Clinical trial results:
Multi-centre, randomized, double-blind, parallel-group study evaluating the effect of Fluticasone Furoate/ Vilanterol (FF/VI) Inhalation Powder once daily compared with Vilanterol (VI) Inhalation Powder Once Daily on Bone Mineral Density (BMD) in subjects with Chronic Obstructive Pulmonary Disease (COPD)

Summary

EudraCT number	2012-004801-28
Trial protocol	DE ES NL
Global end of trial date	26 March 2018

Results information

Result version number	v1 (current)
This version publication date	06 April 2019
First version publication date	06 April 2019

Trial information

Trial identification

Sponsor protocol code	102972

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.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	21 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the effect of the inhaled corticosteroid FF on bone mineral density assessed at the total hip by comparing FF/VI treatment with VI treatment in participants with moderate COPD.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 2014
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	Canada: 27
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Netherlands: 56
Country: Number of subjects enrolled	Spain: 59
Country: Number of subjects enrolled	United States: 107
Worldwide total number of subjects	283
EEA total number of subjects	149

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)	129

From 65 to 84 years	152
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted on participants with chronic obstructive pulmonary disease (COPD) in five countries to assess the long-term safety effects of Fluticasone Furoate (FF) component of the FF/Vilanterol (VI) inhalation powder.

Pre-assignment

Screening details:

A total of 482 participants were screened of which 199 were screen failures. A total of 283 participants were randomized in a 1:1 ratio to receive either VI or FF/VI.

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, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Participants administered VI

Arm description:

Following run-in period of 14 to 21 days, eligible participants were administered VI 25 microgram (mcg) once daily via ELLIPTA inhaler for 156 weeks.

Arm type	Experimental
Investigational medicinal product name	Vilanterol (VI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants were administered VI 25 microgram (mcg) once daily via ELLIPTA for 156 weeks

Arm title	Participants administered FF/VI

Arm description:

Following run-in period of 14 to 21 days, eligible participants were administered FF 100 mcg along with VI 25 mcg once daily via ELLIPTA inhaler for 156 weeks.

Arm type	Experimental
Investigational medicinal product name	Vilanterol (VI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants were administered VI 25 mcg /FF 100 mcg once daily via ELLIPTA inhaler for 156 weeks

Investigational medicinal product name	Fluticasone Furoate (FF)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants were administered VI 25 mcg /FF 100 mcg once daily via ELLIPTA inhaler for 156 weeks

Number of subjects in period 1	Participants administered VI	Participants administered FF/VI
Started	142	141
Completed	87	83
Not completed	55	58
Consent withdrawn by subject	13	17
Physician decision	3	6
Adverse event, non-fatal	23	20
Lost to follow-up	4	4
Protocol deviation	1	-
Lack of efficacy	11	11

Baseline characteristics

Reporting groups	
Reporting group title	Participants administered VI
Reporting group description:	
Following run-in period of 14 to 21 days, eligible participants were administered VI 25 microgram (mcg) once daily via ELLIPTA inhaler for 156 weeks.	
Reporting group title	Participants administered FF/VI
Reporting group description:	
Following run-in period of 14 to 21 days, eligible participants were administered FF 100 mcg along with VI 25 mcg once daily via ELLIPTA inhaler for 156 weeks.	

Reporting group values	Participants administered VI	Participants administered FF/VI	Total
Number of subjects	142	141	283
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	62	67	129
From 65-84 years	79	73	152
85 years and over	1	1	2
Age Continuous			
Safety population			
Units: Years			
arithmetic mean	66.0	64.4	
standard deviation	± 8.19	± 9.04	-
Sex: Female, Male			
Safety population			
Units: Subjects			
Female	70	71	141
Male	72	70	142
Race/Ethnicity, Customized			
Safety population			
Units: Subjects			
Central/South Asian Heritage	0	1	1
Black or African American	1	1	2
White	141	139	280

End points

End points reporting groups

Reporting group title	Participants administered VI
Reporting group description:	
Following run-in period of 14 to 21 days, eligible participants were administered VI 25 microgram (mcg) once daily via ELLIPTA inhaler for 156 weeks.	
Reporting group title	Participants administered FF/VI
Reporting group description:	
Following run-in period of 14 to 21 days, eligible participants were administered FF 100 mcg along with VI 25 mcg once daily via ELLIPTA inhaler for 156 weeks.	

Primary: Percentage change from Baseline in Bone mineral density (BMD) measured at total hip

End point title	Percentage change from Baseline in Bone mineral density (BMD) measured at total hip

End point description:

BMD analysis performed on log (BMD ratio to Baseline) using a repeated measures model with covariates of treatment group, age,gender,Baseline BMI,visit,log Baseline BMD,log Baseline BMD by visit and treatment group by visit interactions.These estimates were then converted into annual changes and averaged to calculate the overall treatment estimates and difference which were used for testing non-inferiority.The analysis shown is for the "While on Treatment"estimand of the difference in percentage(%) change from Baseline per annum between FF/VI±BMD medication/SCS (systemic corticosteroids) and VI±BMD medication/SCS.Baseline is defined as the measurement performed at Visit 1.% change is calculated as (BMD value post-Baseline/Baseline value)-1*by 100.Only those participants with data available at the specified data points were analyzed (represented by n=X in the category titles).All randomized participants who received at least 1 dose of study treatment were included in Safety Population

End point type	Primary

End point timeframe:

Baseline (Visit 1) and 26, 52, 78, 104, 130 and 156 Weeks

End point values	Participants administered VI	Participants administered FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132[1]	130[2]		
Units: Percentage change				
least squares mean (confidence interval 95%)				
Overall % change per year, n = 132, 130	0.18 (-0.18 to 0.55)	-0.27 (-0.63 to 0.09)		
% change by Week 26, n= 130, 130	0.37 (-0.07 to 0.82)	0.31 (-0.13 to 0.76)		
% change by Week 52, n = 104, 121	0.35 (-0.21 to 0.91)	-0.43 (-0.96 to 0.10)		
% change by Week 78, n = 97, 102	0.22 (-0.41 to 0.85)	-0.68 (-1.29 to -0.07)		
% change by Week 104, n = 94, 96	-0.16 (-0.84 to 0.52)	-1.02 (-1.68 to -0.36)		
% change by Week 130, n = 88, 84	0.00 (-0.73 to 0.75)	-1.02 (-1.75 to -0.29)		

% change by Week 156, n = 76, 75	-0.16 (-1.02 to 0.71)	-1.29 (-2.13 to -0.45)		

Notes:

[1] - Safety Population

[2] - Safety Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Treatment comparison for overall weeks

Comparison groups	Participants administered VI v Participants administered FF/VI
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Percentage Change from Baseline
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	0.06

Notes:

[3] - Non-inferiority was demonstrated if the lower limit of 95 % confidence interval (CI) for the overall treatment difference change from Baseline between FF/VI and VI was greater than -1 % year

Secondary: Percentage change from Baseline in BMD measurements at total hip by gender (male participants)

End point title	Percentage change from Baseline in BMD measurements at total hip by gender (male participants)

End point description:

BMD analysis performed on log (BMD ratio to Baseline) using separate repeated measures models for each gender with covariates of treatment group, age, Baseline BMI, visit, log Baseline BMD, log Baseline BMD by visit and treatment group by visit interactions. These estimates were then converted into annual changes and averaged to calculate the overall treatment estimates and difference which were used for testing non-inferiority. The analysis shown is for the "While on Treatment" estimand of the difference in percentage change from Baseline per annum between FF/VI ± BMD medication/SCS (systemic corticosteroids) and VI ± BMD medication/SCS. Baseline is defined as the measurement performed at Visit 1. Percentage change is calculated as (BMD value post-Baseline divided by Baseline value) -1 multiplied by 100.Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Visit 1) and 26, 52, 78, 104, 130 and 156 Weeks

End point values	Participants administered VI	Participants administered FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[4]	63[5]		
Units: Percent change				
least squares mean (confidence interval 95%)				

Overall Week % change per year, n = 67, 63	0.27 (-0.23 to 0.77)	-0.20 (-0.70 to 0.31)		
% change by Week 26, n = 66, 63	0.45 (-0.06 to 0.97)	0.44 (-0.09 to 0.97)		
% change by Week 52, n = 52, 56	0.48 (-0.31 to 1.27)	-0.43 (-1.19 to 0.33)		
% change by Week 78, n = 51, 46	0.06 (-0.81 to 0.95)	-0.68 (-1.56 to 0.21)		
% change by Week 104, n = 50, 43	0.07 (-0.86 to 1.00)	-0.68 (-1.62 to 0.27)		
% change by Week 130, n = 44, 39	0.37 (-0.75 to 1.50)	-0.89 (-2.02 to 0.26)		
% change by Week 156, n = 40, 35	0.05 (-1.26 to 1.37)	-1.39 (-2.71 to -0.05)		

Notes:

[4] - Safety Population

[5] - Safety Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Overall Weeks for Male	
Comparison groups	Participants administered VI v Participants administered FF/VI
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Percentage Change from Baseline
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	0.24

Notes:

[6] - Non-inferiority was demonstrated if the lower limit of 95% CI for the overall treatment difference change from Baseline between FF/VI and VI was greater than -1 % year

Secondary: Percentage change from Baseline in BMD measurements at total hip by gender (female participants)

End point title	Percentage change from Baseline in BMD measurements at total hip by gender (female participants)

End point description:

BMD analysis performed on log (BMD ratio to Baseline) using separate repeated measures models for each gender with covariates of treatment group, age, Baseline BMI, visit, log Baseline BMD, log Baseline BMD by visit and treatment group by visit interactions. These estimates were then converted into annual changes and averaged to calculate the overall treatment estimates and difference which were used for testing non-inferiority. The analysis shown is for the "While on Treatment" estimand of the difference in percentage change from Baseline per annum between FF/VI ± BMD medication/SCS (systemic corticosteroids) and VI ± BMD medication/SCS. Baseline is defined as the measurement performed at Visit 1. Percentage change is calculated as (BMD value post-Baseline divided by Baseline value) -1 multiplied by 100.Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Visit 1) and 26, 52, 78, 104, 130 and 156 Weeks

End point values	Participants administered VI	Participants administered FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[7]	67[8]		
Units: Percent change				
least squares mean (confidence interval 95%)				
Overall Week % change per year, n = 65, 67	0.09 (-0.46 to 0.64)	-0.31 (-0.84 to 0.22)		
% change by Week 26, n = 64, 67	0.28 (-0.45 to 1.02)	0.20 (-0.51 to 0.92)		
% change by Week 52, n = 52, 65	0.13 (-0.67 to 0.94)	-0.42 (-1.16 to 0.33)		
% change by Week 78, n = 46, 56	0.37 (-0.54 to 1.28)	-0.63 (-1.48 to 0.23)		
% change by Week 104, n = 44, 53	-0.40 (-1.40 to 0.61)	-1.26 (-2.19 to -0.32)		
% change by Week 130, n = 44, 45	-0.18 (-1.12 to 0.77)	-0.99 (-1.90 to -0.08)		
% change by Week 156, n = 36, 40	-0.42 (-1.56 to 0.73)	-1.19 (-2.27 to -0.11)		

Notes:

[7] - Safety Population

[8] - Safety Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Overall Weeks for females	
Comparison groups	Participants administered VI v Participants administered FF/VI
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	Percentage Change from Baseline
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	0.36

Notes:

[9] - Non-inferiority was demonstrated if the lower limit of 95% CI for the overall treatment difference change from Baseline between FF/VI and VI was greater than -1 % year

Secondary: Percentage change from Baseline in BMD measurements at lumbar spine (L1 to L4) by gender (male participants)

End point title	Percentage change from Baseline in BMD measurements at lumbar spine (L1 to L4) by gender (male participants)

End point description:

BMD analysis performed on log (BMD ratio to Baseline) using separate repeated measures models for each gender with covariates of treatment group, age, Baseline BMI, visit, log Baseline BMD, log Baseline

BMD by visit and treatment group by visit interactions. These estimates were then converted into annual changes and averaged to calculate the overall treatment estimates and difference which were used for testing non-inferiority. The analysis shown is for the "While on Treatment" estimand of the difference in percentage change from Baseline per annum between FF/VI ± BMD medication/SCS (systemic corticosteroids) and VI ± BMD medication/SCS. Baseline is defined as the measurement performed at Visit 1. Percentage change is calculated as (BMD value post-Baseline divided by Baseline value) -1 multiplied by 100.Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Visit 1) and 26, 52, 78, 104, 130 and 156 Weeks

End point values	Participants administered VI	Participants administered FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69[10]	64[11]		
Units: Percent change				
least squares mean (confidence interval 95%)				
Overall, male % change per year, n = 69, 64	1.41 (0.79 to 2.04)	0.38 (-0.26 to 1.02)		
% change by Week 26, n = 67, 64	1.03 (0.26 to 1.80)	0.42 (-0.36 to 1.21)		
% change by Week 52, n = 53, 56	1.91 (0.89 to 2.94)	0.11 (-0.88 to 1.11)		
% change by Week 78, n = 52, 45	2.09 (0.84 to 3.35)	0.64 (-0.67 to 1.97)		
% change by Week 104, n = 52, 43	2.72 (1.48 to 3.98)	0.42 (-0.88 to 1.75)		
% change by Week 130, n = 47, 38	1.95 (0.76 to 3.16)	0.47 (-0.82 to 1.78)		
% change by Week 156, n = 43, 35	2.96 (1.68 to 4.25)	1.49 (0.13 to 2.86)		

Notes:

[10] - Safety Population

[11] - Safety Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Overall Weeks for Male

Comparison groups	Participants administered VI v Participants administered FF/VI
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Change from Baseline
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	-0.13

Secondary: Percentage change from Baseline in BMD measurements at lumbar spine (L1 to L4) by gender (female participants)

End point title	Percentage change from Baseline in BMD measurements at lumbar spine (L1 to L4) by gender (female participants)

End point description:

BMD analysis performed on log (BMD ratio to Baseline) using separate repeated measures models for each gender with covariates of treatment group, age, Baseline BMI, visit, log Baseline BMD, log Baseline BMD by visit and treatment group by visit interactions. These estimates were then converted into annual changes and averaged to calculate the overall treatment estimates and difference which were used for testing non-inferiority. The analysis shown is for the "While on Treatment" estimand of the difference in percentage change from Baseline per annum between FF/VI ± BMD medication/SCS (systemic corticosteroids) and VI ± BMD medication/SCS. Baseline is defined as the measurement performed at Visit 1. Percentage change is calculated as (BMD value post-Baseline divided by Baseline value) -1 multiplied by 100.Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Visit 1) and 26, 52, 78, 104, 130 and 156 Weeks

End point values	Participants administered VI	Participants administered FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[12]	68[13]		
Units: Percent change				
least squares mean (confidence interval 95%)				
Overall Week % change per year, n = 66, 68	0.17 (-0.42 to 0.77)	0.12 (-0.45 to 0.70)		
% change by Week 26, n = 66, 68	0.10 (-0.67 to 0.88)	-0.19 (-0.95 to 0.58)		
% change by Week 52, n = 51, 66	-0.48 (-1.44 to 0.48)	0.57 (-0.31 to 1.46)		
% change by Week 78, n = 46, 57	0.33 (-0.60 to 1.26)	0.25 (-0.61 to 1.11)		
% change by Week 104, n = 43, 54	0.65 (-0.50 to 1.80)	0.64 (0.41 to 1.70)		
% change by Week 130, n = 44, 49	1.33 (0.01 to 2.67)	0.10 (-1.12 to 1.33)		
% change by Week 156, n = 36, 42	0.80 (-0.74 to 2.36)	0.10 (-1.32 to 1.53)		

Notes:

[12] - Safety Population

[13] - Safety Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Participants administered VI v Participants administered FF/VI

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	other[14]
Parameter estimate	Percentage Change from Baseline
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	0.78

Notes:

[14] - Overall Weeks for females

Secondary: Percentage change from Baseline in BMD measurements at lumbar spine (L1 to L4)

End point title	Percentage change from Baseline in BMD measurements at lumbar spine (L1 to L4)

End point description:

BMD analysis performed on log (BMD ratio to Baseline) using a repeated measures model with covariates of treatment group, age, gender, Baseline BMI, visit, log Baseline BMD, log Baseline BMD by visit and treatment group by visit interactions. These estimates were then converted into annual changes and averaged to calculate the overall treatment estimates and difference which were used for testing non-inferiority. The analysis shown is for the "While on Treatment" estimand of the difference in percentage change from Baseline per annum between FF/VI ± BMD medication/SCS (systemic corticosteroids) and VI ± BMD medication/SCS. Baseline is defined as the measurement performed at Visit 1. Percentage change is calculated as (BMD value post-Baseline divided by Baseline value) -1 multiplied by 100.Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline (Visit 1) and 26, 52, 78, 104, 130 and 156 Weeks

End point values	Participants administered VI	Participants administered FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[15]	132[16]		
Units: Percentage Change				
least squares mean (confidence interval 95%)				
Overall week % change per year, n=135, 132	0.79 (0.36 to 1.22)	0.28 (-0.15 to 0.71)		
% change by Week 26, n = 133, 132	0.55 (0.01 to 1.10)	0.13 (-0.41 to 0.68)		
% change by Week 52, n = 104, 122	0.71 (0.01 to 1.42)	0.40 (-0.26 to 1.07)		
% change by Week 78, n= 98, 102	1.20 (0.43 to 1.99)	0.45 (-0.31 to 1.21)		
% change by Week 104, n = 95, 97	1.66 (0.82 to 2.51)	0.61 (-0.22 to 1.44)		
% change by Week 130, n = 91, 87	1.70 (0.80 to 2.61)	0.30 (-0.60 to 1.20)		
% change by Week 156, n = 79, 77	1.84 (0.86 to 2.84)	0.83 (-0.14 to 1.81)		

Notes:
[15] - Safety Population
[16] - Safety Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Overall week	
Comparison groups	Participants administered VI v Participants administered FF/VI
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage Change from Baseline
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.11
upper limit	0.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events and non-serious adverse events were collected from randomization of the study until 159 weeks.

Adverse event reporting additional description:

Safety Population. The non-serious AEs are reported using a frequency threshold of >3%.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Participants administered VI

Reporting group description:

Following run-in period of 14 to 21 days, eligible participants were administered VI 25 microgram (mcg) once daily via ELLIPTA inhaler for 156 weeks.

Reporting group title	Participants administered FF/VI

Reporting group description:

Following run-in period of 14 to 21 days, eligible participants were administered FF 100 mcg along with VI 25 mcg once daily via ELLIPTA inhaler for 156 weeks.

Serious adverse events	Participants administered VI	Participants administered FF/VI	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 142 (29.58%)	41 / 141 (29.08%)	
number of deaths (all causes)	6	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer stage 0, with cancer in situ			

subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertension			

subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Chest pain			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Contrast media reaction			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Drug hypersensitivity			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectocele			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	10 / 142 (7.04%)	6 / 141 (4.26%)	
occurrences causally related to treatment / all	0 / 13	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 142 (0.70%)	3 / 141 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 142 (1.41%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic respiratory failure			

subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance abuse			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			

subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
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			
Femoral neck fracture			
subjects affected / exposed	0 / 142 (0.00%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hip fracture			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			

subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 142 (1.41%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			

subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac asthma			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
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	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
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 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (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			
Cerebrovascular accident			
subjects affected / exposed	1 / 142 (0.70%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain injury			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			

subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dementia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular disorder			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			

subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis cholestatic			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vesical fistula			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 142 (2.82%)	11 / 141 (7.80%)	
occurrences causally related to treatment / all	1 / 4	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	0 / 142 (0.00%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (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			

Dehydration			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Participants administered VI	Participants administered FF/VI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	126 / 142 (88.73%)	130 / 141 (92.20%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	6 / 142 (4.23%)	2 / 141 (1.42%)	
occurrences (all)	7	3	
Procedural pain			
subjects affected / exposed	6 / 142 (4.23%)	1 / 141 (0.71%)	
occurrences (all)	7	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 142 (7.75%)	10 / 141 (7.09%)	
occurrences (all)	12	10	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 142 (11.27%)	26 / 141 (18.44%)	
occurrences (all)	24	44	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	5 / 142 (3.52%)	4 / 141 (2.84%)	
occurrences (all)	6	4	
Immune system disorders			

Seasonal allergy			
subjects affected / exposed	5 / 142 (3.52%)	2 / 141 (1.42%)	
occurrences (all)	6	2	
Eye disorders			
Cataract			
subjects affected / exposed	3 / 142 (2.11%)	6 / 141 (4.26%)	
occurrences (all)	3	9	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 142 (7.75%)	9 / 141 (6.38%)	
occurrences (all)	12	9	
Abdominal pain upper			
subjects affected / exposed	4 / 142 (2.82%)	7 / 141 (4.96%)	
occurrences (all)	5	10	
Constipation			
subjects affected / exposed	3 / 142 (2.11%)	6 / 141 (4.26%)	
occurrences (all)	4	7	
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 142 (3.52%)	4 / 141 (2.84%)	
occurrences (all)	5	5	
Toothache			
subjects affected / exposed	3 / 142 (2.11%)	5 / 141 (3.55%)	
occurrences (all)	3	8	
Vomiting			
subjects affected / exposed	2 / 142 (1.41%)	5 / 141 (3.55%)	
occurrences (all)	2	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 142 (10.56%)	13 / 141 (9.22%)	
occurrences (all)	15	15	
Oropharyngeal pain			
subjects affected / exposed	8 / 142 (5.63%)	12 / 141 (8.51%)	
occurrences (all)	8	17	
Dyspnoea			
subjects affected / exposed	5 / 142 (3.52%)	6 / 141 (4.26%)	
occurrences (all)	6	6	

Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	5 / 142 (3.52%)	5 / 141 (3.55%)	
occurrences (all)	6	5	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 142 (0.70%)	6 / 141 (4.26%)	
occurrences (all)	1	10	
Anxiety			
subjects affected / exposed	5 / 142 (3.52%)	0 / 141 (0.00%)	
occurrences (all)	5	0	
Depression			
subjects affected / exposed	0 / 142 (0.00%)	5 / 141 (3.55%)	
occurrences (all)	0	5	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	13 / 142 (9.15%)	20 / 141 (14.18%)	
occurrences (all)	27	28	
Pain in extremity			
subjects affected / exposed	6 / 142 (4.23%)	10 / 141 (7.09%)	
occurrences (all)	6	13	
Osteoarthritis			
subjects affected / exposed	9 / 142 (6.34%)	6 / 141 (4.26%)	
occurrences (all)	14	7	
Musculoskeletal pain			
subjects affected / exposed	6 / 142 (4.23%)	4 / 141 (2.84%)	
occurrences (all)	6	6	
Muscle spasms			
subjects affected / exposed	4 / 142 (2.82%)	5 / 141 (3.55%)	
occurrences (all)	4	5	
Osteoporosis			
subjects affected / exposed	4 / 142 (2.82%)	5 / 141 (3.55%)	
occurrences (all)	4	5	
Arthritis			
subjects affected / exposed	5 / 142 (3.52%)	2 / 141 (1.42%)	
occurrences (all)	5	2	

Arthralgia			
subjects affected / exposed	14 / 142 (9.86%)	13 / 141 (9.22%)	
occurrences (all)	15	19	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	31 / 142 (21.83%)	40 / 141 (28.37%)	
occurrences (all)	57	75	
Bronchitis			
subjects affected / exposed	16 / 142 (11.27%)	11 / 141 (7.80%)	
occurrences (all)	23	12	
Influenza			
subjects affected / exposed	5 / 142 (3.52%)	20 / 141 (14.18%)	
occurrences (all)	5	30	
Upper respiratory tract infection			
subjects affected / exposed	13 / 142 (9.15%)	12 / 141 (8.51%)	
occurrences (all)	18	20	
Urinary tract infection			
subjects affected / exposed	12 / 142 (8.45%)	12 / 141 (8.51%)	
occurrences (all)	18	24	
Sinusitis			
subjects affected / exposed	3 / 142 (2.11%)	13 / 141 (9.22%)	
occurrences (all)	3	17	
Pneumonia			
subjects affected / exposed	5 / 142 (3.52%)	8 / 141 (5.67%)	
occurrences (all)	5	8	
Oral candidiasis			
subjects affected / exposed	4 / 142 (2.82%)	7 / 141 (4.96%)	
occurrences (all)	5	13	
Cystitis			
subjects affected / exposed	5 / 142 (3.52%)	5 / 141 (3.55%)	
occurrences (all)	6	7	
Pharyngitis			
subjects affected / exposed	4 / 142 (2.82%)	5 / 141 (3.55%)	
occurrences (all)	5	8	
Herpes zoster			

subjects affected / exposed occurrences (all)	0 / 142 (0.00%) 0	6 / 141 (4.26%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2013	Amendment No.: 01 This protocol amendment is being implemented to revise and clarify exclusion criteria concerning participation in pulmonary rehabilitation programs; clarify the description of DEXA procedures and clinical labs; correction of typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported