Clinical trial results:
Efficacy and safety of switching from sitagliptin to liraglutide in subjects with type 2 diabetes not achieving adequate glycaemic control on sitagliptin and metformin

Summary

EudraCT number	2012-004931-22
Trial protocol	ES HU
Global end of trial date	15 June 2015

Results information

Result version number	v1 (current)
This version publication date	08 June 2016
First version publication date	08 June 2016

Trial information

Trial identification

Sponsor protocol code	NN2211-4059

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01907854
WHO universal trial number (UTN)	U1111-1136-2073

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	14 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 June 2015
Global end of trial reached?	Yes
Global end of trial date	15 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm superiority of switch from sitagliptin 100 mg/day to liraglutide 1.8 mg/day, both + metformin vs. continued sitagliptin 100 mg/day + metformin on glycaemic control after 26 weeks of treatment in subjects with type 2 diabetes.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Seoul, Oct 2008) and ICH Good Clinical Practice (01-May-1996) and 21 CFR 312.120.

Background therapy:

Metformin was considered as background medication (NIMP) and was open-label throughout the trial. Subjects were to continue their pre-trial metformin treatment. Pre-trial dose level, dosing frequency and formulation had to remain the same throughout the trial, at the discretion of the investigator. An oral anti-diabetic, Metformin is administered as a tablet. The total daily dose was to be greater than equal to 1000 mg/day, divided into 1-3 doses.

Evidence for comparator:

Not applicable

Actual start date of recruitment	02 December 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	Spain: 59
Country: Number of subjects enrolled	Hungary: 66
Country: Number of subjects enrolled	Canada: 60
Country: Number of subjects enrolled	India: 70
Country: Number of subjects enrolled	Israel: 39
Country: Number of subjects enrolled	United States: 113
Worldwide total number of subjects	407
EEA total number of subjects	125

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)	321
From 65 to 84 years	85
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 86 sites in 6 countries as follows:
Canada: 14 sites; Hungary: 8 sites; India: 7 sites; Israel: 8 sites; Spain: 6 sites; United States: 43 sites.

Pre-assignment

Screening details:

Subjects were adult males or females with Type 2 diabetes mellitus (T2DM) who had inadequate glycemic control with stable doses of sitagliptin and metformin for 90 days prior to screening.

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:

A randomised double-blind, double-dummy, active-controlled design was chosen in accordance with the trial objectives. The double-dummy design was applied to eliminate potential bias of efficacy and safety results to the widest possible extent. Stratification was implemented in order to avoid bias arising from differences in glycosylated hemoglobin (HbA1c) and metformin dose at screening between the two arms.

Arms

Are arms mutually exclusive?	Yes
Arm title	Liraglutide

Arm description:

Subjects in this arm received treatments for a duration of 26 weeks; once-daily (OD) liraglutide (s.c., [under the skin] injection 0.6 mg/day, with weekly dose escalations of 0.6 mg/day up to a maintenance dose of 1.8 mg/day) + metformin tablets (≥1500 mg/day [or documented maximum tolerated dose ≥1000 mg/day) + OD sitagliptin placebo tablets.

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 initiated with a starting dose of 0.6 mg/day, with subsequent weekly dose escalations of 0.6 mg/day in accordance with the approved dose escalation for liraglutide until the maintenance dose of 1.8 mg/day in this trial was reached. Escalation from 0.6 to 1.2 then 1.8 mg/day could be extended by 7 days in total if subjects did not tolerate an increase in dose during dose escalation, at the discretion of the investigator. The liraglutide maintenance dose of 1.8 mg/day had to remain unchanged throughout the remainder of the trial. Liraglutide was to be injected subcutaneously (sc., under the skin) in the thigh, upper arm (deltoid region) or abdomen. The injection site did not have to be consistent throughout the trial. Injections could be done at any time of the day irrespective of meals.

Investigational medicinal product name	Sitagliptin placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching sitagliptin placebo is an oral anti-diabetic administered as a tablet. Sitagliptin 100 mg was administered once daily irrespective of meals. The dose and daily time of tablet administration was to remain the same throughout the treatment period.

Arm title	Sitagliptin

Arm description:

Subjects in this arm received treatments for a duration of 26 weeks; OD sitagliptin tablets (100 mg) + metformin tablets (≥1500 mg/day [or documented maximum tolerated dose ≥1000 mg/day]) + OD s.c., injection of liraglutide placebo.

Arm type	Active comparator
Investigational medicinal product name	Sitagliptin
Investigational medicinal product code	
Other name	Januvia
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sitagliptin is an oral anti-diabetic administered as a tablet. Sitagliptin 100 mg was administered once daily irrespective of meals. The dose and daily time of tablet administration was to remain the same throughout the treatment period.

Investigational medicinal product name	Liraglutide 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:

Matching liraglutide placebo was initiated with a starting dose of 0.6 mg/day, with subsequent weekly dose escalations of 0.6 mg/day in accordance with the approved dose escalation for liraglutide until the maintenance dose of 1.8 mg/day in this trial was reached. Escalation from 0.6 to 1.2 then 1.8 mg/day could be extended by 7 days in total if subjects did not tolerate an increase in dose during dose escalation, at the discretion of the investigator. The liraglutide maintenance dose of 1.8 mg/day had to remain unchanged throughout the remainder of the trial. Liraglutide was to be injected subcutaneously in the thigh, upper arm (deltoid region) or abdomen. The injection site did not have to be consistent throughout the trial. Injections could be done at any time of the day irrespective of meals.

Number of subjects in period 1	Liraglutide	Sitagliptin
Started	203	204
Exposed	202	204
Completed	187	191
Not completed	16	13
Consent withdrawn by subject	9	7
Unclassified	4	3
Lost to follow-up	2	2
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Liraglutide
Reporting group description:	
Subjects in this arm received treatments for a duration of 26 weeks; once-daily (OD) liraglutide (s.c., [under the skin] injection 0.6 mg/day, with weekly dose escalations of 0.6 mg/day up to a maintenance dose of 1.8 mg/day) + metformin tablets (≥1500 mg/day [or documented maximum tolerated dose ≥1000 mg/day) + OD sitagliptin placebo tablets.	
Reporting group title	Sitagliptin
Reporting group description:	
Subjects in this arm received treatments for a duration of 26 weeks; OD sitagliptin tablets (100 mg) + metformin tablets (≥1500 mg/day [or documented maximum tolerated dose ≥1000 mg/day]) + OD s.c., injection of liraglutide placebo.	

Reporting group values	Liraglutide	Sitagliptin	Total
Number of subjects	203	204	407
Age categorical			
Units: Subjects			
Age continuous			
Demographics and baseline age characteristics of exposed subjects were summarised in continuous variables. The number of exposed subjects in liraglutide arm was 202 subjects and sitagliptin arm was 204 subjects. Only the exposed subjects have contributed to the baseline age values reported here.			
Units: years			
arithmetic mean	56.3	56.5	
standard deviation	± 10.6	± 9.7	-
Gender categorical			
Demographics and baseline gender characteristics of randomised subjects were summarised in categorical variables. Although, the number of exposed subjects in liraglutide arm was 202 subjects and sitagliptin arm was 204 subjects; randomised subjects (203 and 204) have contributed to the baseline gender values reported here.			
Units: Subjects			
Female	85	79	164
Male	118	125	243
HbA1c			
Demographics and baseline HbA1c characteristics of exposed subjects were summarised in continuous variables. The number of exposed subjects in liraglutide arm was 202 subjects and sitagliptin arm was 204 subjects. Only the exposed subjects have contributed to the baseline age values reported here.			
Units: percentage of glycosylated haemoglobin			
arithmetic mean	8.3	8.2	
standard deviation	± 0.6	± 0.6	-
Body Weight			
Demographics and baseline body weight characteristics of exposed subjects were summarised in continuous variables. The number of exposed subjects in liraglutide arm was 202 subjects and sitagliptin arm was 204 subjects. Only the exposed subjects have contributed to the baseline body weight reported here.			
Units: kilograms			
arithmetic mean	88.9	91.2	
standard deviation	± 19.8	± 19.6	-
Fasting plasma glucose			
Demographics and baseline fasting plasma glucose characteristics of exposed subjects were summarised in continuous variables. The number of exposed subjects in liraglutide arm was 200 subjects and			

sitagliptin arm was 203 subjects. Only the exposed subjects have contributed to the baseline fasting plasma glucose values reported here.			
Units: mmol/L			
arithmetic mean	10	9.7	
standard deviation	± 2.7	± 2.5	-

End points

End points reporting groups

Reporting group title	Liraglutide

Reporting group description:

Subjects in this arm received treatments for a duration of 26 weeks; once-daily (OD) liraglutide (s.c., [under the skin] injection 0.6 mg/day, with weekly dose escalations of 0.6 mg/day up to a maintenance dose of 1.8 mg/day) + metformin tablets (≥1500 mg/day [or documented maximum tolerated dose ≥1000 mg/day) + OD sitagliptin placebo tablets.

Reporting group title	Sitagliptin

Reporting group description:

Subjects in this arm received treatments for a duration of 26 weeks; OD sitagliptin tablets (100 mg) + metformin tablets (≥1500 mg/day [or documented maximum tolerated dose ≥1000 mg/day]) + OD s.c., injection of liraglutide placebo.

Primary: Change in HbA1c

End point title	Change in HbA1c

End point description:

Change from baseline in HbA1c was analysed after 26 weeks of treatment. Analysis population set: full analysis set (FAS); all randomised subjects receiving at least one dose of any of the trial products. Missing values were imputed using mixed model for repeated measurements (MMRM).

End point type	Primary

End point timeframe:

From baseline to Week 26

End point values	Liraglutide	Sitagliptin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	182		
Units: percentage of glycosylated haemoglobin				
arithmetic mean (standard deviation)	-1.146 (± 0.9748)	-0.529 (± 1.0148)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Changes in HbA1c from baseline to the 26 weeks' measurements were analysed using MMRM, with treatment, baseline HbA1c level (≤8.5% and >8.5%), metformin dose (<1500 mg/day and ≥1500 mg/day), the interaction between baseline HbA1c level and metformin dose, and country as factors and the HbA1c value at baseline as a covariate, all variables nested within week as a factor.

Comparison groups	Liraglutide v Sitagliptin

Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	-0.4

Notes:

[1] - Superiority of liraglutide over sitagliptin would be concluded if the 95% CI for the treatment difference was entirely below 0%.

Secondary: Change in body weight

End point title	Change in body weight

End point description:

Change from baseline in body weight was analysed after 26 weeks of treatment. Analysis population set: full analysis set (FAS); all randomised subjects receiving at least one dose of any of the trial products. Missing values were imputed using MMRM.

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Liraglutide	Sitagliptin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	200		
Units: kilogram(s)				
arithmetic mean (standard deviation)	-3.32 (± 3.135)	-1.8 (± 2.974)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Change in body weight from baseline to week 26 was analysed using MMRM, with treatment, baseline HbA1c level (≤ 8.5% and > 8.5%), metformin dose (<1500 mg/day and ≥1500 mg/day), the interaction between baseline HbA1c level and metformin dose, and country as factors and the body weight at baseline as a covariate and all variables nested within week as a factor.

Comparison groups	Liraglutide v Sitagliptin

Number of subjects included in analysis	392
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.34
upper limit	-0.99

Notes:

[2] - Superiority of liraglutide was concluded when 95% CI for the treatment difference for change from baseline in body weight after 26 weeks was entirely below 0%, implying that the 2-sided p-value for the hypothesis of no treatment difference was < 5% .

Secondary: Change in fasting plasma glucose

End point title	Change in fasting plasma glucose

End point description:

Change from baseline in fasting blood glucose was analysed after 26 weeks of treatment. Analysis population set: full analysis set (FAS); all randomised subjects receiving at least one dose of any of the trial products. Missing values were imputed using MMRM.

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Liraglutide	Sitagliptin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	199		
Units: nmol/L				
arithmetic mean (standard deviation)	-1.967 (± 2.3585)	-0.588 (± 2.1363)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting blood lipids

End point title	Change in fasting blood lipids

End point description:

Ratio to baseline in fasting blood lipids (total cholesterol, low density lipoprotein [LDL], very low density lipoprotein [VLDL], high density lipoprotein [HDL], triglycerides, and free fatty acids) were analysed after 26 weeks of treatment. Analysis population set: full analysis set; all randomised subjects receiving at least one dose of any of the trial products. Missing values were imputed using MMRM. Here we are presenting ratio to baseline data.

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Liraglutide	Sitagliptin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155[3]	156[4]		
Units: ratio				
arithmetic mean (standard deviation)				
Total Cholesterol	1.011 (± 0.1906)	1.045 (± 0.2323)		
LDL Cholesterol	1.049 (± 0.3899)	1.121 (± 0.4661)		
VLDL Cholesterol	1.062 (± 0.4236)	1.075 (± 0.4625)		
HDL Cholesterol	1.004 (± 0.1528)	0.997 (± 0.1548)		
Triglycerides	1.089 (± 0.4975)	1.099 (± 0.4889)		
Free Fatty Acids	1.086 (± 0.774)	1.104 (± 0.5839)		

Notes:

[3] - For Free Fatty Acids 154 subjects were analysed.

[4] - For Free Fatty Acids 150 subjects were analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in systolic blood pressure and diastolic blood pressure

End point title	Change in systolic blood pressure and diastolic blood pressure

End point description:

Change from baseline in systolic blood pressure and diastolic blood pressure were analysed after 26 weeks of treatment. Analysis population set: full analysis set; all randomised subjects receiving at least one dose of any of the trial products. Missing values were imputed using MMRM.

End point type	Secondary

End point timeframe:

From baseline to Week 26

End point values	Liraglutide	Sitagliptin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	200		
Units: mmHg				
arithmetic mean (standard deviation)				
systolic blood pressure	-3.6 (± 11.596)	-2.57 (± 11.593)		
diastolic blood pressure	-0.23 (± 7.085)	-0.81 (± 7.193)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects who achieve HbA1c <7.0% (53 mmol/mol) (American Diabetes Association target)

End point title	Subjects who achieve HbA1c <7.0% (53 mmol/mol) (American Diabetes Association target)

End point description:

Number of subjects who achieve HbA1c <7.0% were analysed after 26 weeks of treatment. Analysis population set: full analysis set; all randomised subjects receiving at least one dose of any of the trial products. Missing values were imputed using MMRM.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment

End point values	Liraglutide	Sitagliptin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	182		
Units: Percentage of subjects				
number (not applicable)				
Yes	50.6	26.9		
No	49.4	73.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent adverse events

End point title	Number of treatment emergent adverse events

End point description:

A treatment emergent adverse event (TEAE) was defined as an event that had an onset date (or increase in severity) 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 number of TEAEs was recorded during 26 weeks of treatment plus a one -week of follow-up. Number of Analysis population set: safety analysis set; all randomised subjects receiving at least one dose of any of the trial products.

End point type	Secondary

End point timeframe:

During 26 weeks of treatment plus one week of follow-up period.

End point values	Liraglutide	Sitagliptin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	204		
Units: Events	455	318		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
27 weeks (26 weeks of treatment period + 1 week follow-up)	
Adverse event reporting additional description:	
Adverse events were collected for safety analysis set that included all subjects who received at least one dose of any of the trial products.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

Reporting groups	
Reporting group title	Sitagliptin
Reporting group description:	
Subjects in this arm received sitagliptin + metformin + liraglutide placebo for a duration of 26 weeks of treatment (a 3−4 week dose escalation period followed by a maintenance period).	
Reporting group title	Liraglutide
Reporting group description:	
Subjects in this arm received liraglutide + metformin + sitagliptin placebo for a duration of 26 weeks and more (a 3−4 week dose escalation period followed by a maintenance period).	

Serious adverse events	Sitagliptin	Liraglutide	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 204 (3.43%)	6 / 202 (2.97%)	
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)			
Bladder cancer			
subjects affected / exposed	1 / 204 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 204 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	0 / 204 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 204 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 204 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prinzmetal angina			
subjects affected / exposed	0 / 204 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Joint arthroplasty			
subjects affected / exposed	0 / 204 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 204 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 204 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 204 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumococcal sepsis			
subjects affected / exposed	1 / 204 (0.49%)	0 / 202 (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	1 / 204 (0.49%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Sitagliptin	Liraglutide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 204 (29.90%)	96 / 202 (47.52%)	
Investigations			
Lipase increased			
subjects affected / exposed	9 / 204 (4.41%)	11 / 202 (5.45%)	
occurrences (all)	9	12	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 204 (5.88%)	13 / 202 (6.44%)	
occurrences (all)	16	16	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	19 / 204 (9.31%)	33 / 202 (16.34%)	
occurrences (all)	21	45	
Nausea			
subjects affected / exposed	16 / 204 (7.84%)	44 / 202 (21.78%)	
occurrences (all)	21	59	
Vomiting			
subjects affected / exposed	10 / 204 (4.90%)	15 / 202 (7.43%)	
occurrences (all)	15	18	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 204 (3.43%)	12 / 202 (5.94%)	
occurrences (all)	7	14	
Upper respiratory tract infection			
subjects affected / exposed	13 / 204 (6.37%)	12 / 202 (5.94%)	
occurrences (all)	15	12	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 204 (3.43%)	18 / 202 (8.91%)	
occurrences (all)	7	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2013	Global Amendment: Storage condition description for sitagliptin and placebo has been updated to reflect the current storage conditions. Minor changes in several sections have been made in to order to ensure clarity and alignment across trials.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported