Protocol Registration Receipt
03/27/2014

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

Study Evaluating 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 (COPD)

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01323621

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 Drug: Double-dummy placebo Drug: Salbutamol as needed	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), defined as the maximal amount of air that can be forcefully exhaled in one second. 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 post-dose on Treatment Day 84. Baseline trough FEV1 was calculated as 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. Analysis of covariance (ANCOVA) was conducted with covariates for country, smoking status, reversibility, and Baseline FEV1.

Secondary Outcome Measures:

- Time to Onset on Treatment Day 1 [Time Frame: Baseline and 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 to onset was calculated over 0 to 4 hours (5 min, 15 min, 30 min, 60 min, 120 min, and 240 min) post-dose.

Enrollment: 512
Study Start Date: March 2011
Study Completion Date: January 2012
Primary Completion Date: January 2012

Arms	Assigned Interventions
Experimental: Fluticasone Furoate / GW642444 (vilanterol) Inhaled Corticosteroid (ICS)/ Long acting Beta Agonist (LABA)	Drug: Fluticasone Furoate 100mcg/ GW642444 (vilanterol) 25mcg inhalation powder Drug: Double-dummy placebo inhalation powder Drug: Salbutamol as needed inhalation powder
Active Comparator: Fluticasone Propionate / salmeterol Inhaled Corticosteroid (ICS)/ Long acting Beta Agonist (LABA)	Drug: Fluticasone Propionate 250mcg / salmeterol 50mcg inhalation powder Drug: Double-dummy placebo inhalation powder Drug: Salbutamol as needed 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 ≤ 70% of predicted normal (NHANES III)

Exclusion Criteria:

- Current diagnosis of asthma
- Subjects with other respiratory disorders including active tuberculosis, α1-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, Alabama

GSK Investigational Site

Jasper, Alabama, United States, 35501

United States, California

GSK Investigational Site

Riverside, California, United States, 92506

United States, Florida

GSK Investigational Site

DeLand, Florida, United States, 32720

United States, Idaho

GSK Investigational Site

Coeur D'Alene, Idaho, United States, 83814

United States, Minnesota

GSK Investigational Site

Minneapolis, Minnesota, United States, 55402

United States, Ohio

GSK Investigational Site

Cincinnati, Ohio, United States, 45231

United States, Oklahoma

GSK Investigational Site

Oklahoma City, Oklahoma, United States, 73103

United States, Oregon

GSK Investigational Site

Medford, Oregon, United States, 97504

United States, South Carolina

GSK Investigational Site

Gaffney, South Carolina, United States, 29340

GSK Investigational Site

Orangeburg, South Carolina, United States, 29118

GSK Investigational Site

Seneca, South Carolina, United States, 29678

GSK Investigational Site

Spartanburg, South Carolina, United States, 29303

United States, Texas

GSK Investigational Site

Boerne, Texas, United States, 78006

Germany

GSK Investigational Site

Luebeck, Schleswig-Holstein, Germany, 23552

Italy

GSK Investigational Site

Napoli, Campania, Italy, 80131

GSK Investigational Site

San Felice a Cancello Caserta, Campania, Italy, 81027

GSK Investigational Site

Telese Terme (BN), Campania, Italy, 82037

GSK Investigational Site

Parma, Emilia-Romagna, Italy, 43100

GSK Investigational Site

Roma, Lazio, Italy, 00185

GSK Investigational Site

Rozzano (MI), Lombardia, Italy, 20089

GSK Investigational Site

Torrette (AN), Marche, Italy, 60126

GSK Investigational Site

Cagliari, Sardegna, Italy, 09126

GSK Investigational Site

Palermo, Sicilia, Italy, 90146

GSK Investigational Site

Firenze, Toscana, Italy, 50134

GSK Investigational Site

Padova, Veneto, Italy, 35128

South Africa

GSK Investigational Site

Bellville, South Africa, 7531

GSK Investigational Site

Bloemfontein, South Africa, 9301

GSK Investigational Site
Bloemfontein, South Africa, 9301
GSK Investigational Site
Bloemfontein, South Africa, 9301
GSK Investigational Site
Cape Town, South Africa, 7572
GSK Investigational Site
George, South Africa, 6529
GSK Investigational Site
Port Elizabeth, South Africa, 6045
GSK Investigational Site
Reiger Park, South Africa, 1459
GSK Investigational Site
Somerset West, South Africa, 7130
GSK Investigational Site
Thabazimbi, South Africa, 0380
GSK Investigational Site
Witbank, South Africa, 1034
GSK Investigational Site
Benoni, Gauteng, South Africa, 1501

Spain

GSK Investigational Site
Alicante, Spain, 03114
GSK Investigational Site
Córdoba, Spain, 14004
GSK Investigational Site
Lugo, Spain, 27003
GSK Investigational Site
Mérida (Badajoz), Spain, 06800
GSK Investigational Site
Ponferrada (León), Spain, 24411
GSK Investigational Site
Valladolid, Spain, 47005

Ukraine

GSK Investigational Site

Cherkassy, Ukraine, 18009

GSK Investigational Site

Donetsk, Ukraine, 83099

GSK Investigational Site

Kharkiv, Ukraine, 61002

GSK Investigational Site

Kharkiv, Ukraine, 61035

GSK Investigational Site

Kiev, Ukraine, 03680

GSK Investigational Site

Kiev, Ukraine, 03680

GSK Investigational Site

Kyiv, Ukraine, 03049

GSK Investigational Site

Kyiv, Ukraine, 03680

GSK Investigational Site

Kyiv, Ukraine, 04107

GSK Investigational Site

Mykolayiv, Ukraine, 54003

GSK Investigational Site

Vinnytsia, Ukraine, 21018

Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Responsible Party:	GlaxoSmithKline
Study ID Numbers:	112352
Health Authority:	United States: Food and Drug Administration

---

Study Results

Participant Flow

Pre-Assignment Details

At Visit 1, eligible participants entered a 2-week, single blind (placebo) Run-In Period to obtain Baseline assessments of albuterol (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 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 received supplemental albuterol (salbutamol) (metered dose inhaler [MDI] and/or nebules) 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 a 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 a 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, Single-blind Run In Period

	Placebo + Salbutamol	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Started	739	0	0
Completed	511	0	0
Not Completed	228	0	0
Not Met Inclusion/Exclusion Criteria	121	0	0
Physician Decision	7	0	0
Withdrawal by Subject	12	0	0
Protocol Violation	1	0	0
Lost to Follow-up	1	0	0
Did Not Meet Continuation Criteria	86	0	0

12-week, Double-blind Treatment Period

	Placebo + Salbutamol	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Started	0	252	259
Completed	0	237	239
Not Completed	0	15	20
Adverse Event	0	1	5
Lack of Efficacy	0	2	6
Protocol Violation	0	4	4
Lost to Follow-up	0	1	0

	Placebo + Salbutamol	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Physician Decision	0	2	1
Withdrawal by Subject	0	5	4

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 a 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 a 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	252	259	511
Age, Continuous [units: Years] Mean (Standard Deviation)	61.7 (9.05)	61.6 (9.59)	61.6 (9.32)

	FSC 250/50 µg BID	FF/VI 100/25 µg QD	Total
Gender, Male/Female [units: Participants]			
Female	85	78	163
Male	167	181	348
Race/Ethnicity, Customized [units: participants]			
White - White/Caucasian/European Heritage	238	241	479
African American/African Heritage	14	17	31
White - Arabic/North African Heritage	0	1	1

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), defined as the maximal amount of air that can be forcefully exhaled in one second. 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 post-dose on Treatment Day 84. Baseline trough FEV1 was calculated as 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. Analysis of covariance (ANCOVA) was conducted with covariates for country, smoking status, reversibility, and Baseline FEV1.
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 those participants available at the indicated time points 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 a 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 a 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	217	219

	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Change From Baseline Trough in 24-Hour Weighted Mean FEV1 on Treatment Day 84 [units: Liters] Least Squares Mean (Standard Error)	0.114 (0.0183)	0.142 (0.0182)

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	0.267
Other Estimated Parameter [Least squares mean difference]	0.029
95% Confidence Interval	-0.022 to 0.080

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.]

Other relevant estimation information:

ANCOVA analysis was conducted with covariates for country, smoking status, reversibility, and Baseline FEV1.

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 to onset was calculated over 0 to 4 hours (5 min, 15 min, 30 min, 60 min, 120 min, and 240 min) post-dose.
Time Frame	Baseline and Day 1
Safety Issue?	No

Analysis Population Description

ITT Population

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 a 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 a 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	251	258
Time to Onset on Treatment Day 1	30 (5 to 240)	16 (5 to 240)

	FSC 250/50 µg BID	FF/VI 100/25 µg QD
[units: Minutes] Median (Full Range)		

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 a 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 a 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.

Serious Adverse Events

	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Total # participants affected/at risk	3/252 (1.19%)	5/259 (1.93%)
Cardiac disorders		
Cardiac failure † [A]		

	FSC 250/50 µg BID	FF/VI 100/25 µg QD
# participants affected/at risk	0/252 (0%)	1/259 (0.39%)
# events		
Myocardial infarction † [A]		
# participants affected/at risk	0/252 (0%)	1/259 (0.39%)
# events		
Infections and infestations		
Infective tenosynovitis † [A]		
# participants affected/at risk	0/252 (0%)	1/259 (0.39%)
# events		
Injury, poisoning and procedural complications		
Comminuted fracture † [A]		
# participants affected/at risk	1/252 (0.4%)	0/259 (0%)
# events		
Wrist fracture † [A]		
# participants affected/at risk	1/252 (0.4%)	0/259 (0%)
# events		

	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Lung adenocarcinoma metastatic † [A]		
# participants affected/at risk	0/252 (0%)	1/259 (0.39%)
# events		
Respiratory, thoracic and mediastinal disorders		
Acute respiratory failure † [A]		
# participants affected/at risk	0/252 (0%)	1/259 (0.39%)
# events		
Bronchitis chronic † [A]		
# participants affected/at risk	0/252 (0%)	1/259 (0.39%)
# events		
Chronic obstructive pulmonary disease † [A]		
# participants affected/at risk	0/252 (0%)	1/259 (0.39%)
# events		

	FSC 250/50 µg BID	FF/VI 100/25 µg QD
Pulmonary embolism † [A]		
# participants affected/at risk	1/252 (0.4%)	0/259 (0%)
# events		
Respiratory failure † [A]		
# participants affected/at risk	0/252 (0%)	1/259 (0.39%)
# 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	10/252 (3.97%)	12/259 (4.63%)
Nervous system disorders		
Headache † [A]		
# participants affected/at risk	10/252 (3.97%)	12/259 (4.63%)
# 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:

Name/Official Title: GSK Response Center
Organization: GlaxoSmithKline
Phone: 866-435-7343
Email: