Protocol Registration Receipt
07/10/2014

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Efficacy and Safety Study of Fluticasone Furoate (FF)/GW642444 Inhalation Powder and the Individual Components 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:	NCT01054885

Purpose

The Purpose of this study is to assess the efficacy and safety of two strengths of the FF/GW642444 Inhalation Powder in subject with Chronic Obstructive Pulmonary Disease (COPD)

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

Condition	Intervention	Phase
	Drug: FF/GW642444 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 (h) 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: 1226
Study Start Date: October 2009
Study Completion Date: February 2011
Primary Completion Date: February 2011

Arms	Assigned Interventions
Experimental: Fluticasone Furoate Inhalation Powder Inhaled Corticosteroid (ICS)	Drug: FF Inhalation Powder Inhaled Corticosteroid (ICS)
Experimental: FF Inhalation Pwdr	Drug: FF Inhalation Powder

Arms	Assigned Interventions
Inhaled Corticosteroid (ICS)	Inhaled Corticosteroid (ICS)
Experimental: Fluticasone Furoate/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
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
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

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:

Martinez FJ, Boscia J, Feldman G, Scott-Wilson C, Kilbride S, Fabbri L, Crim C, Calverley PMA. Fluticasone furoate/vilanterol (100/25; 200/25 µg) improves lung function in COPD: A randomised trial. Respir Med. 2013;107(4):550-559.

Responsible Party: GlaxoSmithKline
Study ID Numbers: 112207
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 1909 par. were screened, 1577 entered the RIP, of whom 1226 were randomized, 1224 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.

	Description
FF 100 µg OD	Participants received Fluticasone Furoate (FF) 100 micrograms (µg) OD in the morning from the DPI for 24 weeks.
FF 200 µg OD	Participants received FF 200 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 100/25 µg OD	Participants received FF/VI 100/25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 200/25 µg OD	Participants received FF/VI 200/25 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	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD
Started	1577	0	0	0	0	0
Completed	1226	0	0	0	0	0
Not Completed	351	0	0	0	0	0
Did Not Meet Continuation Criteria	246	0	0	0	0	0
Physician Decision	6	0	0	0	0	0
Withdrawal by Subject	23	0	0	0	0	0
Lost to Follow-up	1	0	0	0	0	0
Adverse Event	7	0	0	0	0	0

	Placebo Run-in	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD
Study Closed/Terminated	68	0	0	0	0	0

	FF/VI 200/25 µg OD
Started	0
Completed	0
Not Completed	0
Did Not Meet Continuation Criteria	0
Physician Decision	0
Withdrawal by Subject	0
Lost to Follow-up	0
Adverse Event	0
Study Closed/Terminated	0

24-week, Double-blind Treatment Period

	Placebo Run-in	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD
Started	0	205	204	203	203	204
Completed	0	146	155	160	161	144
Not Completed	0	59	49	43	42	60
Adverse Event	0	18	12	15	15	17
Lack of Efficacy-No Sub-Reason	0	0	3	1	0	1

	Placebo Run-in	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD
Lack of Efficacy-Sub-Reason Exacerbation	0	12	2	5	11	7
Protocol Violation	0	7	7	2	3	8
Protocol Defined Stopping Criteria	0	7	12	7	7	15
Study Closed/ Terminated	0	0	1	0	0	0
Lost to Follow-up	0	3	2	0	0	2
Physician Decision	0	4	1	6	3	1
Withdrawal by Subject	0	8	9	7	3	9

	FF/VI 200/25 µg OD
Started	205
Completed	158
Not Completed	47
Adverse Event	19
Lack of Efficacy-No Sub-Reason	0
Lack of Efficacy-Sub-Reason Exacerbation	7
Protocol Violation	4
Protocol Defined Stopping	12

	FF/VI 200/25 µg OD
Criteria	
Study Closed/ Terminated	1
Lost to Follow-up	1
Physician Decision	1
Withdrawal by Subject	2

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.
FF 200 µg OD	Participants received FF 200 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 100/25 µg OD	Participants received FF/VI 100/25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 200/25 µg OD	Participants received FF/VI 200/25 µg OD in the morning from the DPI for 24 weeks.

Baseline Measures

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD	Total
Number of Participants	205	204	203	203	204	205	1224
Age, Continuous [units: Years] Mean (Standard Deviation)	61.9 (8.14)	61.8 (8.28)	61.8 (9.02)	61.2 (8.62)	61.9 (8.79)	61.1 (8.67)	61.6 (8.58)
Gender, Male/Female [units: Participants]							
Female	53	54	52	52	60	68	339
Male	152	150	151	151	144	137	885
Race/Ethnicity, Customized [units: Participants]							
African American/African Heritage (HER)	0	2	5	3	4	2	16
American Indian or Alaska Native	0	0	1	0	2	0	3
Japanese/East Asian HER/South East Asian HER	8	5	14	4	8	11	50
White	197	197	183	196	190	192	1155

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours (h) 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.
FF 200 µg OD	Participants received FF 200 µg OD in the morning from the DPI for 24 weeks.

	Description
VI 25 µg OD	Participants received VI 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.
FF/VI 200/25 µg OD	Participants received FF/VI 200/25 µg OD in the morning from the DPI for 24 weeks.

Measured Values

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
Number of Participants Analyzed	147	154	162	160	146	158
Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours (h) Post-dose at Day 168 [units: Liters] Least Squares Mean (Standard Error)	-0.012 (0.0189)	0.034 (0.0187)	0.029 (0.0185)	0.173 (0.0184)	0.202 (0.0190)	0.197 (0.0184)

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

Groups	Placebo, FF 100 µg OD
Method	Mixed Models Analysis
P-Value	0.085
Other Estimated Parameter [Least squares mean difference]	0.046
95% Confidence Interval	-0.006 to 0.098

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 Weighted Mean FEV1 Over 0-4 Hours (h) Post-dose at Day 168

Groups	Placebo, FF 200 µg OD
Method	Mixed Models Analysis
P-Value	0.123
Other Estimated Parameter [Least squares mean difference]	0.041
95% Confidence Interval	-0.011 to 0.093

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 (h) 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]	0.185

95% Confidence Interval	0.133 to 0.237

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 4 for Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours (h) 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]	0.214
95% Confidence Interval	0.161 to 0.266

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 5 for Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours (h) Post-dose at Day 168

Groups	Placebo, FF/VI 200/25 µg OD
Method	Mixed Models Analysis

P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.209
95% Confidence Interval	0.157 to 0.261

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 (h) 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]	0.168
95% Confidence Interval	0.116 to 0.220

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 (h) Post-dose at Day 168

Groups	FF 200 µg OD, FF/VI 200/25 µg OD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.168
95% Confidence Interval	0.117 to 0.219

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 8 for Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours (h) Post-dose at Day 168

Groups	VI 25 µg OD, FF/VI 100/25 µg OD
Method	Mixed Models Analysis
P-Value	0.274
Other Estimated Parameter [Least squares mean difference]	0.029
95% Confidence Interval	-0.023 to 0.081

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 9 for Change From Baseline in Weighted Mean FEV1 Over 0-4 Hours (h) Post-dose at Day 168

Groups	VI 25 µg OD, FF/VI 200/25 µg OD
Method	Mixed Models Analysis
P-Value	0.357
Other Estimated Parameter [Least squares mean difference]	0.024
95% Confidence Interval	-0.027 to 0.075

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).

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.
FF 200 µg OD	Participants received FF 200 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 100/25 µg OD	Participants received FF/VI 100/25 µg OD in the morning from the DPI

	Description
	for 24 weeks.
FF/VI 200/25 µg OD	Participants received FF/VI 200/25 µg OD in the morning from the DPI for 24 weeks.

Measured Values

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
Number of Participants Analyzed	142	148	155	150	137	153
Change From Baseline in Clinic Visit Trough (Pre-bronchodilator and Pre-dose) FEV1 at Day 169 [units: Liters] Least Squares Mean (Standard Error)	0.004 (0.0189)	0.048 (0.0187)	0.012 (0.0185)	0.103 (0.0185)	0.148 (0.0191)	0.135 (0.0185)

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	0.095
Other Estimated Parameter [Least squares mean difference]	0.044
95% Confidence Interval	-0.008 to 0.097

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, FF 200 µg OD
Method	Mixed Models Analysis
P-Value	0.756
Other Estimated Parameter [Least squares mean difference]	0.008
95% Confidence Interval	-0.044 to 0.060

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, VI 25 µg OD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.100
95% Confidence Interval	0.048 to 0.151

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 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]	0.144
95% Confidence Interval	0.091 to 0.197

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

Groups	Placebo, FF/VI 200/25 µg OD
Method	Mixed Models Analysis
P-Value	<0.001

Other Estimated Parameter [Least squares mean difference]	0.131
95% Confidence Interval	0.080 to 0.183

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 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	<0.001
Other Estimated Parameter [Least squares mean difference]	0.100
95% Confidence Interval	0.047 to 0.152

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	FF 200 µg OD, FF/VI 200/25 µg OD
Method	Mixed Models Analysis
P-Value	<0.001
Other Estimated Parameter [Least squares mean difference]	0.123
95% Confidence Interval	0.072 to 0.174

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 8 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	0.093
Other Estimated Parameter [Least squares mean difference]	0.045
95% Confidence Interval	-0.008 to 0.097

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

Groups	VI 25 µg OD, FF/VI 200/25 µg OD
Method	Mixed Models Analysis
P-Value	0.224
Other Estimated Parameter [Least squares mean difference]	0.032
95% Confidence Interval	-0.019 to 0.083

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 weeks.
FF 100 µg OD	Participants received FF 100 µg OD in the morning from the DPI for 24 weeks.
FF 200 µg OD	Participants received FF 200 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 100/25 µg OD	Participants received FF/VI 100/25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 200/25 µg OD	Participants received FF/VI 200/25 µg OD in the morning from the DPI for 24 weeks.

Measured Values

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
Number of Participants Analyzed	146	154	161	161	146	156
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)	0.21 (0.077)	0.10 (0.076)	0.21 (0.075)	0.28 (0.075)	0.45 (0.078)	0.31 (0.075)

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.
FF 200 µg OD	Participants received FF 200 µg OD in the morning from the DPI for 24 weeks.
FVI 25 µg OD	Participants received VI 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.
FF/VI 200/25 µg OD	Participants received FF/VI 200/25 µg OD in the morning from the DPI for 24 weeks.

Measured Values

	Placebo	FF 100 µg OD	FF 200 µg OD	FVI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
Number of Participants Analyzed	204	203	202	201	203	205
Change From Baseline in Peak Post-dose FEV1 (0-4 Hour) on Day 1 [units: Liters] Least Squares Mean (Standard Error)	0.120 (0.0108)	0.144 (0.0109)	0.127 (0.0109)	0.267 (0.0109)	0.272 (0.0109)	0.261 (0.0108)

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.
FF 200 µg OD	Participants received FF 200 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 100/25 µg OD	Participants received FF/VI 100/25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 200/25 µg OD	Participants received FF/VI 200/25 µg OD in the morning from the DPI for 24 weeks.

Measured Values

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
Number of Participants Analyzed	204	203	202	201	203	205
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]	231 (5 to 240)	242 (5 to 242)	17 (5 to 240)	16 (5 to 240)	17 (5 to 240)

[1] > 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.
FF 200 µg OD	Participants received FF 200 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 100/25 µg OD	Participants received FF/VI 100/25 µg OD in the morning from the DPI for 24 weeks.
FF/VI 200/25 µg OD	Participants received FF/VI 200/25 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	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
Total # participants affected/at risk	10/205 (4.88%)	6/204 (2.94%)	10/203 (4.93%)	16/203 (7.88%)	12/204 (5.88%)	15/205 (7.32%)
Blood and lymphatic system disorders						
Leukocytosis † [A]						
# participants affected/at risk	0/205 (0%)	1/204 (0.49%)	0/203 (0%)	0/203 (0%)	0/204 (0%)	0/205 (0%)
# events						
Cardiac disorders						
Acute myocardial infarction † [A]						
# participants affected/at risk	0/205 (0%)	1/204 (0.49%)	0/203 (0%)	0/203 (0%)	0/204 (0%)	0/205 (0%)
# events						
Atrial fibrillation † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	1/203 (0.49%)	0/203 (0%)	0/204 (0%)	0/205 (0%)
# events						
Atrioventricular block first degree † [A]						
# participants affected/at	0/205 (0%)	0/204 (0%)	1/203 (0.49%)	0/203 (0%)	0/204 (0%)	0/205 (0%)

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
risk						
# events						
Bradycardia † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	1/203 (0.49%)	0/203 (0%)	0/204 (0%)	0/205 (0%)
# events						
Cardiac failure chronic † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	0/204 (0%)	1/205 (0.49%)
# events						
Cardiac failure congestive † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	0/205 (0%)
# events						
Myocardial infarction † [A]						
# participants affected/at risk	1/205 (0.49%)	1/204 (0.49%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	1/205 (0.49%)
# events						
Myocardial ischaemia † [A]						
# participants affected/at risk	1/205 (0.49%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	0/204 (0%)	0/205 (0%)
# events						

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
Supraventricular extrasystoles †[A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	1/204 (0.49%)	0/205 (0%)
# events						
Ear and labyrinth disorders						
Vertigo †[A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	0/205 (0%)
# events						
Gastrointestinal disorders						
Abdominal hernia †[A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	0/205 (0%)
# events						
Enteritis †[A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	1/204 (0.49%)	0/205 (0%)
# events						
Hiatus hernia †[A]						
# participants affected/at	0/205 (0%)	0/204 (0%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	0/205 (0%)

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
risk						
# events						
Inguinal hernia † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	0/205 (0%)
# events						
Oesophagitis † [A]						
# participants affected/at risk	0/205 (0%)	1/204 (0.49%)	0/203 (0%)	0/203 (0%)	0/204 (0%)	0/205 (0%)
# events						
Pancreatitis † [A]						
# participants affected/at risk	0/205 (0%)	1/204 (0.49%)	0/203 (0%)	0/203 (0%)	0/204 (0%)	0/205 (0%)
# events						
Peritonitis † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	0/204 (0%)	1/205 (0.49%)
# events						
Rectal haemorrhage † [A]						
# participants affected/at risk	1/205 (0.49%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	0/204 (0%)	0/205 (0%)
# events						

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
General disorders						
Chest discomfort † [A]						
# participants affected/at risk	1/205 (0.49%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	0/204 (0%)	0/205 (0%)
# events						
Device occlusion † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	0/204 (0%)	1/205 (0.49%)
# events						
Immune system disorders						
Anaphylactic reaction † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	0/205 (0%)
# events						
Infections and infestations						
Appendicitis † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	1/204 (0.49%)	1/205 (0.49%)
# events						
Infective exacerbation of chronic obstructive airway						

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
disease † [A]						
# participants affected/at risk	1/205 (0.49%)	0/204 (0%)	1/203 (0.49%)	1/203 (0.49%)	0/204 (0%)	0/205 (0%)
# events						
Pneumonia † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	2/203 (0.99%)	2/203 (0.99%)	0/204 (0%)	3/205 (1.46%)
# events						
Sepsis † [A]						
# participants affected/at risk	0/205 (0%)	1/204 (0.49%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	0/205 (0%)
# events						
Injury, poisoning and procedural complications						
Accidental poisoning † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	0/205 (0%)
# events						
Fibula fracture † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	1/203 (0.49%)	0/203 (0%)	0/204 (0%)	0/205 (0%)
# events						
Incisional hernia † [A]						

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	1/204 (0.49%)	0/205 (0%)
# events						
Joint dislocation † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	0/205 (0%)
# events						
Subdural haematoma † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	1/204 (0.49%)	0/205 (0%)
# events						
Tibia fracture † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	1/203 (0.49%)	0/203 (0%)	0/204 (0%)	0/205 (0%)
# events						
Metabolism and nutrition disorders						
Hyperglycaemia † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	1/203 (0.49%)	0/203 (0%)	0/204 (0%)	0/205 (0%)
# events						
Metabolic disorder † [A]						
# participants affected/at	0/205 (0%)	0/204 (0%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	0/205 (0%)

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
risk						
# events						
Type 2 diabetes mellitus † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	0/205 (0%)
# events						
Musculoskeletal and connective tissue disorders						
Osteoporosis † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	1/204 (0.49%)	0/205 (0%)
# events						
Spinal osteoarthritis † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	1/204 (0.49%)	0/205 (0%)
# events						
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Colon cancer † [A]						
# participants affected/at	0/205 (0%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	0/204 (0%)	1/205 (0.49%)

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
risk						
# events						
Gastric cancer † [A]						
# participants affected/at risk	0/205 (0%)	1/204 (0.49%)	0/203 (0%)	0/203 (0%)	0/204 (0%)	0/205 (0%)
# events						
Oesophageal carcinoma † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	0/205 (0%)
# events						
Prostate cancer † [A]						
# participants affected/at risk	0/205 (0%)	1/204 (0.49%)	0/203 (0%)	0/203 (0%)	0/204 (0%)	0/205 (0%)
# events						
Nervous system disorders						
Cerebral infarction † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	0/204 (0%)	1/205 (0.49%)
# events						
Cerebrovascular accident † [A]						
# participants affected/at	0/205 (0%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	1/204 (0.49%)	0/205 (0%)

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
risk						
# events						
Syncope † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	2/203 (0.99%)	0/203 (0%)	0/204 (0%)	0/205 (0%)
# events						
Thrombotic stroke † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	1/204 (0.49%)	0/205 (0%)
# events						
Respiratory, thoracic and mediastinal disorders						
Bronchiectasis † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	0/205 (0%)
# events						
Chronic obstructive pulmonary disease † [A]						
# participants affected/at risk	5/205 (2.44%)	0/204 (0%)	2/203 (0.99%)	5/203 (2.46%)	5/204 (2.45%)	5/205 (2.44%)
# events						
Pleural effusion † [A]						
# participants affected/at	0/205 (0%)	0/204 (0%)	0/203 (0%)	0/203 (0%)	0/204 (0%)	1/205 (0.49%)

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
risk						
# events						
Pneumothorax † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	1/205 (0.49%)
# events						
Vascular disorders						
Venous insufficiency † [A]						
# participants affected/at risk	0/205 (0%)	0/204 (0%)	0/203 (0%)	1/203 (0.49%)	0/204 (0%)	0/205 (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	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
Total # participants affected/at risk	39/205 (19.02%)	32/204 (15.69%)	46/203 (22.66%)	43/203 (21.18%)	36/204 (17.65%)	40/205 (19.51%)
Infections and infestations						
Nasopharyngitis † [A]						
# participants affected/at	17/205	14/204	20/203	19/203	13/204	13/205

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
risk	(8.29%)	(6.86%)	(9.85%)	(9.36%)	(6.37%)	(6.34%)
# events						
Oral candidiasis † [A]						
# participants affected/at risk	2/205 (0.98%)	5/204 (2.45%)	5/203 (2.46%)	2/203 (0.99%)	8/204 (3.92%)	4/205 (1.95%)
# events						
Oropharyngeal candidiasis † [A]						
# participants affected/at risk	3/205 (1.46%)	0/204 (0%)	7/203 (3.45%)	1/203 (0.49%)	3/204 (1.47%)	4/205 (1.95%)
# events						
Upper respiratory tract infection † [A]						
# participants affected/at risk	5/205 (2.44%)	3/204 (1.47%)	5/203 (2.46%)	9/203 (4.43%)	8/204 (3.92%)	7/205 (3.41%)
# events						
Nervous system disorders						
Headache † [A]						
# participants affected/at risk	15/205 (7.32%)	13/204 (6.37%)	11/203 (5.42%)	20/203 (9.85%)	11/204 (5.39%)	15/205 (7.32%)
# events						
Vascular disorders						

	Placebo	FF 100 µg OD	FF 200 µg OD	VI 25 µg OD	FF/VI 100/25 µg OD	FF/VI 200/25 µg OD
Hypertension † [A]						
# participants affected/at risk	3/205 (1.46%)	3/204 (1.47%)	7/203 (3.45%)	0/203 (0%)	3/204 (1.47%)	1/205 (0.49%)
# 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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