

Protocol Registration Receipt

06/16/2014

Grantor: CDER IND/IDE Number: 077855 Serial Number:

Study to Evaluate the 24-Hour Pulmonary Function Profile of Fluticasone Furoate (FF) /GW642444 (Vilanterol) (VI) Inhalation Powder 100/25mcg Once Daily Compared With Fluticasone Propionate/Salmeterol Inhalation Powder 250/50mcg Twice Daily in Subjects With Chronic Obstructive Pulmonary Disease

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01323634

► Purpose

The purpose of this study is to evaluate the 24-hour spirometry effect (FEV1) of FF/VI 100/25mcg once daily compared with Fluticasone Propionate/Salmeterol 250/50mcg twice daily over a 12-week treatment period in subjects with COPD.

Condition	Intervention	Phase
Pulmonary Disease, Chronic Obstructive	Drug: Fluticasone Furoate 100mcg / GW642444 (vilanterol) 25mcg Drug: Fluticasone Propionate 250mcg/ salmeterol 50mcg	Phase 3

Study Type: Interventional

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

Official Title: A 12-week Study to Evaluate the 24-hour Pulmonary Function Profile of Fluticasone Furoate/Vilanterol (FF/VI) Inhalation Powder 100/25 mcg Once Daily Compared With Fluticasone Propionate/Salmeterol Inhalation Powder 250/50 mcg Twice Daily in Subjects With Chronic Obstructive Pulmonary Disease (COPD)

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Change From Baseline Trough in 24-hour Weighted-mean FEV1 on Treatment Day 84 [Time Frame: Baseline (Day 1) and Day 84] [Designated as safety issue: No]

Pulmonary function was measured by forced expiratory volume in one second (FEV1). The weighted mean was calculated from the pre-dose FEV1 and the post-dose FEV1 measurements at 5, 15, 30, and 60 minutes (min) and 2, 4, 6, 8, 12, 13, 14, 16, 20, and 24 hours on Treatment Day 84. Baseline trough FEV1 was the mean of the two assessments made 30 and 5 minutes pre-dose on Treatment Day 1. Change from Baseline was calculated as the average of the Day 84 values minus the Baseline value.

Secondary Outcome Measures:

- Time to Onset on Treatment Day 1 [Time Frame: Day 1] [Designated as safety issue: No]

Time to onset on Treatment Day 1 is defined as the time to an increase of 100 milliliters (mL) from Baseline in FEV1. Time of onset was calculated over 0 to 4 hours (5 min, 30 min, 60 min, 120 min, and 240 min) post-dose.

Enrollment: 521

Study Start Date: March 2011

Study Completion Date: December 2011

Primary Completion Date: December 2011

Arms	Assigned Interventions
Experimental: Fluticasone Furoate /	Drug: Fluticasone Furoate 100mcg / GW642444

Arms	Assigned Interventions
GW642444 (vilanterol) Inhaled Corticosteroid (ICS)/ Long acting Beta Agonist (LABA)	(vilanterol) 25mcg inhalation powder
Active Comparator: Fluticasone Propionate / salmeterol Inhaled Corticosteroid (ICS)/ Long acting Beta Agonist (LABA)	Drug: Fluticasone Propionate 250mcg/ salmeterol 50mcg inhalation powder

This is a randomized, double-blind, double-dummy, multi-centre parallel group study. Subjects who meet the eligibility criteria at Screening and meet the randomization criteria at the end of a 2-week Run-In period will enter a 12-week treatment period. There will be a 7-day Follow-up period after the treatment period.

Eligibility

Ages Eligible for Study: 40 Years and older

Genders Eligible for Study: Both

Inclusion Criteria:

- Signed and dated written informed consent
- Male or females ≥ 40 years of age
- Established clinical history of COPD by ATS/ERS definition
- Females are eligible to enter and participate if of non-childbearing potential, or if of child bearing potential, has a negative serum pregnancy test at screening, and agrees to one of the acceptable contraceptive methods listed in protocol, used consistently and correctly
- Former or current smoker > 10 pack years
- Post-albuterol spirometry criteria: $FEV1/FVC$ ratio ≤ 0.70 and $FEV1 \leq 70\%$ of predicted normal (NHANES III)

Exclusion Criteria:

- Current diagnosis of asthma
- Subjects with other respiratory disorders including active tuberculosis, $\alpha 1$ -antitrypsin deficiency, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases
- Lung volume reduction surgery within previous 12 months

- Clinically significant abnormalities not due to COPD by chest x-ray
- Hospitalized for poorly controlled COPD within 12 weeks of Screening
- Poorly controlled COPD 6 weeks prior to Screening, defined as acute worsening of COPD that is managed by the subject with corticosteroids or antibiotics or that requires treatment prescribed by a physician
- Lower respiratory infection requiring antibiotics 6 weeks prior to Screening
- Uncontrolled or clinically significant (in opinion of PI) cardiovascular, hypertension, neurological, psychiatric, renal, hepatic, immunological, endocrine, peptic ulcer disease, or hematological abnormalities
- Carcinoma not in complete remission for at least 5 years
- Subjects with history of hypersensitivity to study medications (e.g., beta-agonists, corticosteroid) or components of inhalation powder (e.g., lactose, magnesium stearate)
- Subjects with history of severe milk protein allergy that, in opinion of study physician, contraindicates subject's participation
- Known/suspected history of alcohol or drug abuse in the last 2 years
- Women who are pregnant or lactating or plan to become pregnant
- Subjects medically unable to withhold albuterol and/or ipratropium 4 hours prior to spirometry testing at each study visit
- Use of certain medications such as bronchodilators and corticosteroids for the protocol-specific times prior to Visit 1 (the Investigator will discuss the specific medications)
- Long Term Oxygen Therapy (LTOT) or nocturnal oxygen therapy >12 hours a day
- Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Screening or during the study
- Non-compliance or inability to comply with study procedures or scheduled visits
- Affiliation with investigator site

Contacts and Locations

Locations

United States, California

GSK Investigational Site

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United States, Florida

GSK Investigational Site

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Investigators

Study Director: GSK Clinical Trials GlaxoSmithKline

▶ More Information

Responsible Party: GlaxoSmithKline
Study ID Numbers: 113109
Health Authority: United States: Food and Drug Administration

Study Results

▶ Participant Flow

Pre-Assignment Details

At Visit 1, participants entered a 2-week, single-blind (placebo) Run-in Period to obtain Baseline assessments of salbutamol use and to evaluate adherence with study treatment and procedures, diary card completion, and assessment of disease stability. At Visit 2, participants were randomized to a 12-week, double-blind Treatment Period.

Reporting Groups

	Description
Placebo + Salbutamol	Participants were instructed to take single-blind placebo (ACCUHALER/DISKUS and Novel Dry Powder Inhaler [NDPI]): one inhalation each morning from each device, and one inhalation from the ACCUHALER/DISKUS in the evening. In addition, all participants

	Description
	received supplemental albuterol (salbutamol) (metered dose inhaler [MDI] and/or nebulas) to be used on an as-needed basis. Ipratropium bromide alone was permitted, provided that the participant was on a stable dose from Visit 1 (Screening) and remained on the stable dose throughout the study; however, ipratropium must have been withheld for 4 hours prior to and during each clinic visit.
FSC 250/50 µg BID	Participants received a Fluticasone Propionate and Salmeterol (FSC) 250/50 microgram (µg) inhalation (available as a combination dry inhalation powder of Fluticasone 250 µg and Salmeterol 50 µg in single strip) twice daily (BID) (morning and evening) from the ACCUHALER/DISKUS and placebo once daily (QD) in the morning from the NDPI over the course of 12 weeks.
FF/VI 100/25 µg QD	Participants received a Fluticasone Furoate /Vilanterol (FF/VI) 100/25 µg inhalation (available as dry inhalation powder in two separate strips of FF 100 µg and VI 25 µg) QD in the morning from the NDPI and placebo BID (morning and evening) from the ACCUHALER/DISKUS over the course of 12 weeks.

2-week Run-in Period

	Placebo + Salbutamol	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Started	733	0	0
Completed	521	0	0
Not Completed	212	0	0
Inclusion/Exclusion Criteria not Met	125	0	0
Continuation Criteria not	73	0	0

	Placebo + Salbutamol	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Met			
Withdrawal by Subject	7	0	0
Physician Decision	5	0	0
Protocol Violation	1	0	0
Adverse Event	1	0	0

Double-Blind (DB) Treatment Period

	Placebo + Salbutamol	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Started	0	260	261
Completed	0	235	239
Not Completed	0	25	22
Adverse Event	0	8	4
Lack of Efficacy	0	0	2
Protocol Violation	0	6	7
Lost to Follow-up	0	1	1
Physician Decision	0	2	3
Withdrawal by Subject	0	7	4
Did not Receive DB Study Medication	0	1	1



Baseline Characteristics

Reporting Groups

	Description
FSC 250/50 µg BID	Participants received a Fluticasone Propionate and Salmeterol (FSC) 250/50 microgram (µg) inhalation (available as a combination dry inhalation powder of Fluticasone 250 µg and Salmeterol 50 µg in single strip) twice daily (BID) (morning and evening) from the ACCUHALER/DISKUS and placebo once daily (QD) in the morning from the NDPI over the course of 12 weeks.
FF/VI 100/25 µg QD	Participants received a Fluticasone Furoate /Vilanterol (FF/VI) 100/25 µg inhalation (available as dry inhalation powder in two separate strips of FF 100 µg and VI 25 µg) QD in the morning from the NDPI and placebo BID (morning and evening) from the ACCUHALER/DISKUS over the course of 12 weeks.

Baseline Measures

	FSC 250/50 µg BID	FF/VI 100/25 µg QD	Total
Number of Participants	259	260	519
Age, Continuous ^[1] [units: Years] Mean (Standard Deviation)	61.2 (8.32)	61.1 (7.92)	61.2 (8.11)
Gender, Male/Female ^[2] [units: Participants]			
Female	90	96	186
Male	169	164	333
Race/Ethnicity, Customized ^[3] [units: participants]			
African American/ African Heritage	9	5	14

	FSC 250/50 µg BID	FF/VI 100/25 µg QD	Total
American Indian or Alaska Native	0	1	1
White/Caucasian/European Heritage	250	254	504

- [1] Baseline characteristic data are reported for members of the Intent-to-Treat Population, comprised of all randomized participants who received at least one dose of study medication during the treatment period.
- [2] Baseline characteristic data are reported for members of the Intent-to-Treat Population, comprised of all randomized participants who received at least one dose of study medication during the treatment period.
- [3] Baseline characteristic data are reported for members of the Intent-to-Treat Population, comprised of all randomized participants who received at least one dose of study medication during the treatment period.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Change From Baseline Trough in 24-hour Weighted-mean FEV1 on Treatment Day 84
Measure Description	Pulmonary function was measured by forced expiratory volume in one second (FEV1). The weighted mean was calculated from the pre-dose FEV1 and the post-dose FEV1 measurements at 5, 15, 30, and 60 minutes (min) and 2, 4, 6, 8, 12, 13, 14, 16, 20, and 24 hours on Treatment Day 84. Baseline trough FEV1 was the mean of the two assessments made 30 and 5 minutes pre-dose on Treatment Day 1. Change from Baseline was calculated as the average of the Day 84 values minus the Baseline value.

Time Frame	Baseline (Day 1) and Day 84
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
FSC 250/50 µg BID	Participants received a Fluticasone Propionate and Salmeterol (FSC) 250/50 microgram (µg) inhalation (available as a combination dry inhalation powder of Fluticasone 250 µg and Salmeterol 50 µg in single strip) twice daily (BID) (morning and evening) from the ACCUHALER/DISKUS and placebo once daily (QD) in the morning from the NDPI over the course of 12 weeks.
FF/VI 100/25 µg QD	Participants received a Fluticasone Furoate /Vilanterol (FF/VI) 100/25 µg inhalation (available as dry inhalation powder in two separate strips of FF 100 µg and VI 25 µg) QD in the morning from the NDPI and placebo BID (morning and evening) from the ACCUHALER/DISKUS over the course of 12 weeks.

Measured Values

	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Number of Participants Analyzed	213	228
Change From Baseline Trough in 24-hour Weighted-mean FEV1 on Treatment Day 84 [units: Liters] Least Squares Mean (Standard Error)	0.094 (0.0158)	0.174 (0.0153)

Statistical Analysis 1 for Change From Baseline Trough in 24-hour Weighted-mean FEV1 on Treatment Day 84

Groups	FSC 250/50 µg BID, FF/VI 100/25 µg QD
Method	ANCOVA
P-Value	<0.001
Other Estimated Parameter [Least square mean difference]	0.080
95% Confidence Interval	0.037 to 0.124

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:

[Not specified.]

2. Secondary Outcome Measure:

Measure Title	Time to Onset on Treatment Day 1
Measure Description	Time to onset on Treatment Day 1 is defined as the time to an increase of 100 milliliters (mL) from Baseline in FEV1. Time of onset was calculated over 0 to 4 hours (5 min, 30 min, 60 min, 120 min, and 240 min) post-dose.
Time Frame	Day 1
Safety Issue?	No

Analysis Population Description

ITT Population. Only participants available at the indicated time point were assessed.

Reporting Groups

	Description
FSC 250/50 µg BID	Participants received a Fluticasone Propionate and Salmeterol (FSC) 250/50 microgram (µg) inhalation (available as a combination dry inhalation powder of Fluticasone 250 µg and Salmeterol 50 µg in single strip) twice daily (BID) (morning and evening) from the ACCUHALER/DISKUS and placebo once daily (QD) in the morning from the NDPI over the course of 12 weeks.
FF/VI 100/25 µg QD	Participants received a Fluticasone Furoate /Vilanterol (FF/VI) 100/25 µg inhalation (available as dry inhalation powder in two separate strips of FF 100 µg and VI 25 µg) QD in the morning from the NDPI and placebo BID (morning and evening) from the ACCUHALER/DISKUS over the course of 12 weeks.

Measured Values

	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Number of Participants Analyzed	257	258
Time to Onset on Treatment Day 1 [units: Minutes] Median (Full Range)	30 (5 to 240)	15 (5 to 240)



Reported Adverse Events

Reporting Groups

	Description
FSC 250/50 µg BID	Participants received a Fluticasone Propionate and Salmeterol (FSC) 250/50 microgram (µg) inhalation (available as a combination dry inhalation powder of Fluticasone 250 µg and Salmeterol 50 µg in single

	Description
	strip) twice daily (BID) (morning and evening) from the ACCUHALER/DISKUS and placebo once daily (QD) in the morning from the NDPI over the course of 12 weeks.
FF/VI 100/25 µg QD	Participants received a Fluticasone Furoate /Vilanterol (FF/VI) 100/25 µg inhalation (available as dry inhalation powder in two separate strips of FF 100 µg and VI 25 µg) QD in the morning from the NDPI and placebo BID (morning and evening) from the ACCUHALER/DISKUS over the course of 12 weeks.

Time Frame

Serious adverse events (SAEs) and non-serious adverse events were collected from Baseline to the end of the study (up to 12 weeks).

Additional Description

SAEs and non-serious adverse events are reported for members of the Intent-to-Treat Population, comprised of all randomized participants who received at least one dose of study medication during the treatment period.

Serious Adverse Events

	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Total # participants affected/at risk	8/259 (3.09%)	3/260 (1.15%)
Cardiac disorders		
Atrial fibrillation † ^A		
# participants affected/at risk	1/259 (0.39%)	1/260 (0.38%)
# events		

	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Cardiac failure congestive † A		
# participants affected/at risk	1/259 (0.39%)	0/260 (0%)
# events		
Cardio-respiratory arrest † ^A		
# participants affected/at risk	1/259 (0.39%)	0/260 (0%)
# events		
Hepatobiliary disorders		
Cholecystitis † ^A		
# participants affected/at risk	0/259 (0%)	1/260 (0.38%)
# events		
Infections and infestations		
Bronchitis † ^A		
# participants affected/at risk	1/259 (0.39%)	0/260 (0%)
# events		
Injury, poisoning and procedural complications		
Rib fracture † ^A		

	FSC 250/50 µg BID	FF/VI 100/25 µg QD
# participants affected/at risk	1/259 (0.39%)	0/260 (0%)
# events		
Musculoskeletal and connective tissue disorders		
Lumbar spinal stenosis † ^A		
# participants affected/at risk	0/259 (0%)	1/260 (0.38%)
# events		
Synovial cyst † ^A		
# participants affected/at risk	0/259 (0%)	1/260 (0.38%)
# events		
Respiratory, thoracic and mediastinal disorders		
Acute respiratory failure † ^A		
# participants affected/at risk	0/259 (0%)	1/260 (0.38%)
# events		
Chronic obstructive pulmonary disease † ^A		
# participants affected/at risk	3/259 (1.16%)	0/260 (0%)

	FSC 250/50 µg BID	FF/VI 100/25 µg QD
risk		
# events		
Epistaxis † ^A		
# participants affected/at risk	1/259 (0.39%)	0/260 (0%)
# events		
Pulmonary embolism † ^A		
# participants affected/at risk	0/259 (0%)	1/260 (0.38%)
# events		
Vascular disorders		
Deep vein thrombosis † ^A		
# participants affected/at risk	0/259 (0%)	1/260 (0.38%)
# 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%

	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Total # participants affected/at risk	18/259 (6.95%)	23/260 (8.85%)

	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Infections and infestations		
Nasopharyngitis † ^A		
# participants affected/at risk	7/259 (2.7%)	8/260 (3.08%)
# events		
Nervous system disorders		
Headache † ^A		
# participants affected/at risk	11/259 (4.25%)	16/260 (6.15%)
# 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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