Protocol Registration Receipt
09/12/2013

Grantor: CDER IND/IDE Number: 070297, 077855 Serial Number: 0082, 0053

A 6-month Study to Evaluate the Efficacy and Safety of Fluticasone Furoate (FF)/GW642444 Inhalation Powder in Subjects With Chronic Obstructive Pulmonary Disease (COPD)

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01053988

Purpose

The Purpose of this study is to assess the efficacy and safety of two strengths of the FF/GW642444 Inhalation Powder in subjects with chronic obstructive pulmonary disease (COPD)

Condition	Intervention	Phase
Pulmonary Disease, Chronic Obstructive	Drug: FF/GW642444 Inhalation Powder	Phase 3

Condition	Intervention	Phase
	Drug: FF Inhalation Powder Drug: GW642444 Inhalation Powder Drug: Placebo	

Study Type: Interventional

Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study

Official Title: A 24-Week Study to Evaluate the Efficacy and Safety of Fluticasone Furoate (FF)/GW642444 Inhalation Powder and the Individual Components Delivered Once Daily (AM) Via a Novel Dry Powder Inhaler Compared With Placebo in Subjects With Chronic Obstructive Pulmonary Disease (COPD)

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours Post-dose at Day 168 [Time Frame: Baseline (BL) to Day 168] [Designated as safety issue: No]

  Co-Primary Endpoint: 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. Serial FEV1 measurements were taken electronically by spirometry at BL, weeks 2, 8, 12, and 84 (Day 168). Weighted mean (WM) was calculated using the 0 - 4 h post-dose FEV1 measurements that included the pre-dose (Day 1: 30 minutes [min] and 5 min prior to dosing; other serial visits:23 and 24 h after previous morning dose) and post-dose (5, 15, and 30 min and 1, 2, and 4 h) assessments. BL FEV1 is the mean of the two assessments made 30 and 5 min pre-dose at Day 1. WM change from BL was the WM at the visit minus the BL value. Analysis was performed using a repeated measures model with covariates of treatment, smoking status at screening (stratum), BL- mean of the two assessments made 30 and 5 min pre-dose on Day 1, centre grouping, Day, Day by BL and Day by treatment interactions.
- Change From Baseline in Clinic Visit Trough (Pre-bronchodilator and Pre-dose) FEV1 at Day 169 [Time Frame: Baseline to Day 169] [Designated as safety issue: No]

  Co-Primary Endpoint: 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, 7, 14, 28, 56, 84, 112, 140, 168, and 169. BL 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 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, smoking status at screening (stratum), BL - mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Day 1, centre grouping, Day, Day by BL and Day by treatment interactions.

Secondary Outcome Measures:

- Change From Baseline in Chronic Respiratory Disease Questionnaire Self-administered Standardized (CRQ-SAS) Dyspnea Score at Day 168 [Time Frame: Baseline to Day 168] [Designated as safety issue: No]

Considered an 'Other' endpoint by FDA. CRQ-SAS measures 4 domains (mastery, fatigue, emotional function, and dyspnea) of functioning of participants with COPD: mastery (amount of control the participant feels he/she has over COPD symptoms); fatigue (how tired the participant feels); emotional function (how anxious/depressed the participant feels); and dyspnea (how short of breath the participant feels during physical activities). Each domain is measured on a scale of 1-7 (1=maximum impairment; 7=no impairment). Each domain score is calculated separately. Current assessment was done only for dyspnea domain. BL scores are the derived scores for each domain and total at Day 1 pre-dose. Change from BL was calculated as the average at each visit minus the BL value. Analysis performed used a repeated measures model with covariates of treatment, smoking status at screening (stratum), BL (derived scores at Day 1 pre-dose), centre grouping, Day, Day by BL and Day by treatment interactions.

- Change From Baseline in Peak Post-dose FEV1 (0-4 Hour) on Day 1 [Time Frame: Baseline and Day 1] [Designated as safety issue: No]

  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. BL FEV1 is defined as the mean of the assessments made 30 minutes pre-dose and immediately pre-dose on Day 1. If one of these two assessments was missing then BL was defined as the single pre-dose FEV1 value on Day 1. Peak post-dose FEV1 (0-4 hours) is the maximum post-dose FEV1 recorded over the nominal timepoints of 5, 15 and 30 min, 1, 2 and 4 hours post the Day 1 dose. Change from BL is calculated as the peak post-dose FEV1 (0-4 hour) on Day 1 minus BL FEV1. Analysis performed used an Analysis of Covariance (ANCOVA) model with covariates of treatment, smoking status at screening (stratum), BL - mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Day 1, and centre grouping.

- Time to Onset (Increase of 100 Milliliter [mL] From Baseline in 0-4 Hours Post-dose FEV1) on Treatment Day 1 [Time Frame: Baseline and Day 1] [Designated as safety issue: No]

  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. Baseline FEV1 is defined as the mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Day 1. Time to onset on Treatment Day 1 is defined as a 100 mL increase from Baseline in FEV1. Time to increase of 100 mL from Baseline was calculated over the 5, 15, 30 minutes, and 1, 2, and 4 hours time points. A participant who had at least one post-dose FEV1 on Day 1, but did not achieve a 100 mL or more increase from Baseline at any scheduled time-point at which FEV1 was assessed up to and including 4 hours was censored.

Enrollment: 1031
Study Start Date: October 2009
Study Completion Date: February 2011
Primary Completion Date: February 2011

Arms	Assigned Interventions
Experimental: FF/GW642444 Inhalation Powder Inhaled Corticosteroid (ICS)/ Long Acting Beta Agonist(LABA)	Drug: FF/GW642444 Inhalation Powder Inhaled Corticosteroid (ICS)/ Long Acting Beta Agonist(LABA) for COPD Other Names: FF Inhalation Powder

Arms	Assigned Interventions
	Placebo GW642444 Inhalation Powder
Experimental: FF Inhalation Powder Inhaled Corticosteroid (ICS)	Drug: FF Inhalation Powder Inhaled Corticosteroid (ICS)
Experimental: GW642444 Inhalation Powder Long Acting Beta Agonist(LABA)	Drug: GW642444 Inhalation Powder Long Acting Beta Agonist(LABA)
Placebo Comparator: Placebo Placebo	Drug: Placebo Placebo
Experimental: FF/GW642444 Inhalation Pwdr Inhaled Corticosteroid (ICS)/ Long Acting Beta Agonist(LABA)	Drug: FF/GW642444 Inhalation Powder Inhaled Corticosteroid (ICS)/ Long Acting Beta Agonist(LABA) for COPD Other Names: FF Inhalation Powder Placebo GW642444 Inhalation Powder

Eligibility

Ages Eligible for Study: 40 Years and older
Genders Eligible for Study: Both

Inclusion Criteria:

- Type of subject: outpatient
- Informed consent: Subjects must give their signed and dated written informed consent to participate.
- Gender: Male or female subjects A female is eligible to enter and participate in the study if she is of:
- Non-child bearing potential OR
- Child bearing potential, has a negative pregnancy test at screening, and agrees to one of the acceptable contraceptive methods defined in the protocol
- Age: ≥40 years of age at Screening (Visit 1)

- COPD diagnosis: Subjects with a clinical history of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society [Celli, 2004]
- Tobacco use: Subjects with a current or prior history of ≥10 pack-years of cigarette smoking at Screening (Visit 1).
- Severity of Disease: Subjects with a Screening (Visit 1) measured post-albuterol/salbutamol:
- FEV1/FVC ratio of ≤0.70 and
- FEV1 ≤70% of predicted normal values
- Dyspnea: Achieved a score of ≥2 on the Modified Medical Research Council Dyspnea Scale (mMRC) at Screening (Visit 1).

Exclusion Criteria:

Subjects meeting any of the following criteria must not be enrolled in the study:

- Pregnancy: Women who are pregnant or lactating or are planning on becoming pregnant during the study.
- Asthma: Subjects with a current diagnosis of asthma
- α1-antitrypsin deficiency: Subjects with α1-antitrypsin deficiency as the underlying cause of COPD
- Other respiratory disorders: Subjects with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases, or other active pulmonary diseases
- Lung resection: Subjects with lung volume reduction surgery within the 12 months prior to Screening (Visit 1)
- Chest X-ray (or CT scan): Subjects with a chest X-ray (or CT scan) that reveals evidence of clinically significant abnormalities not believed to be due to the presence of COPD.
- Hospitalization: Subjects who are hospitalized due to poorly controlled COPD within 12 weeks of Visit 1.
- Poorly controlled COPD: Subjects with poorly controlled COPD, defined as the occurrence of the following in the 6 weeks prior to Visit 1: Acute worsening of COPD that is managed by subject with corticosteroids or antibiotics or that requires treatment prescribed by a physician.
- Lower respiratory tract infection: Subjects with lower respiratory tract infection that required the use of antibiotics within 6 weeks prior to Visit 1.
- Other diseases/abnormalities: Subjects with historical or current evidence of clinically significant cardiovascular (i.e., pacemaker), neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or haematological abnormalities that are uncontrolled.
- Peptic Ulcer disease: Subjects with clinically significant peptic ulcer disease that is uncontrolled.
- Hypertension: Subjects with clinically significant hypertension that is uncontrolled.
- Cancer: Subjects with carcinoma that has not been in complete remission for at least 5 years. Carcinoma in situ of the cervix, squamous cell carcinoma and basal cell carcinoma of the skin would not be excluded if the subject has been considered cured within 5 years since diagnosis.
- Drug/food allergy: Subjects with a history of hypersensitivity to any of the study medication or components of the inhalation powder
- Drug/alcohol abuse: Subjects with a known or suspected history of alcohol or drug abuse within the last 2 years
- Medication prior to spirometry: Subjects who are medically unable to withhold their albuterol/salbutamol and/or their ipratropium 4 hours prior to spirometry testing at each study visit
- Additional medication: Use of certain medications such as bronchodilators and corticosteroids for the protocol-specified times prior to Visit 1 (the Investigator will discuss the specific medications)
- Oxygen therapy: Subjects receiving treatment with long-term oxygen therapy (LTOT) or nocturnal oxygen therapy required for greater than 12 hours a day.

Oxygen prn use (i.e., ≤12 hours per day) is not exclusionary.

- Sleep apnea: Subjects with clinically significant sleep apnea who require use of continuous positive airway pressure (CPAP) device or non-invasive positive pressure ventilation (NIPPV) device.
- Pulmonary rehabilitation: Subjects who have participated in the acute phase of a Pulmonary Rehabilitation Program within 4 weeks prior to Screening (Visit 1) or who will enter the acute phase of a Pulmonary Rehabilitation Program during the study.
- Non-compliance: Subjects at risk of non-compliance, or unable to comply with the study procedures. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits.
- Questionable validity of consent: Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation or other conditions that will limit the validity of informed consent to participate in the study.
- Prior use of study medication/other investigational drugs
- Affiliation with investigator site: Study investigators, sub-investigators, study coordinators, employees of a participating investigator or immediate family members of the aforementioned are excluded from participating in this study.

Contacts and Locations

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Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Publications:

Kerwin EM, Scott-Wilson C, Sanford L, Rennard S, Agusti A, Barnes N, Crim C. A randomised trial of fluticasone furoate/vilanterol (50/25 µg; 100/25 µg) on lung function in COPD. Respir Med. 2013;107(4):560-569.

Responsible Party:	GlaxoSmithKline
Study ID Numbers:	112206
Health Authority:	United States: Food and Drug Administration

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Study Results

Participant Flow

Pre-Assignment Details

Eligible participants (par.) completed a 2-week single-blind (placebo) Run-in Period (RIP) to assess Baseline rescue use, symptoms, disease stability. Par. were then randomized to a 24-week Treatment Period. A total of 1804 par. were screened, 1390 entered the RIP, of whom 1031 were randomized, 1030 received at least one dose of study medication.

Reporting Groups

	Description
Placebo Run-in	Participants received placebo once daily (OD) in the morning for 2 weeks.
Placebo	Participants received placebo once daily (OD) in the morning from the dry powder inhaler (DPI) for 24 weeks.
FF 100 µg OD	Participants received Fluticasone Furoate (FF) 100 micrograms (µg) OD in the morning from the DPI for 24 weeks.
VI 25 µg OD	Participants received Vilanterol (VI [GW642444]) 25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 50/25 µg OD	Participants received FF/VI 50/25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 100/25 µg OD	Participants received FF/VI 100/25 µg OD in the morning from the DPI for 24 weeks.

2-week, Single-blind Run-In Period

	Placebo Run-in	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
Started	1390	0	0	0	0	0
Completed	1030	0	0	0	0	0
Not Completed	360	0	0	0	0	0
Did Not Meet Continuation Criteria	220	0	0	0	0	0
Study Closed/Terminated	98	0	0	0	0	0
Withdrawal by Subject	30	0	0	0	0	0

	Placebo Run-in	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
Adverse Event	6	0	0	0	0	0
Physician Decision	5	0	0	0	0	0
Lost to Follow-up	1	0	0	0	0	0

24-week, Double-blind Treatment Period

	Placebo Run-in	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
Started	0	207	206	205	206	206
Completed	0	138	145	142	147	151
Not Completed	0	69	61	63	59	55
Adverse Event	0	15	23	24	17	14
Lack of Efficacy-No Sub-Reason	0	3	2	2	3	0
Lack of Efficacy-Sub-Reason Exacerbation	0	17	16	13	9	12
Protocol Violation	0	3	4	2	1	4
Met Protocol-Defined Stopping Criteria	0	11	5	8	13	9
Lost to Follow-up	0	4	0	2	1	3
Physician Decision	0	5	2	5	5	4
Withdrawal by Subject	0	11	9	7	10	9

Baseline Characteristics

Reporting Groups

	Description
Placebo	Participants received placebo OD in the morning from the DPI for 24 weeks.
FF 100 µg OD	Participants received FF 100 µg OD in the morning from the DPI for 24 weeks.
VI 25 µg OD	Participants received VI 25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 50/25 µg OD	Participants received FF/VI 50/25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 100/25 µg OD	Participants received FF/VI 100/25 µg OD in the morning from the DPI for 24 weeks.

Baseline Measures

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD	Total
Number of Participants	207	206	205	206	206	1030
Age, Continuous [units: Years] Mean (Standard Deviation)	62.1 (8.80)	62.7 (9.47)	63.4 (9.58)	62.8 (9.13)	62.3 (8.49)	62.7 (9.09)
Gender, Male/Female [units: Participants]						
Female	66	74	65	71	69	345
Male	141	132	140	135	137	685

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD	Total
Race/Ethnicity, Customized [units: Participants]						
African American/African Heritage (HER)	7	3	7	6	9	32
American Indian or Alaska Native	1	0	0	1	1	3
Central/South Asian HER	0	0	1	0	0	1
Japanese/East Asian HER/South East Asian HER	44	64	56	43	46	253
White	155	139	141	156	150	741

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours Post-dose at Day 168
Measure Description	Co-Primary Endpoint: 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. Serial FEV1 measurements were taken electronically by spirometry at BL, weeks 2, 8, 12, and 84 (Day 168). Weighted mean (WM) was calculated using the 0 - 4 h post-dose FEV1 measurements that included the pre-dose (Day 1: 30 minutes [min] and 5 min prior to dosing; other serial visits:23 and 24 h after previous morning dose) and post-dose (5, 15, and 30 min and 1, 2, and 4 h) assessments. BL FEV1 is the mean of the two assessments made 30 and 5 min pre-dose at Day 1. WM change from BL was the WM at the visit minus the BL

	value. Analysis was performed using a repeated measures model with covariates of treatment, smoking status at screening (stratum), BL-mean of the two assessments made 30 and 5 min pre-dose on Day 1, centre grouping, Day, Day by BL and Day by treatment interactions.
Time Frame	Baseline (BL) to Day 168
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all randomized par. who received at least one dose of study medication. 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 in the analysis

Reporting Groups

	Description
Placebo	Participants received placebo OD in the morning from the DPI for 24 weeks.
FF 100 µg OD	Participants received FF 100 µg OD in the morning from the DPI for 24 weeks.
VI 25 µg OD	Participants received VI 25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 50/25 µg OD	Participants received FF/VI 50/25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 100/25 µg OD	Participants received FF/VI 100/25 µg OD in the morning from the DPI for 24 weeks.

Measured Values

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
Number of Participants Analyzed	139	145	144	146	151
Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours Post-dose at Day 168 [units: Liters] Least Squares Mean (Standard Error)	0.026 (0.0184)	0.080 (0.0182)	0.129 (0.0182)	0.218 (0.0181)	0.200 (0.0179)

Statistical Analysis 1 for Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours Post-dose at Day 168

Groups	Placebo, FF 100 µg OD
Method	Mixed Models Analysis
P-Value	0.040
Other Estimated Parameter [Least squares mean difference]	0.053
95% Confidence Interval	0.003 to 0.104

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

Nominal p-value

Other relevant information, such as adjustments or degrees of freedom:

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Statistical Analysis 2 for Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours Post-dose at Day 168

Groups	Placebo, VI 25 µg OD
Method	Mixed Models Analysis

P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.103
95% Confidence Interval	0.052 to 0.153

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Statistical Analysis 3 for Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours Post-dose at Day 168

Groups	Placebo, FF/VI 50/25 µg OD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.192
95% Confidence Interval	0.141 to 0.243

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

Nominal p-value

Other relevant information, such as adjustments or degrees of freedom:

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Statistical Analysis 4 for Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours Post-dose at Day 168

Groups	Placebo, FF/VI 100/25 µg OD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.173
95% Confidence Interval	0.123 to 0.224

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Statistical Analysis 5 for Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours Post-dose at Day 168

Groups	FF 100 µg OD, FF/VI 100/25 µg OD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.120
95% Confidence Interval	0.070 to 0.170

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Statistical Analysis 6 for Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours Post-dose at Day 168

Groups	VI 25 µg OD, FF/VI 50/25 µg OD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.090
95% Confidence Interval	0.039 to 0.140

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

Nominal p-value

Other relevant information, such as adjustments or degrees of freedom:

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Statistical Analysis 7 for Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours Post-dose at Day 168

Groups	VI 25 µg OD, FF/VI 100/25 µg OD
Method	Mixed Models Analysis
P-Value	0.006
Other Estimated Parameter [Least squares mean difference]	0.071
95% Confidence Interval	0.021 to 0.121

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

Nominal p-value

Other relevant information, such as adjustments or degrees of freedom:

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

2. Primary Outcome Measure:

Measure Title	Change From Baseline in Clinic Visit Trough (Pre-bronchodilator and Pre-dose) FEV1 at Day 169
Measure Description	Co-Primary Endpoint: 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, 7, 14, 28, 56, 84, 112, 140, 168, and 169. BL 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 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, smoking status at screening (stratum), BL - mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Day 1, centre grouping, Day, Day by BL and Day by treatment interactions.
Time Frame	Baseline to Day 169
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all randomized par. who received at least one dose of study medication. 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 in the analysis

Reporting Groups

	Description
Placebo	Participants received placebo OD in the morning from the DPI for 24 weeks.
FF 100 µg OD	Participants received FF 100 µg OD in the morning from the DPI for 24 weeks.
VI 25 µg OD	Participants received VI 25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 50/25 µg OD	Participants received FF/VI 50/25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 100/25 µg OD	Participants received FF/VI 100/25 µg OD in the morning from the DPI for 24 weeks.

Measured Values

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
Number of Participants Analyzed	136	143	143	144	146
Change From Baseline in Clinic Visit Trough (Pre-bronchodilator and Pre-dose) FEV1 at Day 169 [units: Liters] Least Squares Mean (Standard Error)	0.037 (0.0199)	0.070 (0.0196)	0.103 (0.0196)	0.166 (0.0196)	0.151 (0.0194)

Statistical Analysis 1 for Change From Baseline in Clinic Visit Trough (Pre-bronchodilator and Pre-dose) FEV1 at Day 169

Groups	Placebo, FF 100 µg OD
Method	Mixed Models Analysis
P-Value	0.241
Other Estimated Parameter [Least squares mean difference]	0.033
95% Confidence Interval	-0.022 to 0.088

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Statistical Analysis 2 for Change From Baseline in Clinic Visit Trough (Pre-bronchodilator and Pre-dose) FEV1 at Day 169

Groups	Placebo, VI 25 µg OD
Method	Mixed Models Analysis
P-Value	0.017
Other Estimated Parameter [Least squares mean difference]	0.067
95% Confidence Interval	0.012 to 0.121

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Statistical Analysis 3 for Change From Baseline in Clinic Visit Trough (Pre-bronchodilator and Pre-dose) FEV1 at Day 169

Groups	Placebo, FF/VI 50/25 µg OD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.129
95% Confidence Interval	0.074 to 0.184

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

Nominal p-value

Other relevant information, such as adjustments or degrees of freedom:

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Statistical Analysis 4 for Change From Baseline in Clinic Visit Trough (Pre-bronchodilator and Pre-dose) FEV1 at Day 169

Groups	Placebo, FF/VI 100/25 µg OD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.115
95% Confidence Interval	0.060 to 0.169

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Statistical Analysis 5 for Change From Baseline in Clinic Visit Trough (Pre-bronchodilator and Pre-dose) FEV1 at Day 169

Groups	FF 100 µg OD, FF/VI 100/25 µg OD
Method	Mixed Models Analysis
P-Value	0.003
Other Estimated Parameter [Least squares mean difference]	0.082
95% Confidence Interval	0.028 to 0.136

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

Nominal p-value

Other relevant information, such as adjustments or degrees of freedom:

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Statistical Analysis 6 for Change From Baseline in Clinic Visit Trough (Pre-bronchodilator and Pre-dose) FEV1 at Day 169

Groups	VI 25 µg OD, FF/VI 50/25 µg OD
Method	Mixed Models Analysis
P-Value	0.025

Other Estimated Parameter [Least squares mean difference]	0.062
95% Confidence Interval	0.008 to 0.117

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

Nominal p-value

Other relevant information, such as adjustments or degrees of freedom:

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

Statistical Analysis 7 for Change From Baseline in Clinic Visit Trough (Pre-bronchodilator and Pre-dose) FEV1 at Day 169

Groups	VI 25 µg OD, FF/VI 100/25 µg OD
Method	Mixed Models Analysis
P-Value	0.082
Other Estimated Parameter [Least squares mean difference]	0.048
95% Confidence Interval	-0.006 to 0.102

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

Restricted maximum likelihood (REML)-based repeated measures approach (MMRM).

3. Secondary Outcome Measure:

Measure Title	Change From Baseline in Chronic Respiratory Disease Questionnaire Self-administered Standardized (CRQ-SAS) Dyspnea Score at Day 168
Measure Description	Considered an 'Other' endpoint by FDA. CRQ-SAS measures 4 domains (mastery, fatigue, emotional function, and dyspnea) of functioning of participants with COPD: mastery (amount of control the participant feels he/she has over COPD symptoms); fatigue (how tired the participant feels); emotional function (how anxious/depressed the participant feels); and dyspnea (how short of breath the participant feels during physical activities). Each domain is measured on a scale of 1-7 (1=maximum impairment; 7=no impairment). Each domain score is calculated separately. Current assessment was done only for dyspnea domain. BL scores are the derived scores for each domain and total at Day 1 pre-dose. Change from BL was calculated as the average at each visit minus the BL value. Analysis performed used a repeated measures model with covariates of treatment, smoking status at screening (stratum), BL (derived scores at Day 1 pre-dose), centre grouping, Day, Day by BL and Day by treatment interactions.
Time Frame	Baseline to Day 168
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all randomized par. who received at least one dose of study medication. 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 in the analysis

Reporting Groups

	Description
Placebo	Participants received placebo OD in the morning from the DPI for 24

	Description
	weeks.
FF 100 µg OD	Participants received FF 100 µg OD in the morning from the DPI for 24 weeks.
VI 25 µg OD	Participants received VI 25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 50/25 µg OD	Participants received FF/VI 50/25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 100/25 µg OD	Participants received FF/VI 100/25 µg OD in the morning from the DPI for 24 weeks.

Measured Values

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
Number of Participants Analyzed	135	143	140	145	147
Change From Baseline in Chronic Respiratory Disease Questionnaire Self-administered Standardized (CRQ-SAS) Dyspnea Score at Day 168 [units: Scores on a scale] Least Squares Mean (Standard Error)	0.23 (0.088)	0.29 (0.086)	0.37 (0.086)	0.42 (0.085)	0.53 (0.085)

4. Secondary Outcome Measure:

Measure Title	Change From Baseline in Peak Post-dose FEV1 (0-4 Hour) on Day 1

Measure 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. BL FEV1 is defined as the mean of the assessments made 30 minutes pre-dose and immediately pre-dose on Day 1. If one of these two assessments was missing then BL was defined as the single pre-dose FEV1 value on Day 1. Peak post-dose FEV1 (0-4 hours) is the maximum post-dose FEV1 recorded over the nominal timepoints of 5, 15 and 30 min, 1, 2 and 4 hours post the Day 1 dose. Change from BL is calculated as the peak post-dose FEV1 (0-4 hour) on Day 1 minus BL FEV1. Analysis performed used an Analysis of Covariance (ANCOVA) model with covariates of treatment, smoking status at screening (stratum), BL - mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Day 1, and centre grouping.
Time Frame	Baseline and Day 1
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all randomized participants who received at least one dose of study medication. Only those participants available at the indicated time point and without missing covariate information were analyzed.

Reporting Groups

	Description
Placebo	Participants received placebo OD in the morning from the DPI for 24 weeks.
FF 100 µg OD	Participants received FF 100 µg OD in the morning from the DPI for 24 weeks.
VI 25 µg OD	Participants received VI 25 µg OD in the morning from the DPI for 24 weeks.

	Description
FF/VI 50/25 µg OD	Participants received FF/VI 50/25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 100/25 µg OD	Participants received FF/VI 100/25 µg OD in the morning from the DPI for 24 weeks.

Measured Values

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
Number of Participants Analyzed	207	206	205	205	206
Change From Baseline in Peak Post-dose FEV1 (0-4 Hour) on Day 1 [units: Liters] Least Squares Mean (Standard Error)	0.106 (0.0098)	0.118 (0.0099)	0.247 (0.0099)	0.253 (0.0099)	0.245 (0.0099)

5. Secondary Outcome Measure:

Measure Title	Time to Onset (Increase of 100 Milliliter [mL] From Baseline in 0-4 Hours Post-dose FEV1) on Treatment Day 1
Measure 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. Baseline FEV1 is defined as the mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Day 1. Time to onset on Treatment Day 1 is defined as a 100 mL increase from Baseline in FEV1. Time to increase of 100 mL from Baseline was calculated over the 5, 15, 30 minutes, and 1, 2, and 4 hours time points. A participant who had at least one post-dose FEV1 on Day 1, but did not achieve a

	100 mL or more increase from Baseline at any scheduled time-point at which FEV1 was assessed up to and including 4 hours was censored.
Time Frame	Baseline and Day 1
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all randomized participants who received at least one dose of study medication. Only those participants available at the indicated time point were assessed.

Reporting Groups

	Description
Placebo	Participants received placebo OD in the morning from the DPI for 24 weeks.
FF 100 µg OD	Participants received FF 100 µg OD in the morning from the DPI for 24 weeks.
VI 25 µg OD	Participants received VI 25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 50/25 µg OD	Participants received FF/VI 50/25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 100/25 µg OD	Participants received FF/VI 100/25 µg OD in the morning from the DPI for 24 weeks.

Measured Values

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
Number of Participants Analyzed	207	206	205	205	206

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
Time to Onset (Increase of 100 Milliliter [mL] From Baseline in 0-4 Hours Post-dose FEV1) on Treatment Day 1 [units: Minutes] Median (Full Range)	NA (5 to 240) [1]	NA (5 to 240) [2]	16 (5 to 240)	17 (5 to 240)	17 (5 to 240)

[1] > 50% of participants were censored; therefore, the median could not be calculated.

[2] > 50% of participants were censored; therefore, the median could not be calculated.

Reported Adverse Events

Reporting Groups

	Description
Placebo	Participants received placebo OD in the morning from the DPI for 24 weeks.
FF 100 µg OD	Participants received FF 100 µg OD in the morning from the DPI for 24 weeks.
VI 25 µg OD	Participants received VI 25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 50/25 µg OD	Participants received FF/VI 50/25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 100/25 µg OD	Participants received FF/VI 100/25 µg OD in the morning from the DPI for 24 weeks.

Time Frame

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of the study medication through the end of treatment (up to Week 24).

Additional Description

An on-treatment AE or SAE is defined as an AE with an onset on or after the start date of study medication, but not later than one day after the last date of study medication. SAEs and AEs were collected in members of the ITT Population, comprised of all participants randomized to treatment, who received at least one dose of the study medication

Serious Adverse Events

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
Total # participants affected/at risk	11/207 (5.31%)	16/206 (7.77%)	15/205 (7.32%)	6/206 (2.91%)	11/206 (5.34%)
Cardiac disorders					
Angina unstable † [A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	0/205 (0%)	1/206 (0.49%)	0/206 (0%)
# events					
Coronary artery disease † [A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	0/205 (0%)	1/206 (0.49%)	0/206 (0%)
# events					
Myocardial infarction † [A]					
# participants affected/at risk	1/207 (0.48%)	0/206 (0%)	0/205 (0%)	0/206 (0%)	1/206 (0.49%)
# events					
Supraventricular extrasystoles † [A]					

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
# participants affected/at risk	0/207 (0%)	0/206 (0%)	0/205 (0%)	1/206 (0.49%)	0/206 (0%)
# events					
Ear and labyrinth disorders					
Deafness neurosensory † [A]					
# participants affected/at risk	0/207 (0%)	1/206 (0.49%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Gastrointestinal disorders					
Colitis † [A]					
# participants affected/at risk	1/207 (0.48%)	0/206 (0%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Gastrointestinal haemorrhage † [A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	0/205 (0%)	1/206 (0.49%)	0/206 (0%)
# events					
General disorders					
Chest discomfort † [A]					
# participants affected/at	0/207 (0%)	1/206 (0.49%)	0/205 (0%)	0/206 (0%)	0/206 (0%)

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
risk					
# events					
Sudden cardiac death † [A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	1/205 (0.49%)	0/206 (0%)	0/206 (0%)
# events					
Hepatobiliary disorders					
Cholangitis † [A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	0/205 (0%)	0/206 (0%)	1/206 (0.49%)
# events					
Infections and infestations					
Gastroenteritis † [A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	0/205 (0%)	0/206 (0%)	1/206 (0.49%)
# events					
Pneumonia † [A]					
# participants affected/at risk	1/207 (0.48%)	2/206 (0.97%)	3/205 (1.46%)	1/206 (0.49%)	1/206 (0.49%)
# events					
Pneumonia pneumococcal † [A]					

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
# participants affected/at risk	0/207 (0%)	1/206 (0.49%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Injury, poisoning and procedural complications					
Alcohol poisoning † [A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	0/205 (0%)	1/206 (0.49%)	0/206 (0%)
# events					
Fractured coccyx † [A]					
# participants affected/at risk	1/207 (0.48%)	0/206 (0%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Multiple fractures † [A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	1/205 (0.49%)	0/206 (0%)	0/206 (0%)
# events					
Multiple injuries † [A]					
# participants affected/at risk	1/207 (0.48%)	0/206 (0%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Radius fracture † [A]					
# participants affected/at	1/207 (0.48%)	0/206 (0%)	0/205 (0%)	0/206 (0%)	0/206 (0%)

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
risk					
# events					
Road traffic accident †[A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	1/205 (0.49%)	0/206 (0%)	0/206 (0%)
# events					
Subdural haematoma †[A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	0/205 (0%)	0/206 (0%)	1/206 (0.49%)
# events					
Transplant failure †[A]					
# participants affected/at risk	0/207 (0%)	1/206 (0.49%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Vascular pseudoaneurysm †[A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	0/205 (0%)	1/206 (0.49%)	0/206 (0%)
# events					
Metabolism and nutrition disorders					
Dehydration †[A]					
# participants affected/at	1/207 (0.48%)	1/206 (0.49%)	0/205 (0%)	0/206 (0%)	0/206 (0%)

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
risk					
# events					
Musculoskeletal and connective tissue disorders					
Cervical spinal stenosis † [A]					
# participants affected/at risk	0/207 (0%)	1/206 (0.49%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Intervertebral disc disorder † [A]					
# participants affected/at risk	0/207 (0%)	1/206 (0.49%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Glottis carcinoma † [A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	1/205 (0.49%)	0/206 (0%)	0/206 (0%)
# events					
Lip and/or oral cavity cancer					

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
† [A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	1/205 (0.49%)	0/206 (0%)	0/206 (0%)
# events					
Nasopharyngeal cancer stage IV † [A]					
# participants affected/at risk	1/207 (0.48%)	0/206 (0%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Prostate cancer † [A]					
# participants affected/at risk	1/207 (0.48%)	0/206 (0%)	0/205 (0%)	0/206 (0%)	1/206 (0.49%)
# events					
Small cell lung cancer stage unspecified † [A]					
# participants affected/at risk	0/207 (0%)	1/206 (0.49%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Transitional cell carcinoma † [A]					
# participants affected/at risk	0/207 (0%)	1/206 (0.49%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Nervous system					

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
disorders					
Carotid artery stenosis † [A]					
# participants affected/at risk	0/207 (0%)	2/206 (0.97%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Cerebral haemorrhage † [A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	0/205 (0%)	1/206 (0.49%)	0/206 (0%)
# events					
Hypertonia † [A]					
# participants affected/at risk	0/207 (0%)	1/206 (0.49%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Intracranial aneurysm † [A]					
# participants affected/at risk	0/207 (0%)	1/206 (0.49%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Ischaemic stroke † [A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	0/205 (0%)	0/206 (0%)	2/206 (0.97%)
# events					
Myasthenia gravis † [A]					

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
# participants affected/at risk	0/207 (0%)	0/206 (0%)	0/205 (0%)	1/206 (0.49%)	0/206 (0%)
# events					
Subarachnoid haemorrhage †[A]					
# participants affected/at risk	0/207 (0%)	1/206 (0.49%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Transient ischaemic attack †[A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	1/205 (0.49%)	0/206 (0%)	0/206 (0%)
# events					
Renal and urinary disorders					
Nephrolithiasis †[A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	1/205 (0.49%)	0/206 (0%)	0/206 (0%)
# events					
Renal failure acute †[A]					
# participants affected/at risk	1/207 (0.48%)	0/206 (0%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
Respiratory, thoracic and mediastinal disorders					
Chronic obstructive pulmonary disease † [A]					
# participants affected/at risk	3/207 (1.45%)	2/206 (0.97%)	6/205 (2.93%)	0/206 (0%)	4/206 (1.94%)
# events					
Vascular disorders					
Arteriosclerosis † [A]					
# participants affected/at risk	0/207 (0%)	1/206 (0.49%)	0/205 (0%)	0/206 (0%)	0/206 (0%)
# events					
Peripheral arterial occlusive disease † [A]					
# participants affected/at risk	0/207 (0%)	0/206 (0%)	0/205 (0%)	1/206 (0.49%)	0/206 (0%)
# events					

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 3%

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
Total # participants affected/at	37/207	59/206	53/205	52/206	63/206

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
risk	(17.87%)	(28.64%)	(25.85%)	(25.24%)	(30.58%)
Infections and infestations					
Lower respiratory tract infection †[A]					
# participants affected/at risk	7/207 (3.38%)	1/206 (0.49%)	4/205 (1.95%)	3/206 (1.46%)	1/206 (0.49%)
# events					
Nasopharyngitis †[A]					
# participants affected/at risk	14/207 (6.76%)	18/206 (8.74%)	22/205 (10.73%)	14/206 (6.8%)	22/206 (10.68%)
# events					
Oral candidiasis †[A]					
# participants affected/at risk	1/207 (0.48%)	2/206 (0.97%)	3/205 (1.46%)	8/206 (3.88%)	4/206 (1.94%)
# events					
Oropharyngeal candidiasis †[A]					
# participants affected/at risk	2/207 (0.97%)	4/206 (1.94%)	2/205 (0.98%)	10/206 (4.85%)	6/206 (2.91%)
# events					
Sinusitis †[A]					
# participants affected/at	2/207 (0.97%)	7/206 (3.4%)	3/205 (1.46%)	1/206 (0.49%)	4/206 (1.94%)

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
risk					
# events					
Upper respiratory tract infection † [A]					
# participants affected/at risk	8/207 (3.86%)	13/206 (6.31%)	11/205 (5.37%)	16/206 (7.77%)	21/206 (10.19%)
# events					
Musculoskeletal and connective tissue disorders					
Arthralgia † [A]					
# participants affected/at risk	2/207 (0.97%)	7/206 (3.4%)	2/205 (0.98%)	1/206 (0.49%)	2/206 (0.97%)
# events					
Back pain † [A]					
# participants affected/at risk	4/207 (1.93%)	5/206 (2.43%)	7/205 (3.41%)	7/206 (3.4%)	6/206 (2.91%)
# events					
Nervous system disorders					
Headache † [A]					
# participants affected/at risk	5/207 (2.42%)	17/206 (8.25%)	16/205 (7.8%)	12/206 (5.83%)	18/206 (8.74%)

	Placebo	FF 100 µg OD	VI 25 µg OD	FF/VI 50/25 µg OD	FF/VI 100/25 µg OD
# events					

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

GSK agreements may vary with individual investigators, but will not prohibit any investigator from publishing. GSK supports the publication of results from all centers of a multi-center trial but requests that reports based on single-site data not precede the primary publication of the entire clinical trial.

Limitations and Caveats:

Results Point of Contact:

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