Protocol Registration Receipt
07/10/2014

A Study to Compare the Impact of Fulticasone Furoate/Vilanterol vs. Tiotropium on Arterial Stiffness in COPD

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01395888

Purpose

This study is designed to evaluate the effect of fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) Inhalation Powder once daily (QD) on arterial stiffness compared with Tiotropium QD over 12 week treatment period in subjects with COPD and aortic pulse wave velocity (aPWV) > 12.0 m/s at Visit 1. Arterial stiffness will be measured as aPWV. This is a comparator, randomised, double-blind, double-dummy, parallel group, multi-centre 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 an approximate 7-day Follow-up period after the treatment period.

Condition	Intervention	Phase
Pulmonary Disease, Chronic Obstructive	Drug: fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) 100/25 mcg Novel Dry Powder Inhaler (NDPI) Drug: Tiotropium	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study
Official Title: A 12week Study to Evaluate the Effect of Fluticasone Furoate (FF, GW685698)/Vilanterol (VI, GW642444) 100/25 mcg Inhalation Powder Delivered Once Daily Via a Novel Dry Powder Inhaler (NDPI) on Arterial Stiffness Compared With Tiotropium Bromide 18 mcg Delivered Once Daily Via a HandiHaler in Subjects With Chronic Obstructive Pulmonary Disease (COPD).

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Mean Change From Baseline (BL) in Aortic Pulse Wave Velocity (aPWV) at the End of the 12-week Treatment Period (Day 84) [Time Frame: Baseline to Day 84 (Early Withdrawal)] [Designated as safety issue: No]

  PWV is defined as the speed of travel of the pressure pulse along an arterial segment and can be obtained for any arterial segment accessible to palpation. aPWV is measured with tonometers positioned transcutaneously at the base of the common carotid artery and over the femoral artery. PWV increases with arterial stiffness and is defined by the Moens-Korteweg equation: PWV=square root of Eh/2pR, where E is Young's modulus of the arterial wall, h is the wall thickness, R is the arterial radius at the end of diastole, and p is the blood density. Change from Baseline was calculated as the Day 84 value minus the Baseline value. The analysis was performed using a repeated measures model with covariates of treatment, visit, age, gender, smoking status at screening, geographical region, Baseline aPWV, and interaction terms of Baseline by visit and treatment by visit.

Enrollment: 260
Study Start Date: June 2011
Study Completion Date: August 2012
Primary Completion Date: August 2012

Arms	Assigned Interventions
Experimental: Relovair Inhaled long-acting bronchodilator and corticosteroid combination	Drug: fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) 100/25 mcg Novel Dry Powder Inhaler (NDPI) fluticasone furoate (FF, GW685698)/vilanterol (VI,

Arms	Assigned Interventions
	GW642444) 100/25 mcg Inhalation Powder delivered once daily via a Novel Dry Powder Inhaler (NDPI)
Active Comparator: Tiotropium Inhaled long-acting anticholinergic	Drug: Tiotropium • Tiotropium (18 mcg) administered QD via a HandiHaler

This is a Phase IIIb comparator, double-blind, double-dummy, randomised (1:1), parallel group, multi-centre study. At Visit 1 (Screening Visit), subjects who meet the pre-defined Inclusion Criteria and none of the Exclusion Criteria will enter a 2-week, single-blind placebo Run-in Period. The purpose of the Run-In Period is to monitor albuterol/salbutamol use at baseline, and to ensure that subjects' COPD is at a stable stage at randomization. Subject's adherence with study procedures, diary completion will also be evaluated during the Run-In Period. At the end of the Run-in period, subjects will be assessed and those who meet the randomisation criteria will receive one of the following two double-blind treatments for 12 weeks:

- FF (100 mcg)/VI (25 mcg) administered QD via a NDPI in the morning
- Tiotropium (18 mcg) administered QD via a HandiHaler in the morning

To ensure blinding of the treatments and to ensure a double-dummy design matching NDPI and HandiHaler will be utilised. Each subject will be instructed to self administer blinded study drug during the double blind treatment period as follows:

- Each morning take 1 inhalation from NDPI containing FF (100 mcg)/VI (25 mcg) followed by 1 inhalation from placebo capsule delivered via HandiHaler.
- Each morning take 1 inhalation from matching placebo NDPI followed by 1 inhalation from a capsule containing tiotropium 18 mcg delivered via HandiHaler.

An inhaled short acting beta2-receptor agonist, salbutamol/albuterol will be provided to subjects to use as needed throughout the Run-in and Treatment periods for relief of COPD symptoms. Ipratropium bromide is permitted if the subject is on a stable dose from Screening (Visit 1) and remains on the stable dose throughout the study. Subjects who experience an exacerbation of their COPD (which requires medication in addition to an increase in rescue medication) or a lower respiratory tract infection (LRTI) during the run-in period are not eligible to enter the treatment period. Any subject who experiences a similar COPD exacerbation (sec 4.4) or LRTI at any time on therapy will be withdrawn from the study. The aPWV will be measured at Screening and clinic Visits 3-5. Disease specific health status will be evaluated using the St. George's Respiratory Questionnaire (SGRQ-C), Euro Qol Questionnaire (EQ-5D) for COPD patients and the COPD Assessment Test (CAT) at Visit 2 (Day 1) and at Visit 5 (Weeks 12). The 12-lead ECG will be evaluated at Visit 1 (Screening) only. Vital signs (blood pressure and pulse rate), spirometry measurements, and clinical laboratory tests (hematology and chemistry) and other study-specific safety assessments will be obtained at selected clinic visits. A follow-up phone call will occur approximately 7 days after the last clinic visit. The overall study duration from Screening to Follow-up for each subject is approximately 15 weeks. Subjects will be considered to have completed the study upon completion of assessments and procedures up to and including completion of Follow-up Phone Contact (7 ± 2 days post Visit 5).

Eligibility

Ages Eligible for Study: 40 Years to 80 Years
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.
- Age: greater then or equal to 40 years of age at Screening (Visit 1)
- COPD diagnosis: Subjects with a clinical history of COPD in accordance with the following definition by the American Thoracic Society (ATS) /European Respiratory Society(ERS).
- Subjects with a current or prior history ofgreater then or equal to 10 pack-years of cigarette smoking at Screening (Visit 1).
- Subjects with a measured post-albuterol/salbutamol FEV1 less then 70% of predicted at Screening (Visit 1).
- Subjects with a measured post-albuterol/salbutamol FEV1/FVC ratio of less then or equal to 0.70 at Screening (Visit 1).
- Exacerbation History: Subjects who have been hospitalised or have been treated with oral corticosteroids or antibiotics for their COPD within the last 3 years prior to Screening (V1).
- Baseline aPWV: subjects with a measured aPWV greater then 12.0 m/s at Screening (Visit 1).

Exclusion Criteria:

- Body Mass Index of less then or equal to 35

Contacts and Locations

Locations

Argentina

GSK Investigational Site
Buenos Aires, Argentina, C1425BEN

GSK Investigational Site
Ciudad Autónoma de Buenos Aires, Argentina, C1426ABP

GSK Investigational Site
San Juan, Argentina, 5400

GSK Investigational Site

Tucuman, Argentina, 4000

GSK Investigational Site

Tucumán, Argentina, T4000DGF

GSK Investigational Site

Buenos Aires, Buenos Aires, Argentina, C1424BSF

GSK Investigational Site

Ciudad Autonoma de Buenos Aires, Buenos Aires, Argentina, C1056ABJ

GSK Investigational Site

Mendoza, Mendoza, Argentina, M5500CCG

GSK Investigational Site

Mendoza, Mendoza, Argentina, 5500

GSK Investigational Site

Rosario, Santa Fe, Argentina, S2000JKR

France

GSK Investigational Site

Bethune Cedex, France, 62408

GSK Investigational Site

Grenoble Cedex 09, France, 38043

GSK Investigational Site

Lille, France, 59000

GSK Investigational Site

Montpellier cedex 5, France, 34295

GSK Investigational Site

Reims Cedex, France, 51092

GSK Investigational Site

Saint-Michel, France, 16470

Germany

GSK Investigational Site

Berlin, Berlin, Germany, 10787

GSK Investigational Site

Berlin, Berlin, Germany, 13125

GSK Investigational Site

Berlin, Berlin, Germany, 10789

GSK Investigational Site

Hamburg, Hamburg, Germany, 20354

GSK Investigational Site

Immenhausen, Hessen, Germany, 34376

GSK Investigational Site

Schwerin, Mecklenburg-Vorpommern, Germany, 19055

GSK Investigational Site

Hannover, Niedersachsen, Germany, 30159

GSK Investigational Site

Goch, Nordrhein-Westfalen, Germany, 47574

GSK Investigational Site

Magdeburg, Sachsen-Anhalt, Germany, 39112

GSK Investigational Site

Geesthacht, Schleswig-Holstein, Germany, 21502

Italy

GSK Investigational Site

Eboli (SA), Campania, Italy, 84025

GSK Investigational Site

Bologna, Emilia-Romagna, Italy, 40138

GSK Investigational Site

Crema, Lombardia, Italy, 26013

GSK Investigational Site

Pavia, Lombardia, Italy, 27100

GSK Investigational Site

Cassano Murge (BA), Puglia, Italy, 70020

Norway

GSK Investigational Site

Bergen, Norway, 5017

GSK Investigational Site

Bergen, Norway, N-5021

GSK Investigational Site

Drammen, Norway, 3004

GSK Investigational Site

Fredrikstad, Norway, 1606

GSK Investigational Site

Skedsmokorset, Norway, N-2020

Russian Federation

GSK Investigational Site

Chita, Russian Federation, 672000

GSK Investigational Site

Kemerovo, Russian Federation, 650002

GSK Investigational Site

Kokhma, Russian Federation, 153511

GSK Investigational Site

Moscow, Russian Federation, 105077

GSK Investigational Site

Moscow, Russian Federation, 115093

GSK Investigational Site

Penza, Russian Federation, 440067

GSK Investigational Site

Saratov, Russian Federation, 410053

GSK Investigational Site

St. Petersburg, Russian Federation, 197022

GSK Investigational Site

Vladivostok, Primorskiy Kray, Russian Federation, 690022

GSK Investigational Site

Voronezh, Russian Federation, 394018

GSK Investigational Site

Yaroslavl, Russian Federation, 150062

GSK Investigational Site

Yaroslavl, Russian Federation, 150003

Ukraine

GSK Investigational Site

Cherkassy, Ukraine, 18009

GSK Investigational Site

Donetsk, Ukraine, 83099

GSK Investigational Site

Kharkiv, Ukraine, 61035

GSK Investigational Site

Kiev, Ukraine, 03680

GSK Investigational Site

Kyiv, Ukraine, 03680
GSK Investigational Site
Kyiv, Ukraine, 03049
GSK Investigational Site
Yalta, Ukraine, 98603

Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Responsible Party:	GlaxoSmithKline
Study ID Numbers:	115247
Health Authority:	United States: Food and Drug Administration

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Study Results

Participant Flow

Recruitment Details

A total of 260 participants were randomized. Three of these participants were randomized in error (they were determined not to have met entry criteria and were classified as run-in/screen failures); thus, they did not receive investigational product and are not captured in the Treatment Period table of the Participant Flow module.

Pre-Assignment Details

At Visit (V) 1, eligible participants (par.) entered a 2-week, single-blind placebo Run-in Period (RIP) to establish a stable baseline. At V 2, eligible par. were randomized to a 12-week, double-blind, double-dummy Treatment Period. 802 par. were screened, 279 par. entered the RIP, and 257 par. were randomized and received >=1 study treatment dose.

Reporting Groups

	Description
Salb/Alb + IBr	Participants were provided with an inhaled short-acting beta2-receptor

	Description
	agonist, salbutamol/albuterol (Salb/Alb), for use as needed throughout the Run-in Period for relief of chronic obstructive pulmonary disease (COPD) symptoms. Ipratropium bromide (IBr) was permitted during the Run-in Period and for up to 4 hours prior to Randomization (Visit 2) if the participant was on a stable dose prior to Screening (Visit 1). Following randomization, IBr was not permitted during exposure to study treatment.
FF/VI 100/25 µg	Participants (par.) self-administered one inhalation of Fluticasone Furoate /Vilanterol (FF/VI) 100/25 micrograms (µg) via a dry powder inhaler (DPI) followed by 2 inhalations from a single placebo capsule delivered via a HandiHaler in the morning for 12 weeks. An inhaled short-acting beta2-receptor agonist, salbutamol/albuterol, was provided for participants to use as needed throughout the Treatment Period for relief of Chronic Obstructive Pulmonary Disease (COPD) symptoms.
Tiotropium Bromide 18 µg	Participants self-administered one inhalation of placebo via an DPI followed by 2 inhalations from a single capsule containing Tiotropiuum Bromide 18 µg via a HandiHaler. An inhaled short-acting beta2-receptor agonist, salbutamol/albuterol, was provided for participants to use as needed throughout the Treatment Period for relief of COPD symptoms.

2-week Run-in Period

	Salb/Alb + IBr	FF/VI 100/25 µg	Tiotropium Bromide 18 µg
Started	279	0	0
Completed	257	0	0
Not Completed	22	0	0

	Salb/Alb + IBr	FF/VI 100/25 µg	Tiotropium Bromide 18 µg
Adverse Event	2	0	0
Continuation Criteria Not Met	13	0	0
Lost to Follow-up	1	0	0
Protocol Violation	2	0	0
Withdrawal by Subject	4	0	0

Treatment Period (TP)

	Salb/Alb + IBr	FF/VI 100/25 µg	Tiotropium Bromide 18 µg
Started	0	127	130
Completed the Treatment Period	0	112 [1]	113 [2]
Completed	0	112 [3]	113 [4]
Not Completed	0	15	17
Adverse Event	0	7	6
Lack of Efficacy	0	4	3
Protocol Violation	0	1	5
Met Protocol-defined Stopping Criteria	0	1	0
Withdrawal by Subject	0	2	3

[1] Participants were considered to have completed the TP if they attended Visit 5 (Week 12).

[2] Participants were considered to have completed the TP if they attended Visit 5 (Week 12).

[3] Par. completed the study if they completed the TP and a safety follow-up phone contact 1 week later.

[4] Par. completed the study if they completed the TP and a safety follow-up phone contact 1 week later.

Baseline Characteristics

Reporting Groups

	Description
FF/VI 100/25 µg	Participants self-administered one inhalation of Fluticasone Furoate /Vilanterol (FF/VI) 100/25 micrograms (µg) via a dry powder inhaler (DPI) followed by 2 inhalations from a single placebo capsule delivered via a HandiHaler in the morning for 12 weeks. An inhaled short-acting beta2-receptor agonist, salbutamol/albuterol, was provided for participants to use as needed throughout the Treatment Period for relief of Chronic Obstructive Pulmonary Disease (COPD) symptoms.
Tiotropium Bromide 18 µg	Participants self-administered one inhalation of placebo via an DPI followed by 2 inhalations from a single capsule containing Tiotropiuum Bromide 18 µg via a HandiHaler. An inhaled short-acting beta2-receptor agonist, salbutamol/albuterol, was provided for participants to use as needed throughout the Treatment Period for relief of COPD symptoms.

Baseline Measures

	FF/VI 100/25 µg	Tiotropium Bromide 18 µg	Total
Number of Participants	127	130	257

	FF/VI 100/25 µg	Tiotropium Bromide 18 µg	Total
Age, Continuous [units: Years] Mean (Standard Deviation)	66.7 (7.20)	67.7 (7.34)	67.3 (7.28)
Gender, Male/Female [units: Participants]			
Female	19	18	37
Male	108	112	220
Race/Ethnicity, Customized White - White/Caucasian/European [units: participants]	127	130	257

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Mean Change From Baseline (BL) in Aortic Pulse Wave Velocity (aPWV) at the End of the 12-week Treatment Period (Day 84)
Measure Description	PWV is defined as the speed of travel of the pressure pulse along an arterial segment and can be obtained for any arterial segment accessible to palpation. aPWV is measured with tonometers positioned transcutaneously at the base of the common carotid artery and over the femoral artery. PWV increases with arterial stiffness and is defined by the Moens-Korteweg equation: PWV=square root of Eh/2pR, where E is Young's modulus of the arterial wall, h is the wall thickness, R is the arterial radius at the end of diastole, and p is the blood density. Change from Baseline was calculated as the Day 84 value minus the Baseline value. The analysis was performed using a repeated

	measures model with covariates of treatment, visit, age, gender, smoking status at screening, geographical region, Baseline aPWV, and interaction terms of Baseline by visit and treatment by visit.
Time Frame	Baseline to Day 84 (Early Withdrawal)
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all participants (par.) who were randomized to and received >=1 dose of randomized medication in the TP. The analysis model included all par. in the ITT Population without missing covariate information (MCI) and with >=1 post-BL measurement. Par. presented represent those with data available at Day 84 without MCI.

Reporting Groups

	Description
FF/VI 100/25 µg	Participants self-administered one inhalation of Fluticasone Furoate /Vilanterol (FF/VI) 100/25 micrograms (µg) via a dry powder inhaler (DPI) followed by 2 inhalations from a single placebo capsule delivered via a HandiHaler in the morning for 12 weeks. An inhaled short-acting beta2-receptor agonist, salbutamol/albuterol, was provided for participants to use as needed throughout the Treatment Period for relief of Chronic Obstructive Pulmonary Disease (COPD) symptoms.
Tiotropium Bromide 18 µg	Participants self-administered one inhalation of placebo via an DPI followed by 2 inhalations from a single capsule containing Tiotropiuum Bromide 18 µg via a HandiHaler. An inhaled short-acting beta2-receptor agonist, salbutamol/albuterol, was provided for participants to use as needed throughout the Treatment Period for relief of COPD symptoms.

Measured Values

	FF/VI 100/25 µg	Tiotropium Bromide 18 µg
Number of Participants Analyzed	106	102
Mean Change From Baseline (BL) in Aortic Pulse Wave Velocity (aPWV) at the End of the 12-week Treatment Period (Day 84) [units: meters per second (m/sec)] Least Squares Mean (Standard Error)	-0.859 (0.2590)	-1.118 (0.2620)

Statistical Analysis 1 for Mean Change From Baseline (BL) in Aortic Pulse Wave Velocity (aPWV) at the End of the 12-week Treatment Period (Day 84)

Groups	FF/VI 100/25 µg, Tiotropium Bromide 18 µg
Method	Mixed Models Analysis
P-Value	0.484
Other Estimated Parameter [Least Squares Mean Difference]	0.259
95% Confidence Interval	-0.468 to 0.986

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)

Reported Adverse Events

Reporting Groups

	Description
FF/VI 100/25 µg	Participants self-administered one inhalation of Fluticasone Furoate /Vilanterol (FF/VI) 100/25 micrograms (µg) via a dry powder inhaler (DPI) followed by 2 inhalations from a single placebo capsule delivered via a HandiHaler in the morning for 12 weeks. An inhaled short-acting beta2-receptor agonist, salbutamol/albuterol, was provided for participants to use as needed throughout the Treatment Period for relief of Chronic Obstructive Pulmonary Disease (COPD) symptoms.
Tiotropium Bromide 18 µg	Participants self-administered one inhalation of placebo via an DPI followed by 2 inhalations from a single capsule containing Tiotropiuum Bromide 18 µg via a HandiHaler. An inhaled short-acting beta2-receptor agonist, salbutamol/albuterol, was provided for participants to use as needed throughout the Treatment Period for relief of COPD symptoms.

Serious Adverse Events

	FF/VI 100/25 µg	Tiotropium Bromide 18 µg
Total # participants affected/at risk	7/127 (5.51%)	8/130 (6.15%)
Gastrointestinal disorders		
Acute abdomen †[A]		
# participants affected/at risk	1/127 (0.79%)	0/130 (0%)

	FF/VI 100/25 µg	Tiotropium Bromide 18 µg
# events		
Pancreatolithiasis † [A]		
# participants affected/at risk	1/127 (0.79%)	0/130 (0%)
# events		
General disorders		
Pyrexia † [A]		
# participants affected/at risk	1/127 (0.79%)	0/130 (0%)
# events		
Hepatobiliary disorders		
Bile duct obstruction † [A]		
# participants affected/at risk	1/127 (0.79%)	0/130 (0%)
# events		
Infections and infestations		
Peritonsillar abscess † [A]		
# participants affected/at risk	0/127 (0%)	1/130 (0.77%)
# events		

	FF/VI 100/25 µg	Tiotropium Bromide 18 µg
Pneumonia † [A]		
# participants affected/at risk	2/127 (1.57%)	0/130 (0%)
# events		
Injury, poisoning and procedural complications		
Multiple injuries † [A]		
# participants affected/at risk	0/127 (0%)	1/130 (0.77%)
# events		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Bronchial carcinoma † [A]		
# participants affected/at risk	1/127 (0.79%)	0/130 (0%)
# events		
Nervous system disorders		
Altered state of consciousness † [A]		

	FF/VI 100/25 µg	Tiotropium Bromide 18 µg
# participants affected/at risk	1/127 (0.79%)	0/130 (0%)
# events		
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease † [A]		
# participants affected/at risk	2/127 (1.57%)	5/130 (3.85%)
# events		
Pulmonary embolism † [A]		
# participants affected/at risk	0/127 (0%)	1/130 (0.77%)
# events		
Skin and subcutaneous tissue disorders		
Skin ulcer † [A]		
# participants affected/at risk	0/127 (0%)	1/130 (0.77%)
# 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%

	FF/VI 100/25 µg	Tiotropium Bromide 18 µg
Total # participants affected/at risk	8/127 (6.3%)	8/130 (6.15%)
Infections and infestations		
Nasopharyngitis † [A]		
# participants affected/at risk	5/127 (3.94%)	4/130 (3.08%)
# events		
Nervous system disorders		
Headache † [A]		
# participants affected/at risk	3/127 (2.36%)	5/130 (3.85%)
# 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: