occurrences (all)	5	16	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 225 (7.11%)	8 / 225 (3.56%)	
occurrences (all)	20	9	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 225 (4.89%)	24 / 225 (10.67%)	
occurrences (all)	14	29	
Dyspepsia			
subjects affected / exposed	2 / 225 (0.89%)	16 / 225 (7.11%)	
occurrences (all)	2	20	
Nausea			
subjects affected / exposed	7 / 225 (3.11%)	50 / 225 (22.22%)	
occurrences (all)	8	62	
Vomiting			
subjects affected / exposed	2 / 225 (0.89%)	20 / 225 (8.89%)	
occurrences (all)	3	28	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	12 / 225 (5.33%)	12 / 225 (5.33%)	
occurrences (all)	13	13	
Infections and infestations			
Influenza			
subjects affected / exposed	16 / 225 (7.11%)	8 / 225 (3.56%)	
occurrences (all)	21	11	
Nasopharyngitis			
subjects affected / exposed	14 / 225 (6.22%)	13 / 225 (5.78%)	
occurrences (all)	16	19	
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	5 / 225 (2.22%) 5	22 / 225 (9.78%) 22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2012	Changes to Table of contents; Section 1: Summary; Section 2: Flow chart; Section 4.2.3: Objectives and endpoints; Section 5.3: Treatment of subjects; Section 6.2: Inclusion criteria; Section 6.3: Exclusion criteria; Section 6.6: Rationale for trial population; Section 8.5.4: Insulin dose adjustment; Section 8.6.4: Self-measured plasma glucose; Section 8.6.5: Diabetes Treatment Satisfaction Questionnaire; Section 8.7.4: Eye examination (fundoscopy/ fundus photography); Section 8.7.7: Urinalysis; Section 9.1: Trial products; Section 12.7.2: Event Adjudication Committee; Section 17.4.2: Safety endpoints; Section 18: Ethics; Section 27: References; SI/IC version 1.0; Section 1.1: An invitation to participate; SI/IC version 1.0 Section 2.2: Other risks associated with the treatment; Appendix B: Medical events of special interest
17 May 2013	Changes to Tables of contents; List of abbreviations; Section 1: number of subjects; Section 6.4: Withdrawal criteria; Section 7: Trial schedule; Section 8.4: Laboratory assessments; Section 8.7: Assessments for safety; Section 12.3: Follow-up of adverse events; Section 17.3: Primary endpoint; Master SI/IC version 2.0 Section 1.5.3 added and new SI/IC for gene testing added. Attachment I updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported