Clinical trial results:
A 24-week study to evaluate the effect of fluticasone furoate (GW685698) /vilanterol (GW642444) 100/25 µg Inhalation Powder delivered once-daily via a Novel Dry Powder Inhaler on arterial stiffness compared with placebo and vilanterol in subjects with Chronic Obstructive Pulmonary Disease (COPD).

Summary

EudraCT number	2010-023091-10
Trial protocol	DE NO
Global end of trial date	04 November 2014

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	01 July 2015

Trial information

Trial identification

Sponsor protocol code	HZC113108

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, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	29 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the effect of FF/VI Inhalation Powder 100/25 µg administered once daily compared with placebo on arterial stiffness measured as Aortic Pulse Wave Velocity (aPWV) in subjects with COPD and aPWV ≥ 11.0 m/s at baseline.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 March 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 551
Country: Number of subjects enrolled	Norway: 41
Country: Number of subjects enrolled	Korea, Republic of: 211
Country: Number of subjects enrolled	Philippines: 542
Country: Number of subjects enrolled	Thailand: 253
Country: Number of subjects enrolled	United States: 1413
Worldwide total number of subjects	3011
EEA total number of subjects	592

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)	1685
From 65 to 84 years	1307
85 years and over	19

Subject disposition

Recruitment

Recruitment details:

3011 par. were screened, 559 entered Run-in Period (RIP), of whom 444 randomized and received at >=1 dose of study medication; 430 included in the Intent-to-Treat (ITT) Population. Par. were considered to have completed the TP if they attended Wk 24 and completed the study if also attended the 1-wk follow-up contact and no early withdrawal.

Pre-assignment

Screening details:

Eligible participants (par.) at screening entered a 2-week, single-blind placebo RIP to obtain albuterol (salbutamol) use at Baseline, and to ensure that par.'s COPD was stable at randomization. At the end of the RIP, par. meeting the randomization criteria entered the double-blind treatment period (TP) of 24 weeks (Wk).

Period 1

Period 1 title	2-week, Single-blind Run-In Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	Placebo-Run-in

Arm description:

Participants received placebo once daily (QD) in the morning for 2 weeks. In addition, participants were provided an inhaled short-acting beta2-receptor agonist (SABA), albuterol (salbutamol) (metered dose inhaler [MDI] or nebules), to be used as a rescue medication for relief of chronic obstructive pulmonary disease (COPD) symptoms during the Run-in and Treatment Periods.

Arm type	Placebo
Investigational medicinal product name	Placebo QD
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

QD in the morning via DPI

Number of subjects in period 1	Placebo-Run-in
Started	559
Completed	444
Not completed	115
Did Not Meet Continuation Criteria	102
Consent withdrawn by subject	9
Physician decision	1
Adverse event, non-fatal	1
Lost to follow-up	2

Period 2

Period 2 title	24-week, Double-blind Treatment Period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo QD

Arm description:

Participants received placebo QD in the morning via a dry powder inhaler (DPI) for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

Arm type	Placebo
Investigational medicinal product name	Placebo QD
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

QD in the morning via DPI

Arm title	VI 25 µg QD

Arm description:

Participants received vilanterol (VI) 25 micrograms (µg) inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

Arm type	Experimental
Investigational medicinal product name	Vilanterol 25 µg QD
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

QD in the morning via DPI

Arm title	FF/VI 100/25 µg QD

Arm description:

Participants received fluticasone furoate (FF)/VI 100/25 µg inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

Arm type	Experimental
Investigational medicinal product name	Fluticasone Furoate/Vilanterol 100/25 µg QD
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

QD in the morning via DPI

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Eligible par. at screening entered a 2-week, single-blind placebo RIP to obtain albuterol (salbutamol) use at Baseline, and to ensure that par.'s COPD was stable at randomization. At the end of the RIP, par. meeting the randomization criteria entered the double-blind treatment period (TP) of 24 weeks (Wk).

Number of subjects in period 2[2][3]	Placebo QD	VI 25 µg QD	FF/VI 100/25 µg QD
Started	141	154	135
Completed the Treatment Period	96 [4]	124	110 [5]
Completed	97	124	111
Not completed	44	30	24
Physician decision	3	1	1
Consent withdrawn by subject	7	4	1
Adverse event, non-fatal	8	6	7
Lack of Efficacy-Sub-Reason Exacerbation	13	13	6
Protocol-defined Stopping Criteria	4	3	6
Lack of Efficacy-No Sub-Reason	2	-	-
Lost to follow-up	3	-	-
Protocol deviation	4	3	3

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 3011 participants (par.) were screened, 559 entered the Run-in Period (RIP), of whom 444 were randomized and received at least one dose of study medication; 430 of these were included in the Intent-to-Treat (ITT) Population.

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 3011 participants (par.) were screened, 559 entered the Run-in Period (RIP), of whom 444 were randomized and received at least one dose of study medication; 430 of these were included in the Intent-to-Treat (ITT) Population.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone reflects the number of participants completing the Treatment Period. Par. were considered to have completed the TP if they attended Wk 24 and completed the study if also attended the 1-wk follow-up contact and no early withdrawal.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone reflects the number of participants completing the Treatment Period. Par. were considered to have completed the TP if they attended Wk 24 and completed the study if also attended the 1-wk follow-up contact and no early withdrawal.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo QD
Reporting group description:	
Participants received placebo QD in the morning via a dry powder inhaler (DPI) for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.	
Reporting group title	VI 25 µg QD
Reporting group description:	
Participants received vilanterol (VI) 25 micrograms (µg) inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.	
Reporting group title	FF/VI 100/25 µg QD
Reporting group description:	
Participants received fluticasone furoate (FF)/VI 100/25 µg inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.	

Reporting group values	Placebo QD	VI 25 µg QD	FF/VI 100/25 µg QD
Number of subjects	141	154	135
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	68.2	68.7	68.5
standard deviation	± 8.1	± 7.69	± 8.01
Gender categorical			
Units: Subjects			
Female	22	36	31
Male	119	118	104
Race			
Units: Subjects			
African American/African Heritage	7	4	6
Asian - Central/South Asian Heritage	1	0	0
Asian - East Asian Heritage	21	23	18
Asian - South East Asian Heritage	45	51	47
Asian - Mixed Race	1	0	0
White - Arabic/North African Heritage	1	1	0
White - White/Caucasian/European Heritage	64	75	64
Mixed Race	1	0	0

Reporting group values	Total		
Number of subjects	430		
Age categorical			
Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	89		
Male	341		
Race Units: Subjects			
African American/African Heritage	17		
Asian - Central/South Asian Heritage	1		
Asian - East Asian Heritage	62		
Asian - South East Asian Heritage	143		
Asian - Mixed Race	1		
White - Arabic/North African Heritage	2		
White - White/Caucasian/European Heritage	203		
Mixed Race	1		

End points

End points reporting groups

Reporting group title	Placebo-Run-in

Reporting group description:

Participants received placebo once daily (QD) in the morning for 2 weeks. In addition, participants were provided an inhaled short-acting beta2-receptor agonist (SABA), albuterol (salbutamol) (metered dose inhaler [MDI] or nebules), to be used as a rescue medication for relief of chronic obstructive pulmonary disease (COPD) symptoms during the Run-in and Treatment Periods.

Reporting group title	Placebo QD

Reporting group description:

Participants received placebo QD in the morning via a dry powder inhaler (DPI) for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

Reporting group title	VI 25 µg QD

Reporting group description:

Participants received vilanterol (VI) 25 micrograms (µg) inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

Reporting group title	FF/VI 100/25 µg QD

Reporting group description:

Participants received fluticasone furoate (FF)/VI 100/25 µg inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

Primary: Mean change from Baseline (BL) in Aortic Pulse Wave Velocity (aPWV) at the end of the 24-week Treatment Period (Day 168)

End point title	Mean change from Baseline (BL) in Aortic Pulse Wave Velocity (aPWV) at the end of the 24-week Treatment Period (Day 168)

End point description:

PWV is defined as the speed of travel of the pressure pulse along an arterial segment and can be obtained for any arterial segment accessible to palpation. aPWV is measured with tonometers positioned transcutaneously at the base of the common carotid artery and over the femoral artery. PWV increases with arterial stiffness and is defined by the Moens-Korteweg equation: PWV=square root of (Eh/2ρR), where E is Young's modulus of the arterial wall, h is the wall thickness, R is the arterial radius at the end of diastole, and ρ is the blood density. Change from BL was calculated as the Day 168 value minus the BL value. The analysis was performed using a repeated measures model with covariates of treatment, visit, age, gender, smoking history, history of exacerbation strata, geographical region, BL aPWV and interaction terms of BL by visit and treatment by visit. ITT Population: all randomized par. who received at least one dose of study medication.

End point type	Primary

End point timeframe:

BL to Day 168
Number of par. presented represent those with data available at the time point being presented; however, all par. in the ITT Population without missing covariate information and with at least one post BL measurement are included.

End point values	Placebo QD	VI 25 µg QD	FF/VI 100/25 µg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	117	103	
Units: meters per second (m/sec)				
least squares mean (standard error)	-1.97 (± 0.279)	-1.95 (± 0.241)	-1.75 (± 0.256)	

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo QD v VI 25 µg QD
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.969 [1]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	0.74

Notes:

[1] - Restricted maximum likelihood (REML)-based repeated measures approach (MMRM)

Statistical analysis title	Analysis 2
Comparison groups	Placebo QD v FF/VI 100/25 µg QD
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.568 [2]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.96

Notes:

[2] - Restricted maximum likelihood (REML)-based repeated measures approach (MMRM)

Statistical analysis title	Analysis 3
Comparison groups	VI 25 µg QD v FF/VI 100/25 µg QD

Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.566 [3]
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	0.89

Notes:

[3] - Restricted maximum likelihood (REML)-based repeated measures approach (MMRM)

Secondary: Change from BL in clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at Day 168

End point title	Change from BL in clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at Day 168

End point description:

Pulmonary function was measured by forced expiratory volume in one second (FEV1), defined as the maximal amount of air that can be forcefully exhaled from the lungs in one second. Trough FEV1 measurements were taken electronically by spirometry at Screening, Days 1, 28, 84, 126, and 168. BL FEV1 was defined as the mean of the assessments made 30 minutes pre-dose and 5 minutes pre-dose on Treatment Day 1. Trough FEV1 was defined as the mean of the FEV1 values obtained 24 hours after previous morning's dosing. Change from BL was calculated as the average at each visit minus the BL value. Analysis was preformed using a repeated measures model with covariates of visit, treatment, history of exacerbation strata, geographical region, BL FEV1 and interaction terms of BL by visit and treatment by visit.

End point type	Secondary

End point timeframe:

BL to Day 168
Number of par. presented represent those with data available at the time point being presented; however, all par. in the ITT Population without missing covariate information and with at least one post BL measurement are included.

End point values	Placebo QD	VI 25 µg QD	FF/VI 100/25 µg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	96	123	111	
Units: Liters (L)				
least squares mean (standard error)	-0.049 (± 0.0221)	0.033 (± 0.0202)	0.106 (± 0.021)	

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo QD v VI 25 µg QD

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 [4]
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	0.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.141

Notes:

[4] - Nominal p-value; Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Statistical analysis title	Analysis 2
Comparison groups	Placebo QD v FF/VI 100/25 µg QD
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	0.155
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.095
upper limit	0.215

Notes:

[5] - Nominal p-value; Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Statistical analysis title	Analysis 3
Comparison groups	VI 25 µg QD v FF/VI 100/25 µg QD
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 [6]
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	0.074
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.131

Notes:

[6] - Nominal p-value; Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Secondary: Mean number of occasions rescue medication [albuterol (salbutamol)]

used during a 24-hour period averaged over the entire 24-week Treatment Period	
End point title	Mean number of occasions rescue medication [albuterol (salbutamol)] used during a 24-hour period averaged over the entire 24-week Treatment Period

End point description:

Participants were given daily record cards for daily completion from BL (Week -1) through Week 24 (Visit 6) each morning and prior to taking study medication (i.e., single-blind and double-blind study medication) supplemental medication (albuterol [salbutamol] if received) and ipratropium bromide (if received). Participants recorded number of occasions supplemental albuterol/salbutamol (MDI and/or nebules) used over the previous 24 hours and any medical problems that they had experienced and any medication used to treat these medical problems over the previous 24 hours. Analysis was performed using an analysis of covariance (ANCOVA) model with covariates of treatment, BL mean of occasions of rescue medication use (Week -1), history of exacerbation, and geographical region. ITT Population: all randomized participants who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

BL (Week -1), Week 1 to Week 24
Only those participants with at least 1 on treatment rescue medication measurement during the treatment period and without missing covariate information were analyzed.

End point values	Placebo QD	VI 25 µg QD	FF/VI 100/25 µg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	139	152	135	
Units: Occasions per 24 hours				
least squares mean (standard error)	1.97 (± 0.093)	1.5 (± 0.089)	1.47 (± 0.095)	

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo QD v VI 25 µg QD
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	-0.22

Notes:

[7] - Nominal p-value

Statistical analysis title	Analysis 2
Comparison groups	Placebo QD v FF/VI 100/25 µg QD

Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [8]
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.24

Notes:

[8] - Nominal p-value

Statistical analysis title	Analysis 3
Comparison groups	VI 25 µg QD v FF/VI 100/25 µg QD
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.803
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.22

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAE) and non-serious AEs were collected from the start of the double-blind (DB) treatment period (Visit 2) through the follow-up contact (7 days after Visit 6 [Week 25]).

Adverse event reporting additional description:

SAEs and non-serious AEs reported for par. of the Safety Population (Pop) comprised of ITT Pop plus par. from the excluded site who qualified for the ITT Pop. On-treatment AE or SAE is defined as an AE with an onset date on or after the start date of DB study medication, but not later than one day after the last dose of DB study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo QD

Reporting group description:

Participants received placebo QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol) , to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

Reporting group title	VI 25 µg QD

Reporting group description:

Participants received VI 25 µg inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol), to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

Reporting group title	FF/VI 100/25 µg QD

Reporting group description:

Participants received FF/VI 100/25 µg inhalation QD in the morning via a DPI for 24 weeks. In addition, participants were provided an inhaled SABA, albuterol (salbutamol) to be used as a rescue medication for relief of COPD symptoms during the Run-in and Treatment Periods.

Serious adverse events	Placebo QD	VI 25 µg QD	FF/VI 100/25 µg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 145 (3.45%)	12 / 158 (7.59%)	9 / 141 (6.38%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events			
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 145 (0.00%)	0 / 158 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			

subjects affected / exposed	0 / 145 (0.00%)	1 / 158 (0.63%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal cancer			
subjects affected / exposed	0 / 145 (0.00%)	0 / 158 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung neoplasm malignant			
subjects affected / exposed	1 / 145 (0.69%)	0 / 158 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 145 (0.00%)	0 / 158 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	0 / 145 (0.00%)	1 / 158 (0.63%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 145 (0.00%)	0 / 158 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 145 (0.00%)	0 / 158 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 145 (0.00%)	0 / 158 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Angina pectoris			
subjects affected / exposed	1 / 145 (0.69%)	0 / 158 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 145 (0.69%)	0 / 158 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 145 (0.00%)	1 / 158 (0.63%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 145 (0.00%)	1 / 158 (0.63%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Faecaloma			
subjects affected / exposed	0 / 145 (0.00%)	0 / 158 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 158 (0.00%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 158 (0.63%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 145 (0.69%)	5 / 158 (3.16%)	2 / 141 (1.42%)
occurrences causally related to treatment / all	1 / 1	0 / 5	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 145 (0.00%)	1 / 158 (0.63%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 145 (0.00%)	1 / 158 (0.63%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 145 (1.38%)	1 / 158 (0.63%)	2 / 141 (1.42%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 158 (0.63%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 158 (0.00%)	1 / 141 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 145 (0.00%)	1 / 158 (0.63%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 158 (0.63%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Type 2 diabetes mellitus			
subjects affected / exposed	0 / 145 (0.00%)	1 / 158 (0.63%)	0 / 141 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo QD	VI 25 µg QD	FF/VI 100/25 µg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 145 (16.55%)	27 / 158 (17.09%)	34 / 141 (24.11%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 145 (3.45%)	9 / 158 (5.70%)	8 / 141 (5.67%)
occurrences (all)	6	11	13
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 145 (0.69%)	2 / 158 (1.27%)	6 / 141 (4.26%)
occurrences (all)	1	2	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 145 (2.76%)	1 / 158 (0.63%)	5 / 141 (3.55%)
occurrences (all)	4	1	7
Back pain			
subjects affected / exposed	5 / 145 (3.45%)	5 / 158 (3.16%)	4 / 141 (2.84%)
occurrences (all)	5	8	8
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 145 (3.45%)	12 / 158 (7.59%)	9 / 141 (6.38%)
occurrences (all)	5	14	11
Oral candidiasis			
subjects affected / exposed	1 / 145 (0.69%)	2 / 158 (1.27%)	9 / 141 (6.38%)
occurrences (all)	1	2	12
Upper respiratory tract infection			
subjects affected / exposed	6 / 145 (4.14%)	4 / 158 (2.53%)	2 / 141 (1.42%)
occurrences (all)	9	4	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 August 2011	To revise Inclusion Criterion #8: Baseline aortic pulse wave velocity

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported