Clinical trial results:
A 12-Week Study to Evaluate the Efficacy and Safety of Fluticasone Furoate/Vilanterol Inhalation Powder (FF/VI) 100/25 mcg Once Daily Compared with Vilanterol Inhalation Powder (VI) 25 mcg Once Daily in Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Summary

EudraCT number	2013-004548-44
Trial protocol	BG PL RO
Global end of trial date	08 July 2015

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	30 June 2016

Trial information

Trial identification

Sponsor protocol code	200820

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02105974
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,
Scientific contact	GSK Response Center, GlaxoSmithKline, +1 8664357343,

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 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the contribution on lung function (as measured by trough forced expiratory volume in one second [FEV1]) of fluticasone furoate (FF) 100 mcg to the FF/vilanterol (VI) 100/25 mcg QD combination by comparison of the latter with VI 25 mcg QD and the safety of FF/VI 100/25 mcg QD over a 12-week treatment period in subjects with COPD. ELLIPTA™ is a registered trademark of GlaxoSmithKline.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 April 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	United States: 284
Country: Number of subjects enrolled	Germany: 223
Country: Number of subjects enrolled	Japan: 653
Country: Number of subjects enrolled	Korea, Republic of: 135
Country: Number of subjects enrolled	Poland: 145
Country: Number of subjects enrolled	Romania: 182
Country: Number of subjects enrolled	Russian Federation: 250
Country: Number of subjects enrolled	South Africa: 116
Country: Number of subjects enrolled	Taiwan: 78
Country: Number of subjects enrolled	Ukraine: 220
Country: Number of subjects enrolled	Bulgaria: 137
Worldwide total number of subjects	2423
EEA total number of subjects	687

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)	1074
From 65 to 84 years	1325
85 years and over	24

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 238 sites. Participants (par) with a history of chronic obstructive pulmonary disease (COPD) meeting eligibility criteria at screening were enrolled in a 2-week, single-blind (placebo) run-in period to obtain baseline use of albuterol (salbutamol), COPD symptom scores and disease stability.

Pre-assignment

Screening details:

Par meeting continuation criteria during the run-in period were randomized (1:1) to receive FF/VI 100/25 µg QD or VI 25 µg QD. Of the 2423 par screened, 1622 were randomized. 1620 received at least one dose of double-blind study medication and comprised the Intent-to-Treat population.

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) or oxitropium bromide (applicable sites in Japan), 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	2265
Completed	1622
Not completed	643
Study closed/terminated	1
Consent withdrawn by subject	23
Adverse event, non-fatal	6
Did not meet inclusion/exclusion criteria	603
Lost to follow-up	2

Investigator discretion	8

Period 2

Period 2 title	12 Week (Wk) Treatment Period (TP)
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	FF/VI 100/25 µg QD

Arm description:

Participants received fluticasone furoate/vilaterol (FF/VI) 100/25 microgram(µg) inhalation via a dry powder inhaler (DPI) once daily (QD) in the morning for 12 weeks. In addition, all participants were provided with albuterol (salbutamol) or oxitropium bromide (applicable sites in Japan) to be used as rescue medication (via metered-dose inhaler [MDI] or nebules) for relief of COPD symptoms during the Run-In and Treatment Periods.

Arm type	Experimental
Investigational medicinal product name	Fluticasone furoate/vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Single dose of combination of FF 100 microgram (µg) and VI 25 µg in morning via ELLIPTA for 12 weeks

Arm title	VI 25 µg QD

Arm description:

Participants received VI 25 µg inhalation QD via a DPI in the morning for 12 weeks. In addition, all participants were provided with albuterol (salbutamol) or oxitropium bromide (applicable sites in Japan) to be used as rescue medication (via metered-dose inhaler [MDI] or nebules) for relief of COPD symptoms during the Run-In and Treatment Periods.

Arm type	Active comparator
Investigational medicinal product name	Vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Single dose of VI 25 µg in morning via ELLIPTA for 12 weeks

Notes:

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

Justification: Eligible participants (par.) at screening entered a 2-week, single-blind placebo run-in period (RIP) to obtain Baseline assessments of albuterol (salbutamol) use, COPD symptom scores and disease stability. At the end of the RIP, par. meeting the continuation criteria entered the double-blind treatment period (TP) of 24 weeks (Wk).

Number of subjects in period 2[2][3]	FF/VI 100/25 µg QD	VI 25 µg QD
Started	806	814
Completed the treatment (trt) period	764	754 [4]
Completed	764	756
Not completed	42	58
Physician decision	7	4
Adverse event, non-fatal	14	18
Participant reached stopping criteria	1	2
Withdrawal by Subject	12	18
Lost to follow-up	-	1
Lack of efficacy	6	9
Protocol deviation	2	6

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 2,423 par were consented for the study, of whom 158 were withdrawn during the Pre-Screen period. A total of 2,265 par were screened, of whom 1,622 were randomized; 1,620 received at least one dose of double-blind study medication and comprised 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: Of the 1622 subjects who completed period 1, 2 subjects were randomized in error and were not included as starting period 2.

[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: Subjects (756) were considered to have completed the study if they attended the last clinic visit (Visit 7), had a follow-up phone contact and did not have an early withdrawal visit. Subjects were considered to have completed the treatment period (754) if they attended the last clinic visit (Visit 7) and did not withdraw at the visit and had an exposure stop date on or after the day prior to Visit 7.

Baseline characteristics

Reporting groups	
Reporting group title	FF/VI 100/25 µg QD
Reporting group description:	
Participants received fluticasone furoate/vilaterol (FF/VI) 100/25 microgram(µg) inhalation via a dry powder inhaler (DPI) once daily (QD) in the morning for 12 weeks. In addition, all participants were provided with albuterol (salbutamol) or oxitropium bromide (applicable sites in Japan) to be used as rescue medication (via metered-dose inhaler [MDI] or nebules) 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 via a DPI in the morning for 12 weeks. In addition, all participants were provided with albuterol (salbutamol) or oxitropium bromide (applicable sites in Japan) to be used as rescue medication (via metered-dose inhaler [MDI] or nebules) for relief of COPD symptoms during the Run-In and Treatment Periods.	

Reporting group values	FF/VI 100/25 µg QD	VI 25 µg QD	Total
Number of subjects	806	814	1620
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	65.3	65.4	
standard deviation	± 8.58	± 9.02	-
Gender categorical Units: Subjects			
Female	201	189	390
Male	605	625	1230
Race Units: Subjects			
African American/African Heritage	6	10	16
Asian - East Asian Heritage	77	77	154
Asian - Japanese Heritage	185	185	370
White - White/Caucasian/European Heritage	538	541	1079
Mixed Race	0	1	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) or oxitropium bromide (applicable sites in Japan), 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	FF/VI 100/25 µg QD

Reporting group description:

Participants received fluticasone furoate/vilaterol (FF/VI) 100/25 microgram(µg) inhalation via a dry powder inhaler (DPI) once daily (QD) in the morning for 12 weeks. In addition, all participants were provided with albuterol (salbutamol) or oxitropium bromide (applicable sites in Japan) to be used as rescue medication (via metered-dose inhaler [MDI] or nebules) 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 via a DPI in the morning for 12 weeks. In addition, all participants were provided with albuterol (salbutamol) or oxitropium bromide (applicable sites in Japan) to be used as rescue medication (via metered-dose inhaler [MDI] or nebules) for relief of COPD symptoms during the Run-In and Treatment Periods.

Primary: Mean change from baseline (BL) in Clinic Visit trough (pre-bronchodilator and pre-dose) FEV1 (to evaluate the contribution of FF), on Treatment Day 84 (visit 7, week 12)

End point title	Mean change from baseline (BL) in Clinic Visit trough (pre-bronchodilator and pre-dose) FEV1 (to evaluate the contribution of FF), on Treatment Day 84 (visit 7, week 12)

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 on Days 2, 14, 28, 56 and 84. BL was defined as the mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Treatment Day 1. Trough FEV1 was defined as the mean of the FEV1 values obtained 23 and 24 hours after previous morning's dosing. Change from BL was calculated as the average at each visit minus the BL value. Analysis was performed using a repeated measures model with covariates of treatment, reversibility status (stratum), baseline, Region, Day by Baseline, and Day by treatment interactions.

End point type	Primary

End point timeframe:

Baseline to Day 84. 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	FF/VI 100/25 µg QD	VI 25 µg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	759	749		
Units: Liter				
least squares mean (standard error)	0.116 (± 0.0074)	0.082 (± 0.0075)		

Statistical analyses

Statistical analysis title	STATISTICAL ANALYSIS 1
Comparison groups	FF/VI 100/25 µg QD v VI 25 µg QD
Number of subjects included in analysis	1508
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [1]
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	0.034
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.014
upper limit	0.055

Notes:

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

Secondary: Percentage of rescue-free 24-hour periods over the entire 12-week treatment period

End point title	Percentage of rescue-free 24-hour periods over the entire 12-week treatment period

End point description:

Par were given a Daily Diary for completion each morning and prior to taking study medication (single- and double-blind), supplemental medication albuterol [salbutamol] (if received) or oxitropium bromide (applicable sites in Japan) and ipratropium (if applicable) starting from the morning following the Screening Visit (Week-2) through Week 12 (Visit 7). Par recorded the number of occasions supplemental albuterol/salbutamol or oxitropium bromide 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. Rescue-free 24-hour periods are defined as the 24-hour periods in which the rescue medication was not used. The percentage of such 24-hour periods are summarized for the entire treatment period (12 weeks). Analysis was performed using an analysis of covariance (ANCOVA) model with covariates of treatment, reversibility status (stratum), baseline (week -1) and region.

End point type	Secondary

End point timeframe:

BL (Week -1), Week 1 to Week 12. 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	FF/VI 100/25 µg QD	VI 25 µg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	801	802		
Units: Percentage of rescue-free periods				
least squares mean (standard error)	47.03 (± 1.07)	44.41 (± 1.069)		

Statistical analyses

Statistical analysis title	STATISTICAL ANALYSIS 1
Comparison groups	FF/VI 100/25 µg QD v VI 25 µg QD
Number of subjects included in analysis	1603
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.084
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	2.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	5.59

Secondary: Time to First On-treatment Moderate or Severe COPD Exacerbation

End point title	Time to First On-treatment Moderate or Severe COPD Exacerbation

End point description:

Time to first on-treatment exacerbation was analysed using a Cox proportional hazards model with terms for treatment, reversibility status and percent predicted FEV1 at screening. Exacerbation of COPD is defined by a worsening of symptoms requiring additional treatment. Moderate COPD exacerbation is worsening symptoms of COPD that require treatment with antibiotics and/or systemic corticosteroids. Severe COPD exacerbation is worsening symptoms of COPD that require treatment with in-patient hospitalization. The number of participants with On-Treatment moderate or severe COPD exacerbations are presented.

End point type	Secondary

End point timeframe:

From the start of double blind study medication until visit 7 (week 12)/Early withdrawal

End point values	FF/VI 100/25 µg QD	VI 25 µg QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	806	814		
Units: Participants				
number (not applicable)	69	114		

Statistical analyses

Statistical analysis title	STATISTICAL ANALYSIS 2
Comparison groups	FF/VI 100/25 µg QD v VI 25 µg QD
Number of subjects included in analysis	1620
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.78

Notes:

[2] - Nominal p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of double-blind (DB) study treatment (Visit 2) through the follow up contact (up to 13 weeks).

Adverse event reporting additional description:

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	18.0

Reporting groups

Reporting group title	VI 25 µg QD

Reporting group description:

Participants received VI 25 µg inhalation QD via a DPI in the morning for 12 weeks. In addition, all participants were provided with albuterol (salbutamol) or oxitropium bromide (applicable sites in Japan) to be used as rescue medication (via metered-dose inhaler (MDI) or nebules) 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/vilaterol (FF/VI) 100/25 microgram(µg) inhalation via a dry powder inhaler (DPI) once daily (QD) in the morning for 12 weeks. In addition, all participants were provided with albuterol (salbutamol) or oxitropium bromide (applicable sites in Japan) to be used as rescue medication (via metered-dose inhaler (MDI) or nebules) for relief of COPD symptoms during the Run-In and Treatment Periods.

Serious adverse events	VI 25 µg QD	FF/VI 100/25 µg QD	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 814 (4.30%)	27 / 806 (3.35%)	
number of deaths (all causes)	3	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	1 / 814 (0.12%)	1 / 806 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			

subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	0 / 814 (0.00%)	1 / 806 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	0 / 814 (0.00%)	1 / 806 (0.12%)	
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	0 / 814 (0.00%)	1 / 806 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral adenoma			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 814 (0.00%)	2 / 806 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	17 / 814 (2.09%)	10 / 806 (1.24%)	
occurrences causally related to treatment / all	0 / 20	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic respiratory failure			
subjects affected / exposed	0 / 814 (0.00%)	1 / 806 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epistaxis			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 814 (0.00%)	1 / 806 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 814 (0.00%)	1 / 806 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			

subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (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			
Contusion			
subjects affected / exposed	0 / 814 (0.00%)	1 / 806 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 814 (0.12%)	1 / 806 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 814 (0.00%)	1 / 806 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 814 (0.00%)	1 / 806 (0.12%)	
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	0 / 814 (0.00%)	1 / 806 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 814 (0.00%)	2 / 806 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	0 / 814 (0.00%)	1 / 806 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			

subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (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 / 814 (0.49%)	2 / 806 (0.25%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 814 (0.00%)	1 / 806 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (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	0 / 814 (0.00%)	1 / 806 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 814 (0.12%)	0 / 806 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	0 / 814 (0.00%)	1 / 806 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 814 (0.00%)	1 / 806 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	VI 25 µg QD	FF/VI 100/25 µg QD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 814 (7.86%)	72 / 806 (8.93%)	
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 814 (2.33%)	29 / 806 (3.60%)	
occurrences (all)	32	49	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	48 / 814 (5.90%)	49 / 806 (6.08%)	
occurrences (all)	53	56	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported