TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	Multi-centre, randomized, double-blind, parallel-group study evaluating the effect of Fluticasone Furoate/ Vilanterol (FF/VI) Inhalation Powder once daily compared with Vilanterol (VI) Inhalation Powder Once Daily on Bone Mineral Density (BMD) in subjects with Chronic Obstructive Pulmonary Disease (COPD)

Compound Number: GW685698+GW642444

Effective Date: 14-AUG-2013

Protocol Amendment Number: 01

Subject: COPD, Bone Mineral Density, Fluticasone Furoate (FF), Vilanterol (VI), Novel Dry Powder Inhaler (NDPI)

Author: PPD

Revision Chronology:

2012N150072_00	2013-JAN-07	Original
2012N150072_01	2013-AUG-14	Amendment No.: 01 This protocol amendment is being implemented to revise and clarify exclusion criteria concerning participation in pulmonary rehabilitation programs; clarify the description of DEXA procedures and clinical labs; correction of typographical errors.

SPONSOR SIGNATORY:

PPD

Courtney Crim MD

Director, Clinical
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Discovery and Development
GlaxoSmithKline

14 Aug 2013
Date

SPONSOR INFORMATION PAGE

Clinical Study Identifier:
HZC102972

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

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Regulatory Agency Identifying Number(s): FDA IND Numbers: 077855 and 050703; EudraCT #: 2012-004801-28

INVESTIGATOR AGREEMENT PAGE

For protocol number HZC102972

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

_____ _____

Investigator Signature Date

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
AM	Morning
ANCOVA	Analysis of Covariance
AST	Aspartate Transaminase
AUC	Area Under the Curve
ATS	American Thoracic Society
BMD	Bone Mineral Density
IB	Investigator's Brochure
COPD	Chronic Obstructive Pulmonary Disease
eCRF	Electronic Case Report Form
DEXA	Dual Energy X-ray Absorptiometry
ECG	Electrocardiogram
EISR	Expedited Investigator Safety Report
FEV_1	Forced Expiratory Volume in one Second
FF	Fluticasone Furoate
FF/VI	Fluticasone Furoate/ Vilanterol Inhalation Powder Combination
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
IEC	Independent Ethics Committee
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
ITT	Intent to Treat
IVRS	Interactive Voice Response System
L	Liter
LABA	Long Acting Beta Agonist
LDH	Lactate Dehydrogenase
LSLV	Last Subject Last Visit
LTOT	Long Term Oxygen Therapy
MAOI	Monoamine Oxidase Inhibitor
Mcg	Microgram
MDI	Metered Dose Inhaler
MEDDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MSDS	Material Safety Data Sheet
NDPI	Novel Dry Powder Inhaler
OTC	Over the Counter
PD	Pharmacodynamics
PK	Pharmacokinetics

PEF	Peak Expiratory Flow
PFT	Pulmonary Function Test
PGx	Pharmacogenetics
PM	Evening
PR	Pulse Rate
PRN	As needed
QD	Once Daily
RAMOS	Registration and Medication Ordering System
RAP	Reporting Analysis Plan
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SD	Standard Deviation
SPM	Study Procedures Manual
UC	Urine Cortisol
ULN	Upper Limit of Normal
VI	Vilanterol
WHO	World Health Organization

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PROTOCOL SUMMARY

Rationale

Chronic obstructive pulmonary disease (COPD) has been defined as a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. The pulmonary component of COPD is characterized by airflow limitation that is not fully reversible, which is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. COPD is a major cause of poor health, resulting in millions of deaths annually worldwide [GOLD, 2010] and contributing significantly to health care costs and morbidity [Chapman, 2006; Lopez, 2006]. According to the World Health Organization, COPD was the fifth leading cause of death worldwide in 2002 and is estimated to be the third leading cause by 2030 [WHO, 2010].

Currently published guidelines on COPD state that the goals of pharmacologic therapy should be to control symptoms, improve health status and exercise tolerance, and reduce the frequency of COPD exacerbations [GOLD, 2010]. Recent clinical research has indicated that an inhaled corticosteroid (ICS) combined with a long acting β_2-agonist (LABA) is more effective than the individual components in managing stable COPD to reduce exacerbations and improve lung function and health status [Ferguson, 2008; Calverley, 2007; Kardos, 2007].

Although inhaled corticosteroids have demonstrated utility in patients with COPD, there is a potential safety concern with long-term use on bone demineralization. These concerns, for the most part, are derived from the well-documented effects of oral corticosteroids on bone density and fracture; however the actual effects of inhaled corticosteroids are not clear and require further study.

Study HZC102972 will prospectively assess the effects of 3 years (156 weeks) exposure to fluticasone furoate/vilanterol (FF/VI) Fluticasone Furoate /Vilanterol (FF/VI) inhalation powder once daily versus VI once daily on bone mineral density in adult subjects with COPD at approximately 40 centres.

Objective(s)

The primary objective of this study is to evaluate the effect of the inhaled corticosteroid FF on bone mineral density (BMD) assessed at the total hip by comparing FF/VI treatment with VI treatment in subjects with moderate COPD.

A secondary objective is to evaluate the effect of the inhaled corticosteroid FF on bone mineral density by gender by comparing FF/VI treatment with VI treatment in subjects with moderate COPD.

Another secondary objective is to evaluate the effect of FF on bone mineral density as assessed at the lumbar spine (L1-L4) by comparing FF/VI treatment with VI treatment in subjects with moderate COPD.

Study Design

This is a multi-center, randomized, double-blind, parallel-group study. The FF/VI inhalation powder once daily and VI inhalation powder once daily will be evaluated in subjects with COPD over 156 weeks. Subjects will sign the informed consent form (ICF) at Visit 0 and will be assigned a subject identifier. See Table 3 for further details. Subjects who meet all study inclusion and none of the exclusion criteria will begin a 14 to 21 day single-blind run-in period following Visit 1. Baseline BMD measurements will be collected between Visits 1 and 2. At Visit 2, eligible subjects will be randomized to double-blind study medication and entered into a 156-week treatment period. Randomisation will be stratified based upon gender. During the treatment period, clinic visits will occur every 3 months. BMD determined by dual-energy x-ray absorptiometry (DEXA) scans will be conducted every 6 months following randomization. A safety Follow-up Visit 15 will occur 7 days after the last treatment study day as a telephone contact. Subjects will be prescribed appropriate COPD therapy at the end of Treatment Visit 14 if required. There are no plans to provide the study drug for compassionate use following study completion.

The target enrolment across approximately 40 study centres is approximately 280 randomized subjects, to achieve approximately 224 who complete the 156-week treatment period. The total duration of subject participation will be approximately 159 to 160 weeks.

Study Endpoints/Assessments

Primary

- BMD measured at the total hip

Secondary

- BMD measurements by gender
- BMD measured at the lumbar spine (L1-L4)

Other

- Adverse Event reporting
- Serious Adverse Event reporting
- Incidence of fractures
- Incidence of pneumonias
- COPD exacerbations

1. INTRODUCTION

1.1. Background

COPD has been defined as a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. The pulmonary component of COPD is characterized by airflow limitation that is not fully reversible, which is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. COPD is a major cause of poor health, resulting in millions of deaths annually worldwide [GOLD, 2010] and contributing significantly to health care costs and morbidity [Chapman, 2006; Lopez, 2006]. According to the World Health Organization, COPD was the fifth leading cause of death worldwide in 2002 and is estimated to be the third leading cause by 2030 [WHO, 2010].

Currently published guidelines on COPD state that the goals of pharmacologic therapy should be to control symptoms, improve health status and exercise tolerance, and reduce the frequency of COPD exacerbations [GOLD, 2010]. Recent clinical research has indicated that an inhaled corticosteroid (ICS) combined with a long acting β_2-agonist (LABA) is more effective than the individual components in managing stable COPD to reduce exacerbations and improve lung function and health status [Ferguson, 2008; Calverley, 2007; Kardos, 2007].

Bronchodilators are considered key to the symptomatic management of COPD and current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend the use of long-acting inhaled bronchodilators in moderate to very severe COPD, because they are more efficacious and more convenient to use than short-acting bronchodilators. The benefits of bronchodilators include not only the control of symptoms but improvements in lung function, hyperinflation, exercise performance, and health status.

Inhaled corticosteroids are considered the most effective anti-inflammatory treatments for all severities of COPD. The benefits of ICS may include control of COPD symptoms, improvement in lung function, decrease in airway hyper-responsiveness and improvement in health status and reduction in exacerbations.

1.2. Rationale

Although inhaled corticosteroids have demonstrated utility in patients with COPD, there is a potential safety concern with long-term use of ICS on bone demineralization. These concerns, for the most part, are derived from the well-documented effects of oral corticosteroids on bone density and fracture; however the actual effects of inhaled corticosteroids are not clear and require further study.

Study HZC102972 will prospectively assess the effects of 3 years (156 weeks) exposure to FF/VI Fluticasone Furoate /Vilanterol (FF/VI) Inhalation Powder Once Daily versus VI Once Daily on bone mineral density in adult subjects with chronic obstructive pulmonary disease (COPD) at approximately 40 centres.

2. OBJECTIVE(S)

The primary objective of this study is to evaluate the effect of the inhaled corticosteroid FF on bone mineral density assessed at the total hip by comparing FF/VI treatment with VI treatment in subjects with moderate COPD.

A secondary objective is to evaluate the effect of the inhaled corticosteroid Fluticasone Furoate (FF) on bone mineral density by gender by comparing FF/VI treatment with VI treatment in subjects with moderate COPD.

Another secondary objective is to evaluate the effect of FF on bone mineral density as assessed at the lumbar spine (L1-L4) by comparing FF/VI treatment with VI treatment in subjects with moderate COPD.

3. INVESTIGATIONAL PLAN

3.1. Study Design

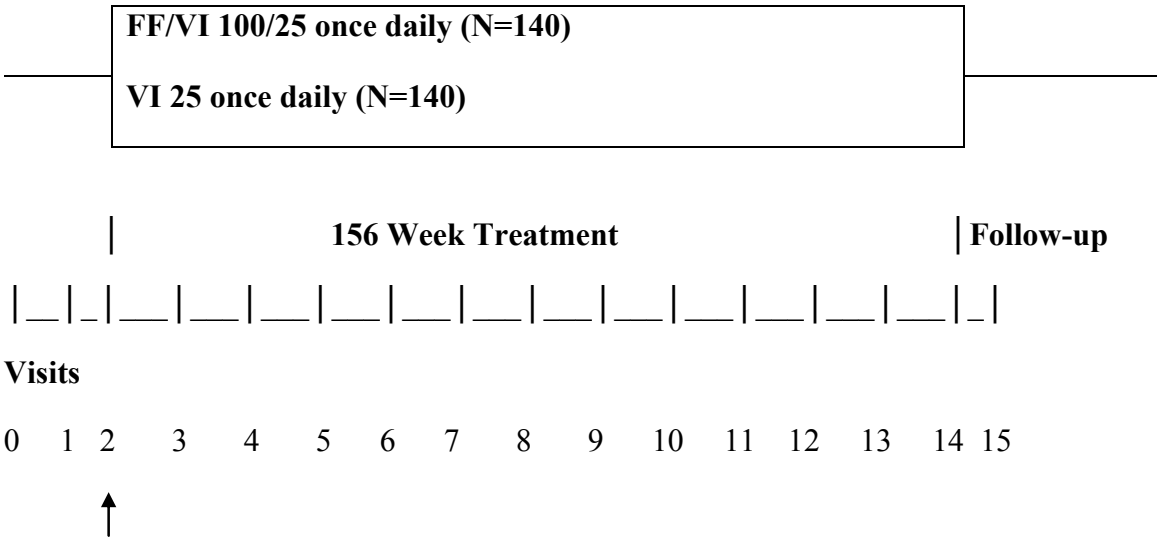
Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

This is a multi-center, randomized, double-blind, parallel-group study. The FF/VI inhalation powder once daily and VI inhalation powder once daily will be evaluated in subjects with COPD over 156 weeks. Subjects will sign the ICF at Visit 0 and will be assigned a subject identifier. See Table 3 for further details. Subjects who meet all study inclusion and none of the exclusion criteria will begin a 14 to 21 day single-blind run-in period following Visit 1. Baseline BMD measurements will be collected between Visits 1 and 2. At Visit 2, eligible subjects will be randomized to double-blind study medication and entered into a 156-week treatment period. Randomisation will be stratified based upon gender. During the treatment period, clinic visits will occur every 3 months. BMD DEXA scans will be conducted every 6 months following randomization. A safety Follow-up Visit 15 will occur 7 days after the last treatment study day as a telephone contact. Subjects will be prescribed appropriate COPD therapy at the end of Treatment Visit 14 if required. There are no plans to provide the study drug for compassionate use following study completion.

Systemic corticosteroid therapies will not be allowed during the run-in period. Subjects may take courses of systemic corticosteroids, where necessary, for treatment of a COPD exacerbation during the double-blind treatment period.

3.1.1. Study Schematic



3.2. Discussion of Design

The purpose of this study is primarily to assess the long-term safety effects of the FF component of the FF/VI inhalation powder on bone mineral density when administered to subjects with COPD over 156 weeks. The American Thoracic Society (ATS)/European Respiratory Society definition of COPD defines the subject population that will be included in this study [Celli, 2004]. BMD at the total hip was chosen as the primary endpoint due to the important morbidity/mortality implications of hip fractures. BMD at the lumbar spine (L1-L4) will be measured and assessed as a secondary endpoint.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

Approximately 400 male and female subjects will be screened to randomize approximately 280 subjects, to obtain at least 224 who complete 156 weeks of treatment. Approximately 40 centres in multiple countries will be required to recruit for the study.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB.

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. **Informed consent:** Subjects must give their signed and dated written informed consent to participate.

2. **Gender:** Male or female subjects. Female subjects must be post-menopausal or using a highly effective method for avoidance of pregnancy. The decision to include or exclude women of childbearing potential may be made at the discretion of the investigator in accordance with local practice in relation to adequate contraception.

3. **Age:** ≥ 40 years of age at Screening (Visit 1)

4. **COPD diagnosis:** Subjects with a clinical history of COPD in accordance with the following definition by the American Thoracic Society/European Respiratory Society [Celli, 2004]: COPD is a preventable and treatable disease characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.

5. **Tobacco use:** Subjects with a current or prior history of ≥10 pack-years of cigarette smoking at screening (Visit 1). Former smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Number of pack years = (number of cigarettes per day/20) x number of years smoked

   Note: Pipe and/or cigar use cannot be used to calculate pack year history.

6. **Severity of Disease:** Subject with a measured post-albuterol/salbutamol FEV_1/FVC ratio of < 0.70 at Screening (Visit 1). Subjects with a measured post-

albuterol/salbutamol 50% ≤ FEV_1 ≤ 70% of predicted normal values calculated using NHANES III reference equations [Hankinson, 1999] at Screening (Visit 1).

7. **Native Hip:** Have at least one evaluable native hip.

4.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

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

1. **Pregnancy:** Women who are pregnant or lactating or are planning on becoming pregnant during the study.

2. **Asthma:** Subjects with a current diagnosis of asthma. (Subjects with a prior history of asthma are eligible if they have a current diagnosis of COPD).

3. **α1-antitrypsin deficiency:** Subjects with α-1 antitrypsin deficiency as the underlying cause of COPD.

4. **Other respiratory disorders:** Subjects with tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases.

5. **Lung resection or transplantation:** Subjects with lung volume reduction surgery within the 12 months prior to Screening Visit 1 or having had a lung transplant.

6. **Chest X-ray:** Subjects with a chest X-ray (or CT scan) that revealed evidence of clinically significant abnormalities not believed to be due to the presence of COPD. A chest X-ray should be taken at Screening Visit 1 if a chest X-ray or CT scan is not available within 12 months prior to Visit 1.

7. **Poorly controlled COPD:** Subjects with poorly controlled COPD, defined as the occurrence of the following in the 12 weeks prior to Screening Visit 1: Acute worsening of COPD that is managed by the subject with corticosteroids or antibiotics or that requires treatment prescribed by a physician or requires hospitalization.

8. **Moderate or severe COPD exacerbation or lower respiratory tract infection:** Subjects with 2 or more moderate or severe COPD exacerbations and/or a lower respiratory tract infection (including pneumonia) within the 12 months prior to Screening Visit 1 or experience a moderate or severe COPD exacerbation and/or a lower respiratory infection (including pneumonia) during the Run-In period.

   NOTE: A moderate COPD exacerbation is defined as requiring systemic corticosteroids and/or antibiotics. A severe COPD exacerbation is defined as requiring hospitalization.

9. **Abnormal clinically significant laboratory finding:** Subjects who have an abnormal, clinically significant finding in any liver chemistry, biochemical, or haematology tests at Screening Visit 1 or upon repeat prior to randomization.

10. **Abnormal and clinically significant 12-lead ECG:** Subjects who have an abnormal, clinically significant ECG finding at Screening Visit 1.

11. **Non-Compliance during Run-In Period**: Failure to demonstrate adequate compliance with run-in medication (< 80% compliant), the ability to withhold COPD medications, and to keep clinic visit appointments.

12. **Bone disorders/conditions:** Subjects with historical or current evidence of bone cancer, severe scoliosis, rheumatoid arthritis, metabolic bone diseases (other than osteoporosis) including hyper-or hypo-parathyroidism, Paget's disease of bone, osteomalacia, or osteogenesis imperfecta. Removal of vertebrae between L1 and L4 of the lumbar spine and/or presence of metal implants or devices, such as plates, rods, or screws in the lumbar spine and/or hip.

13. **Immobility:** Wheel chair bound or paraplegic.

14. **Low vitamin D:** Previously known low-serum 25-hydroxy vitamin D concentration (less than 10ng [25nmoles] per liter).

15. **Other diseases/abnormalities:** Serious, uncontrolled disease (including serious psychological disorders) likely to interfere with the study within the 3-year study.

16. **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.

17. **Drug/food allergy:** Subjects with a history of hypersensitivity to any of the study medications (e.g. beta-agonists, corticosteroid) or components of the inhalation powder (e.g. lactose, magnesium stearate). In addition, patients with a history of severe milk protein allergy that, in the opinion of the study physician, contraindicates the subject's participation will also be excluded.

18. **Drug/alcohol abuse:** Subjects with a known or suspected history of alcohol or drug abuse within the last 2 years.

19. **Prohibited medications prior to spirometry at Visit 1:** Subjects who are medically unable to withhold the following medications prior to spirometry testing at Visit 1:

Medication	**No use within the following time intervals prior to Visit 1 Spirometry Testing**
Inhaled corticosteroids	48 hours
Inhaled ICS/LABA combination products	48 hours
Long-acting anticholinergics (e.g., tiotropium)	48 hours
Theophylline preparations	48 hours
Oral leukotriene inhibitors (zafirlukast, montelukast, zileuton)	48 hours
Oral PDE-4 inhibitors (e.g. roflumilast)	48 hours
Oral beta-agonists	
Long-acting	48 hours
Short-acting	12 hours
Inhaled long acting beta$_2$-agonist (LABA) - Indacaterol	48 hours
Other inhaled LABAs (e.g., salmeterol)	24 hours
Inhaled sodium cromoglycate or nedocromil sodium	24 hours
Ipratropium/ albuterol (salbutamol) combination product	4 hours
Inhaled short-acting beta$_2$-agonists	4 hours
Short-acting anti-cholinergics (e.g., ipratropium bromide)	4 hours

20. **Additional medication:** Use of the following medications within the following time intervals prior to Visit 1 or during the study (unless otherwise specified):

Medication	**No use within the following time intervals prior to Screening Visit 1 or thereafter at any time during the study (unless otherwise specified)**
Depot corticosteroids	12 weeks
Systemic, Oral, parenteral, intra-articular corticosteroids[1]	30 days
Any other investigational drug	30 days or 5 half lives whichever is longer.

1. Subjects may take courses of systemic corticosteroids, where necessary, for treatment of an exacerbation during the double-blind treatment period.

21. **COPD medications:** Use of inhaled corticosteroids (ICS), long-acting beta$_2$-agonists (LABA), or ICS/LABA combination products (other than the study-provided double-

blind study medication) at Visit 2 (Randomization) or during the double-blind treatment period.

22. **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.

23. **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.

24. **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

25. **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.

4.4. Withdrawal Criteria

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue a subject from this study at any time. Every effort should be made by the investigator to keep the subject in the study.

The primary reason for subject withdrawal will be recorded in the electronic Case Report Form (eCRF). Primary reasons for withdrawal will be categorised as:

- adverse event
- withdrew consent
- lost to follow-up
- protocol deviation
- lack of efficacy
- subject reached protocol-defined stopping criteria
- study closed/terminated
- investigator discretion

Subject compliance with double-blind study medication will be assessed from Visits 2 through 14, by reviewing the dose counter on the NDPI. Subjects must be ≥80% to ≤120% compliant on taking study medication between each pair of on-treatment visits. Subjects who fall outside this range should be re-educated on treatment compliance by their site. This re-education should be documented in the subject's source document. If the double-blind study medication is prematurely discontinued during the course of study or medication compliance repeatedly falls outside of acceptable ranges, the study sponsor/site monitor must be contacted to discuss subject eligibility for continued participation in the study.

A subject will also be withdrawn from the study, in consultation with the medical monitor and principal investigator, if any of the following stopping criteria are met:

- **Liver Chemistry**: Meets any of the liver chemistry stopping criteria as defined in Section 6.2.7.
- **Pregnancy:** Positive pregnancy test
- **Laboratory Measurements:** Demonstrate a clinically important change in a laboratory parameter(s).

If a subject is withdrawn due to an exacerbation, the exacerbation section and SAE section, if applicable, of the eCRF should be completed and the subject should be followed until resolution of exacerbation.

If a subject is withdrawn due to pneumonia, the AE/SAE section and the pneumonia/chest x-ray section of the eCRF should be completed and the subject should be followed until clinical resolution of the pneumonia.

4.5. Pre-Screen Failures and Screening Failures

A subject will be assigned a subject number at the time the informed consent is signed.

A subject who is assigned a subject number but does not have Visit 1 will be considered a pre-screen failure.

Any subject who performs a Visit 1 procedure but does not continue in the study beyond Visit 1 or any subject who completes Visit 1 and enters the run-in period, but is subsequently found to be ineligible for the study (e.g. exclusionary laboratory, ECG, or spirometry findings) conducted prior to randomization to the study treatment medication (Visit 2), is classified as a 'screen failure'.

The study interactive voice response system (IVRS) will be contacted to report pre-screen failures. The following information will be collected for subjects who are pre-screen failures:

- Subject number
- Date of ICF signature
- Demographic information including race, age and gender
- Details of COPD medications within 30 days of Visit 0
- Details of COPD exacerbation (yes/no status), if applicable
- Serious Adverse Event information, if applicable, only for an SAE considered as related to study participation (e.g. study treatment, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication
- Investigator signature page

IVRS will be contacted to report screen failures, In addition to the information above, the following information will be collected for screen failures:

- Date of screening visit
- Reason for screen failure (screening failure and inclusion/exclusion criteria)

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

GSK Clinical Trials Supplies will provide the investigational products for use in this study. All blinded study medication will be delivered via the NDPI. At each dispensing each subject will receive NDPI for once-daily administration. The contents of each treatment are described in Table 1 and Table 2.

The NDPI provides a total of 30 doses (60 blisters), with each actuation comprising the contents of one blister from each of the two internal foil strips simultaneously. The NDPIs containing randomized treatment will appear identical on the outside to the subject (and his/her caregiver) and the Investigator.

All subjects will receive supplemental albuterol/salbutamol (MDI and/or nebules) to be used on an as-needed basis throughout the study; for all sites this medication will be sourced locally where possible.

Following the 14 to 21 day, Run-In period, eligible subjects will be randomized (1:1) to one of the following two possible treatments, administered each morning for 156 weeks:

- FF/VI Inhalation Powder 100/25mcg QD
- VI Inhalation Powder 25mcg QD

Randomization in each treatment group will be stratified (1:1) according to gender.

A description of the investigational treatments is provided below:

Table 1 Description of FF/VI Inhalation Powder Novel Dry Powder Inhaler (NDPI)

Formulation	**First strip**: Fluticasone Furoate blended with lactose	**Second strip**: Vilanterol micronised drug (as the 'M' salt triphenylacetate) blended with lactose and magnesium stearate[1]
Dosage Form	Novel dry powder inhaler with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	100mcg per blister	25mcg per blister
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	Inhaled

1. Magnesium stearate 1% w/w of total drug product

Table 2 Description of VI Inhalation Powder Novel Dry Powder Inhaler (NDPI)

Formulation	**First strip**: lactose	**Second strip**: Vilanterol micronised drug (as the 'M' salt triphenylacetate) blended with lactose and magnesium stearate[1]
Dosage Form	NDPI with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	N/A	25mcg per blister
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	Inhaled

1. Magnesium stearate 1% w/w of total drug product

The contents of the label will be in accordance with all applicable regulatory requirements. Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

Adequate precautions must be taken to avoid direct contact with the investigational product. The occupational hazards and recommended handling procedures are provided in the Material Safety Data Sheet (MSDS).

5.1.1. Storage

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the investigational product will be limited to the investigator and authorized site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

The NDPIs are packaged in a foil overwrap with enclosed desiccant. The foil overwrap must not be opened until immediately prior to use. Once the foil overwrap has been opened the NDPI has a 30 day in-use shelf life.

5.1.2. Study Drug Return

At the end of the study, all study-supplied study medication (used and unused) will be destroyed following local standard operating procedures, except where it is suspected that the NDPI or NDPI packaging is defective. The NDPI and packaging should be returned to GSK.

Details for both destruction and return of study medication are found in the SPM.

In addition, any study inhaler that fails to function properly must be identified to GSK personnel for return to GSK for testing. Details of the failure will be documented in the eCRF. The subject should return the NDPI to the clinic as soon as possible and avoid missing any doses if possible. The site should then call IVRS and obtain a new treatment pack number for this subject and dispense a new study medication kit from the site's investigational product supply as instructed by RAMOS, an Interactive Voice Response System (IVRS).

5.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule. Once a randomization number has been assigned to a subject, the same number cannot be reassigned to any other subject in the study.

Subjects will be stratified based on gender.

Subjects will be site-based randomized using RAMOS, an Interactive Voice Response System (IVRS). This is a telephone based system that will be used by the investigator or designee to register the subject (initially at Visit 0, and subsequently at each study visit), randomize the subject and provide medication assignment information. Details on how to use RAMOS to register and randomize subjects is provided in the SPM.

Following the 14-21 day, Run-In period, eligible subjects will be randomized (1:1) to one of the following 2 possible treatments, administered as one inhalation each morning:

- Fluticasone Furoate /Vilanterol 100/25mcg once daily
- Vilanterol 25mcg once daily

5.3. Blinding

Study Medication taken during the 156-week treatment period will be double-blind. Neither the subject nor the study physician will know which study medication the subject is receiving.

The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. Whenever possible, the investigator must first discuss options with the GSK Medical Monitor or appropriate GSK study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the investigator must notify GSK as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to clinical investigators in accordance with local regulations and/or GSK policy.

Subjects will be withdrawn if the treatment code becomes unblinded. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.

5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

5.5. Treatment Compliance

An initial supply of albuterol (salbutamol), a short-acting, $beta_2$-agonist, will be provided to each subject to use as needed for symptomatic relief of COPD symptoms during both the Run-in and Treatment Periods. The subject's use of albuterol (salbutamol) will be assessed at each clinic visit and additional albuterol (salbutamol) will be dispensed to the subject as needed.

Subject compliance with the single-blind placebo NDPI during Run-In will be assessed at Visit 2 by reviewing the dose counter on the NDPI.

Subject compliance with double-blind study medication will be assessed at each treatment visit (from Visits 3 - Visit 14) and any unscheduled visit where study drug is returned by reviewing the dose counter on the NDPI. Subjects must be ≥80% to ≤120% compliant on taking study medication between each pair of on-treatment visits. Subjects who fall outside this range should be re-educated on treatment compliance by their site. This re-education should be documented in the subject's source document. If the double-blind study medication is prematurely discontinued during the course of study or medication compliance repeatedly falls outside of acceptable ranges, the study sponsor/site monitor must be contacted to discuss subject eligibility for continued participation in the study.

5.6. Concomitant Medications and Non-Drug Therapies

All COPD medications taken within 30 days prior to Visit 0 and during the run-in period will be recorded in the eCRF. All COPD and non-COPD concomitant medications taken during the study will be recorded in the eCRF. The minimum requirement includes, but is not limited to name of the medications, and the dates of the administration.

Note: Care is advised when co-administering with strong CYP 3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for an increased systemic exposure to both fluticasone furoate and vilanterol, which could lead to an increase in the potential for adverse reactions.

5.6.1. Permitted Medications and Non-Drug Therapies

The following medications are permitted during the Screening and Treatment periods:

COPD Medications

- Study supplied albuterol/salbutamol (MDI or nebules) for symptomatic relief during the Run-In and Double-Blind Treatment period
- Mucolytics
- Oxygen for intermittent use or PRN therapy ≤ 12 hours per day is allowed. (Subjects requiring LTOT or nocturnal oxygen therapy required for greater than 12 hours a day are excluded from the study.)

- Theophyllines (long and short-acting)
- Short-acting anti-cholinergic agents
- Long-acting anti-cholinergic agents
- Short-acting beta2-agonists; i.e. albuterol
- Beta2-agonist-anti-cholinergic combinations; i.e. Combivent
- Subjects may take courses of systemic corticosteroids, where necessary, for treatment of an exacerbation.

Non-COPD Medications

- Cardioselective beta-blockers (stable dose) and ophthalmic beta-blockers. (Administer with caution as they may block bronchodilatory effects of beta-agonists and produce severe bronchospasm).
- Care is advised when co-administering with strong CYP 3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for an increased systemic exposure to both fluticasone furoate and vilanterol, which could lead to an increase in the potential for adverse reactions.
- Antihistamines and nasal decongestants
- Over-the-counter (OTC) cough suppressants (for short term treatment ≤7days)
- Intranasal sodium cromoglycate or nedocromil sodium
- Intranasal corticosteroids, provided the subject is on a stable daily dose for at least 4 weeks prior to Visit 1 and remains on this dose throughout the study
- Topical (≤1 % hydrocortisone in strength) or ophthalmic corticosteroids
- Influenza and/or pneumonia vaccination
- Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). Administer with caution as they may potentiate the effects of beta-agonists on the vascular system.
- Diuretics. Caution is advised in the co-administration of beta-agonists with nonpotassium sparing diuretics.
- Treatment(s) for smoking cessation
- All medications for other disorders as long as the dose remains constant wherever possible.

5.6.2. Prohibited Medications and Non-Drug Therapies

Medications prohibited at specific time intervals prior to Screening Visit 1 and at any time during the study are identified in Section 4.3 Exclusion Criteria.

If a subject's current medication is going to be changed in order to participate in the study, then consent must be obtained prior to any medication change and the subject will

be required to return to the clinic to complete the Screening Visit 1 once the protocol specified time period has been completed.

5.7. Treatment after the End of the Study

At the end of the treatment period (Visit 14 or Early Withdrawal), subjects can resume conventional COPD therapy as prescribed by the Investigator. There are no plans to provide the study drug for compassionate use following study completion.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition whether or not GSK is providing specific post study treatment.

5.8. Treatment of Study Treatment Overdose

An overdose is defined as a dose greater than what is instructed (see Section 5.1), which results in clinical signs and symptoms. In the event of an overdose of study medication, the investigator should use clinical judgement in treating the overdose and contact the study medical monitor. GSK is not recommending specific treatment guidelines for overdose and toxicity management. The investigator should refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug(s) being used in this study. Such documents may include, but not be limited to, the approved product labeling for albuterol (salbutamol), and the IB or equivalent document provided by GSK for double blind medications.

6. STUDY ASSESSMENTS AND PROCEDURES

The Time and Events Table is provided in Table 3. All study assessments should be conducted by the investigator or his/her qualified designee. Please refer to the SPM for a suggested order of assessments.

Table 3 Time and Events Table

			Double-Blind Treatment period														
Visit Number	**0 Pre-screen[1]**	**1 Screen-ing[2]**	**2 Random-ization**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Early With-draw**	**15 Follow -up**
			Day 1	13 wks ±14 Days	26 wks ±14 Days	39 wks ±14 Days	52 wks ±14 Days	65 wks ±14 Days	78 wks ±14 Days	91 wks ±14 Days	104 wks ±14 Days	117 wks ±14 Days	130 wks ±14 Days	143 wks ±14 Days	156 wks ±14 Days		Visit 14/EW + 7±2 Days
Assessments																	
Informed consent[3]	X																
PGx Consent & Sampling[4]			X														
Demography	X																
Medical History		X															
Physical Exam		X					X				X				X	X	
Spirometry Testing		X	X		X		X		X		X		X		X	X	
Reversibility Testing		X															
Smoking history/ smoking status		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Smoking cessation counseling		X					X				X				X	X	
Register visit on IVRS[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments																	
BMD DEXA scans[6]		X			X		X		X		X		X		X	X	
Oropharyngeal examination[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chest X-ray[8]		X															
Lab Tests[9] / Serum Pregnancy Test[10]		X															

			Double-Blind Treatment period														
Visit Number	**0 Pre-screen[1]**	**1 Screen-ing[2]**	**2 Random-ization**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Early With-draw**	**15 Follow -up**
			Day 1	13 wks ±14 Days	26 wks ±14 Days	39 wks ±14 Days	52 wks ±14 Days	65 wks ±14 Days	78 wks ±14 Days	91 wks ±14 Days	104 wks ±14 Days	117 wks ±14 Days	130 wks ±14 Days	143 wks ±14 Days	156 wks ±14 Days		Visit 14/EW + 7±2 Days
12-lead ECG & Rhythm Strip		X															
Exacerbation Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment[11]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event Assessment[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Diary		X	X	X	X	X	X	X	X	X	X	X	X	X			
Collect/Review Diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medication Assessments																	
Concurrent Medication Assessment[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense albuterol (salbutamol)[14]		X	X	X	X	X	X	X	X	X	X	X	X	X			
Collect albuterol (salbutamol)[14]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Single-Blind Medication		X															
Dispense Double-Blind Medication			X	X	X	X	X	X	X	X	X	X	X	X			
Collect Blinded Medication			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Other Assessment																	

			Double-Blind Treatment period														
Visit Number	**0 Pre-screen[1]**	**1 Screen-ing[2]**	**2 Random-ization**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Early With-draw**	**15 Follow -up**
			Day 1	13 wks ±14 Days	26 wks ±14 Days	39 wks ±14 Days	52 wks ±14 Days	65 wks ±14 Days	78 wks ±14 Days	91 wks ±14 Days	104 wks ±14 Days	117 wks ±14 Days	130 wks ±14 Days	143 wks ±14 Days	156 wks ±14 Days		Visit 14/EW + 7±2 Days
Discharge from Study[15]															X	X	

1. **Visit 0** and **Visit 1** may occur on the same day if the subject does not take or has not taken any protocol excluded medications.
2. Following Screening **Visit 1**, subjects enter a 14 to 21 day single-blind run-in period.
3. Subjects will be assigned a subject number at the time ICF is signed. The ICF must be signed before any study procedures including medication exclusion period(s).
4. Saliva (2ml) sample is collected in the DNA self-collection kit. This should ideally be taken as soon after randomization (Visit 2) as possible, but may be taken at any other visit after randomization if necessary. PGx consent must be signed prior to PGx sampling.
5. A telephone based IVRS system (RAMOS) which will be used by the investigator or designate to register the subject, randomize the subject and provide medication assignment information.
6. Baseline BMD measurements will be collected between **Visit 1** and **Visit 2**.
7. If evidence of infection, culture swab may be taken and appropriate therapy should be instituted at Investigator discretion. Subjects with culture-positive infection may continue in the study on appropriate anti-infective treatment at Investigator discretion.
8. Chest X-ray must be taken if a Chest X-ray or CT scan is not available within the 12 months preceding **Visit 1**. Chest x-rays will be requested for suspected cases of pneumonia.
9. Non-fasting and pre-dose. A blood sample for repeat analysis is collected only if any part of Screening lab needs to be repeated. Results of repeat labs should be received prior to Randomization at Visit 2.
10. Females of child-bearing potential only
11. Adverse events are to be collected from the start of blinded study medication (Visit 2) until the follow-up phone contact.
12. Serious adverse events are to be collected from the start of study drug (Visit 2) until the follow-up phone contact. However, any SAEs assessed as related to study participation will be recorded from the time subjects sign informed consent.
13. All COPD medications taken within 30 days prior to **Visit 0** will be collected.
14. Collect and re-dispense as needed after **Visit 1**.
15. Discharge from study on appropriate therapy.

6.1. Critical Baseline Assessments

No study related procedures may be performed until the informed consent form document has been signed by the subject. A pre-screening visit (Visit 0) may be required in order to administer the informed consent before any changes are made to the subject's current medication regimen. Selection and modification of subject's medications prior to study participation is based on the physician's judgment according to sound medical practice, principles, and each subject's needs. A subject's treatment must not be changed merely for the purpose of enabling the subject's participation in the study. The pre-screening visit and screening visit may occur on the same day if the subject does not take or has not taken any protocol excluded medications. During the pre-screening visit, each subject will have the following demographic information collected:

- Demographic history (including gender, ethnic origin, date of birth)

During Screening Visit 1, each subject will undergo the following assessments**:**

- Medical history (including COPD and smoking history)
- Cardiovascular medical history/risk factors will be assessed at baseline.
- Inclusion/Exclusion criteria assessment
- Concomitant medication review
- ECG and rhythm strip
- Spirometry with reversibility testing
- Physical exam (including vital signs)
- Laboratory assessments (including chemistry, hematology, hepatitis, and pregnancy)

See Section 4.5 for information regarding Screening Failures.

6.2. Safety

6.2.1. Primary Endpoint

- BMD measured at the total hip

6.2.2. Secondary Endpoints

- BMD measured at the lumbar spine (L1-L4)
- BMD measurements by gender

6.2.3. Other Endpoints

- Adverse Event reporting
- Serious Adverse Event reporting

- Incidence of fractures
- Incidence of pneumonias
- COPD exacerbations

6.2.4. Bone Mineral Density

Effects on the skeletal system will be assessed by measuring bone mineral density (BMD) using dual energy x-ray absorptiometry (DEXA) with established methodology. DEXA measurements of the total hip and the L_1-L_4 regions of the spine will be completed at baseline, 26 weeks, 52 weeks, 78 weeks, 104 weeks, 130 weeks, and 156 weeks or end of study treatment.

All DEXA scans will be conducted by qualified technicians and sent electronically for centralized analysis. Quality assurance and calibration of DEXA equipment and densitometric measurements will be monitored by this facility to control for site-to-site variability in BMD measurements.

Acceptable DEXA measurements must be conducted prior to the first dose of randomized study medication.

Subjects with DEXA results meeting pre-defined criteria for clinically significant bone mineral density loss from the Screening scan or any visit scan after randomization will be counseled about the clinical implications of the scan results.

6.2.5. Fractures

For any fractures that occur after the initiation of the double-blind study drug, the location of the fracture, and whether it is considered traumatic or non-traumatic must be recorded on the Fractures page of the eCRF. Severity of a fracture should be determined by the Investigator. Details regarding the information to be captured for fractures will be provided in the SPM.

6.2.6. COPD Exacerbations and Pneumonias

For the purpose of this study, exacerbation of COPD is defined by a worsening of symptoms requiring additional treatment as follows:

- A mild COPD exacerbation: managed by subject with increased use of prn medications
- A moderate COPD exacerbation: requires treatment with antibiotics and/or systemic corticosteroids
- A severe COPD exacerbation: requires hospitalization

Any subject experiencing worsening of symptoms should:

- Contact his/her study investigator and/or research coordinator immediately, and report to the study clinic as required
- If the subject is unable to contact his/her study investigator and/or research coordinator, they should contact their primary care physician (or other health care practitioner as required) and contact their study site as soon as possible
- If the subject seeks emergent/acute care for worsening respiratory symptoms, he/she should inform the caring Health Care Provider (HCP) to contact the investigator as soon as possible.

Subjects with presence of worsening respiratory symptoms will be classified by the Investigator as having:

- A mild/moderate/severe COPD exacerbation and/or pneumonia

OR

- A lower respiratory tract infection (LRTI) [i.e. other than pneumonia]
- Background variability of COPD
- A non-respiratory related disease
- Other respiratory related disease

The time period for collection of COPD exacerbations will begin from the time of Visit 2 (Randomization) and will end when the 7±2day Follow-up period has been completed.

COPD exacerbations should not be recorded as an adverse event, unless they meet the definition of a Serious Adverse Event. For the purposes of this study, COPD exacerbations will be collected and recorded on the exacerbation log in the eCRF. Exacerbations that meet the definition of an SAE, will be recorded on the appropriate eCRF section and should be reported to GSK for all subjects regardless of whether or not they are randomized to blinded study medication.

Subjects are excluded from participating if any of the following apply:

- They have poorly controlled COPD, defined as the occurrence of the following in the 12 weeks prior to Screening Visit 1: Acute worsening of COPD that is managed by the subject with corticosteroids or antibiotics or that requires treatment prescribed by a physician or requires hospitalization.
- They have 2 or more moderate or severe COPD exacerbations and/or a lower respiratory tract infection (including pneumonia) within the 12 months prior to Screening Visit 1 or experience a moderate or severe COPD exacerbation and/or a lower respiratory infection (including pneumonia) during the Run-In period.

The dates of onset and resolution of each COPD exacerbation should be based on when the Investigator and/or subject determines that the COPD symptoms initially started and then returned to pre-exacerbation levels.

If an exacerbation begins as mild, but becomes moderate or severe or begins as moderate and becomes severe, the exacerbation should be captured as one exacerbation and classified by its highest level of severity.

For the purpose of this study, pneumonia is defined as new auscultatory findings compatible with parenchymal lung infection and/or radiographic evidence of parenchymal/air space disease. All suspected cases of pneumonia are encouraged to be confirmed radiographically within 48 hours of diagnosis. All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable). Information regarding chest X-ray-confirmed cases of pneumonia will be recorded in the eCRF. Details regarding the information to be captured for pneumonias will be provided in the SPM.

If, based upon these criteria, a subject's symptoms do not fulfill the diagnosis of an exacerbation and/or pneumonia, then the investigator should use his/her clinical judgment to assess the subject's symptoms (including increased volume of sputum production and/or change in the sputum color) for a diagnosis of LRTI (e.g. acute bronchitis), background variability of COPD, a non-respiratory related disease or other respiratory related disease.

Investigator judgment should be used in deciding whether to report the signs and symptoms (and/or determined diagnosis) as an AE/SAE in the eCRF. Medication(s) used to treat a COPD exacerbation and/or pneumonia are to be recorded in the eCRF.

6.2.7. Liver chemistry stopping and follow up criteria

Phase III-IV liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

Phase III-IV liver chemistry stopping criteria 1-5 are defined below and in Appendix 4:

1. ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT ≥ 3xULN **and** INR>1.5, if INR measured)

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT ≥ 8xULN.

3. ALT ≥ 5xULN but <8 xULN persists for ≥2 weeks

4. ALT ≥ 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

5. ALT ≥ 5xULN but <8 xULN and cannot be monitored weekly for ≥2 weeks

When any of the liver chemistry stopping criteria 1-5 is met, do the following:

- **Immediately** withdraw investigational product for that subject
- Report the event to GSK **within 24 hours** of learning its occurrence
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN **and** INR>1.5, if INR measured); INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Withdraw the subject from the study after completion of the liver chemistry monitoring (unless further safety follow up is required).
- Do not restart investigational product.

In addition, for criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values

For criteria 2, 3, 4 and 5:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (see below)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Subjects with ALT ≥5xULN and <8xULN which exhibit a decrease to ALT x≥3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks:

- Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss subject safety
- Can continue investigational product
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

For criteria 1-5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Cytomegalovirus IgM antibody;
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
  - Hepatitis E IgM antibody
- Blood sample for PK analysis, obtained within 72 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form.

- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form.

The following are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China.**
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. **NOTE**: if hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) – as outlined in: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793/.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

6.2.8. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of double-blind Investigational Product and until the follow up contact.

COPD exacerbations should not be recorded as an adverse event, unless they meet the definition of a Serious Adverse Event. For the purposes of this study, COPD exacerbations will be collected and recorded on the COPD exacerbation log in the eCRF. The time period for collection of COPD exacerbations will begin from the time of Visit 2 (Randomization) and will end when the 7-day Follow-up period has been completed.

The investigators and site staff should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD receiving fluticasone furoate/vilanterol include current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m^2 and patients with an FEV_1<50% predicted. For all suspected cases of pneumonia, Investigators are encouraged to confirm the diagnosis (this includes obtaining a chest x-ray) and to initiate appropriate therapy as promptly as possible. All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable).

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved,

the appropriate AE/SAE CRF page will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

6.2.8.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

6.2.8.2. Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

6.2.9. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

6.2.10. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thrombosis
- Deep Venous Thrombosis
- Revascularization

This information should be recorded within one week of when the AE/SAE(s) are first reported.

6.2.11. Death Events

In addition, all deaths, whether or not they are considered SAEs, will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.

This information should be recorded within one week of when the death is first reported.

6.2.12. Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

6.2.13. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of study treatment and until the follow up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.2.14.

6.2.14. Prompt Reporting of Serious Adverse Events and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool "CV events" and/or "death" data collection tool(s) if applicable	24 hours	Updated "SAE" data collection tool "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	2 weeks	"Pregnancy Notification Form"	2 weeks	"Pregnancy Follow-up Form"
Non-serious adverse events related to study treatment	5 calendar days	"Adverse Reaction" data collection tool	2 weeks	Updated "Adverse Reaction" data collection tool
Liver chemistry abnormalities for Phase I to IV:				
ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) (or ALT≥3xULN **and** INR>1.5, if INR measured)[1]	24 hours[2]	"SAE" data collection tool. "Liver Event CRF" and "Liver Imaging" and/or "Liver Biopsy" CRFs, if applicable[3]	24 hours	Updated "SAE" data collection tool/"Liver Event" Documents[3]
Remaining liver chemistry abnormalities Phase III to IV:				
ALT≥8xULN; ALT≥3xULN with hepatitis or rash or ≥3xULN and <5xULN that persists≥4 weeks	24 hours[2]	"Liver Event" Documents (defined above) [3]	24 hours	Updated "Liver Event" Documents[3]
ALT≥5xULN plus bilirubin <2xULN	24 hours[2]	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks[3]	24 hours	Updated "Liver Event" Documents, if applicable[3]
ALT≥5xULN and bilirubin <2xULN that persists ≥2 weeks	24 hours[2]	"Liver Event" Documents (defined above) [3]	24 hours	Updated "Liver Event" Documents[3]

ALT≥3xULN and <5x ULN and bilirubin <2xULN	24 hours[2]	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[3]	24 hours	Updated "Liver Event" Documents, if applicable[3]

1. INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants.
2. GSK must be contacted at onset of liver chemistry elevations to discuss subject safety
3. Liver Event Documents (i.e., "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible.

The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

6.2.14.1. Regulatory reporting requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

6.2.15. SpirometryTesting

Lung function will be measured by spirometry at Visits 1, 2, 4, 6, 8, 10, 12, and 14, or at Early Withdrawal using site available spirometry equipment that meets or exceeds the minimum performance recommendations of the ATS/ERS [Miller, 2005]. For Visits 2 onward, FEV_1 will be measured prior to administration of morning study medication.

For each observation, at least 3 valid (with no more than 8) efforts will be obtained using ATS/ERS guidelines. The largest FEV_1 and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort. Acceptable spirometry efforts should have a satisfactory start of test and end of test (i.e. a plateau in the volume-time curve) and be free from artifacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons [Miller, 2005]. The subject's position during spirometry measurements (sitting or standing) should remain constant for the duration of the study.

A post-albuterol (salbutamol) FEV_1/FVC ratio of < 0.70 and predicted normal value of $50\% \leq FEV_1 \leq 70\%$ is required at Screening Visit 1.

All predicted values will be taken from Hankinson [Hankinson, 1999].

The investigator will retain a printed copy of the spirometry data in the subject's source documents.

6.2.15.1. Reversibility Testing

At Visit 1, reversibility to albuterol (salbutamol) will be assessed. To determine reversibility, the subject will self-administer 4 puffs (360mcg) of albuterol (salbutamol) without the use of a spacer or holding chamber. Triplicate spirometry efforts will be performed immediately pre-albuterol (salbutamol) and within 30 minutes post-albuterol (salbutamol). The highest FEV_1 from three valid forced expiratory curves will be used to determine reversibility.

Reversibility is defined as an increase in FEV_1 of $\geq$12% and $\geq$200mL following administration of albuterol (salbutamol). Non-reversible is defined as a post-albuterol (salbutamol) increase in FEV_1 of <200mL or a $\geq$200mL increase that is <12% from pre-albuterol (salbutamol) FEV_1.

6.2.16. Laboratory Assessments

Routine, **non-fasting** clinical laboratory (hematology and biochemistry), will be performed in all subjects at the Screening Visit 1.

For women of childbearing potential, a serum pregnancy test will be included in the laboratory panel collected at Visit 1 if applicable.

At the discretion of the investigator, additional samples may be taken for safety reasons. If the subject has an abnormal laboratory finding for any analyte from the Screening Visit laboratory panel, which in the opinion of the Investigator does not preclude the subject from participating in the study, but for which the Investigator feels warrants treatment/correction with a non-excluded medication(s) (e.g., calcium supplement for hypocalcemia), a blood sample for repeat analysis of the analyte(s) should be collected prior to Visit 2 (Randomization). Results of repeat Screening labs should be received prior to Randomization at Visit 2.

All protocol required laboratory assessments, as defined in Appendix 1 must be performed by the central laboratory. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the central laboratory. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

6.2.17. Oropharyngeal Examination

Oropharyngeal examinations for clinical evidence of infection (i.e., Candida albicans) will be performed at each study visit as shown in the Time and Events Table. If there is evidence of infection, a culture swab may be taken and appropriate therapy should be instituted at the discretion of the Investigator. Subjects with culture-positive infection may continue in the study on appropriate anti-infective treatment at the discretion of the Investigator. The results of these assessments, and any relative pharmacotherapy, will be recorded in the subject's clinic notes and in the eCRF. After randomization, all culture positive results must be reported as adverse events.

6.2.18. Diary Card - Medical Problems/Medications Taken

Subjects will be instructed to record any medical problems they may have experienced and any medications used to treat those medical problems in their diaries from Screening (Visit 1) through the Follow-up Phone Contact.

Subjects will be instructed on how to complete the diary and will be asked to return completed diaries at each clinic visit. The study coordinator must review the diary at each clinic visit and will inquire about the diary data during the Follow-up Phone Contact as well. If the subject does not mention an event which is recorded on the diary, he/she should be questioned for further information in order to determine if there was the occurrence of an AE. Any confirmed AE and/or concurrent medication will be entered into the eCRF.

6.2.19. 12-lead ECG Assessment

A single 12-lead ECG and rhythm strip will be recorded prior to spirometry at the Screening Visit 1.

All ECG measurements will be performed with the subject resting in a supine position for approximately 5 minutes before each reading, which should be carried out after measurement of vital signs and before spirometry.

The investigator, a designated sub-investigator, or other appropriately trained site personnel, will be responsible for performing the 12-lead ECG recording on each study visit, if applicable. The investigator must provide his/her dated signature on the original paper tracing, attesting to the authenticity of the ECG machine interpretation.

6.2.20. Smoking Cessation Counselling

During the Screening Visit 1, 6, 10, and 14 or EW visit (if necessary), subjects will be given smoking cessation counselling, which includes advice regarding the following:

- the health effects that smoking may cause.
- the health benefits that may result if they stop smoking.
- if they do not feel capable of discontinuing smoking that their primary care physician may be able to discuss anti-smoking strategies with them.
- that they may discontinue smoking at any time during the study and will not have to be withdrawn from the study if they do so.

6.3. Pharmacogenetic Research

Information regarding pharmacogenetic research is included in Appendix 2. The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments. In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

7. DATA MANAGEMENT

For this study subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK and combined with data (e.g. laboratory data, diary data) provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug. An appropriate medical dictionary that covers all approved drugs in the region will be referenced. eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

The null hypothesis for the primary measure is that the change in BMD assessed at the total hip is worse for the FF/VI combination product arm compared with the VI arm. The alternative hypothesis that the change in BMD assessed at the total hip is not worse for the FF/VI arm compared with the VI arm.

This is also the null and alternative hypothesis for the secondary measure of BMD assessed at the L1-L4 lumbar spine.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

This study will evaluate non-inferiority in both males and females separately as key secondary measures. 56 subjects per gender per treatment would provide 80% power to demonstrate non-inferiority by comparing the lower boundary of a two-sided 95% confidence interval on the treatment difference to -1%/year assuming a true treatment difference of -0.3%/year. In study SCO40041, approximately 20% of subjects did not provide post-baseline data, therefore 70 subjects per gender per treatment will be randomized (280 total subjects). Randomization will be stratified by gender.

For the primary evaluation of BMD for the total hip, males and females will be combined, and will have >90% power to demonstrate non-inferiority by comparing the lower boundary of a two-sided 95% confidence interval on the treatment difference to -1%/year assuming a true treatment difference of -0.3%/year.

8.2.2. Sample Size Sensitivity

The following table presents the power of the study under different circumstances in terms of the standard deviation and the observed treatment difference in change from baseline in bone mineral density for the total hip.

	True Treatment Difference between FF/VI and VI		
SD	**-0.2%/yr**	**-0.3%/yr**	**-0.4%/yr**
1.3%/yr	>99%	99%	96%
1.4%/yr	>99%	**98%**	94%
1.5%/yr	>99%	97%	91%

8.2.3. Sample Size Re-estimation

No sample size re-estimation is planned for this study.

8.3. Data Analysis Considerations

8.3.1. Analysis Populations

All Subjects Enrolled Population: This population will consist of all subjects, for whom a record exists on the study database, including screen failures and any subject who was not screened but signed the informed consent form. This population will be used for reporting subject disposition, reasons for withdrawal prior to randomisation, and inclusion, exclusion and randomisation criteria deviations and SAEs for non-randomised subjects.

(Modified) Intent-to-Treat (ITT) Population: This population will consist of all subjects who are randomised and receive at least one dose of study drug. The ITT Population will be the primary population for all analyses of safety and efficacy measures.

8.3.2. Analysis Data Sets

The bone mineral density data will comprise the primary data set of interest. Details of derived data in analysis datasets to be created will be provided in the Reporting and Analysis Plan (RAP).

8.3.3. Treatment Comparisons

8.3.3.1. Primary Comparisons of Interest

BMD measured for the total hip will be summarized by visit and as change from baseline at each visit for raw values, percent changes from baseline, t-scores, and z-scores. The percent change from baseline in BMD for the total hip will be the primary endpoint, and analyzed using a repeated measures model with terms for treatment, time, time by treatment, baseline BMD, baseline BMI and gender. Contrasts will be formed using the time by treatment variable to provide 95% confidence intervals for the treatment difference with the unit of percent change per year. The 95% confidence interval will be compared to a lower bound of -1%/year in order to assess clinical non-inferiority. Any

additional covariates for the model, along with other details, including model inclusion and exclusion criteria for those covariates, will be determined a priori in a detailed Reporting and Analysis Plan (RAP) that will be completed prior to unblinding of the study.

The percent change from baseline in BMD at the L1-L4 region of the spine will also by summarized and analyzed in the same manner as the BMD data for the total hip.

8.3.4. Interim Analysis

No interim analysis is planned for this study.

8.3.5. Key Elements of Analysis Plan

8.3.5.1. Efficacy Analyses

No efficacy analyses are planned for this study

8.3.5.2. Safety Analyses

8.3.5.2.1. Extent of Exposure

The extent of exposure to study drug will be summarized by treatment group.

8.3.5.2.2. Adverse Events (AEs)

AEs will be coded using the standard GSK dictionary, Medical Dictionary for Regulatory Activities (MedDRA), and grouped by body system. AEs occurring pre-treatment, during active treatment and post-treatment will be summarized separately. The number and percentage of subjects experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be presented for each treatment group. Separate summaries will be provided for all AEs, drug related AEs, SAEs, and for AEs leading to withdrawal.

8.3.5.2.3. Deaths and SAEs

All SAEs will be listed by treatment group. Deaths and SAEs will be documented in case narrative format.

8.3.5.2.4. Fractures

The number and percent of patients experiencing a bone fracture during the study will be summarized.

8.3.5.2.5. COPD Exacerbations and Pneumonias

The number of moderate or severe COPD exacerbations and the percent of patients experiencing moderate or severe COPD exacerbations will be summarized.

8.3.5.3. Pharmacogenetic Analyses

See Appendix 2: Pharmacogenetic Research for details about the Pharmacogenetics Analysis Plan.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

No study related procedures may be performed until the informed consent form document has been signed by the subject. A pre-screening visit may be required in order to administer the informed consent before any changes are made to the subject's current medication regimen. The pre-screening visit and screening visit may occur on the same day if the subject does not take or has not taken any protocol excluded medications.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., PGx assessments described in Appendix 2, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

9.5. Study and Site Closure

Upon completion or termination of the study, the GSK monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by

applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

9.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last subject's last visit (LSLV) [this applies to each data analysis phase for studies with multiple phases, e.g., primary analysis, follow up analysis etc]. In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

9.8. Independent Data Monitoring Committee (IDMC)

There is no IDMC in this study.

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11. APPENDICES

11.1. Appendix 1: Laboratory Assessments

Refer to the Time and Events Table 3 for information regarding the timing of laboratory tests.

CHEMISTRY	HEMATOLOGY	OTHER
Albumin	Hemoglobin	Hepatitis B surface antigen[1]
Alkaline phosphatase	Hematocrit	Hepatitis C virus antibody[1]
Alanine amino-transferase (ALAT or SGPT)	Platelet count	Fungal culture of oral mucosa (if visual evidence of candidiasis)
Aspartate amino-transferase (ASAT or SGOT)	WBC count	hCG qualitative (serum pregnancy)[2]
Bilirubin, direct	Neutrophils, absolute	
Bilirubin, indirect	Neutrophils, segs (%)	
Bilirubin, total	Neutrophils, bands (%)	
Calcium	Basophils (%)	
Chloride	Eosinophils (%)	
CO_2 content/Bicarbonate	Eosinophils , absolute	
Creatinine	Lymphocytes (%)	
Creatine phosphokinase (CPK), total	Monocytes (%)	
Gamma glutamyl transferase (GGT)		
Glucose		
Phosphorus		
Potassium		
Protein, total serum		
Sodium		
Urea nitrogen (BUN)		
Uric Acid		

1. Assessed at Visit 1 (Screening) only, result is not exclusionary
2. Only females of child-bearing potential; refer to Time and Events Table for specific visit information

11.2. Appendix 2: Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	HLA-B* 5701	Carriage of the HLA-B*5701 variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective HLA-B*5701 screening and exclusion of HLA-B*5701 positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective HLA-B*5701 screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. HLA-B*5701 screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia Chung, 2010; Ferrell, 2008	HLA-B*1502	Independent studies indicated that patients carrying HLA-B*1502 are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis and that this marker is prevalent in some populations, particularly with Asian ancestry. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	UGT1A1*28	Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular UGT1A1 gene variation might be too high for another patient without this variation, raising the risk of certain side-effects, that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the UGT1A1*28 variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to FF/VI Inhalation Powder.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to FF/VI Inhalation Powder. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with FF/VI Inhalation Powder, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Relationship between genetic variants and the pharmacokinetics and/or pharmacodynamics of investigational product
- Relationship between genetic variants and safety and/or tolerability of investigational product
- Relationship between genetic variants and efficacy of investigational product

Study Population

Any subject who is enrolled in the clinical study, can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

Saliva samples can be taken for Deoxyribonucleic acid (DNA) extraction and used in PGx assessments.

No additional whole blood samples will be necessary for the PGx analysis. Saliva (2mL) is collected into the DNA self-collection kit. A single sample will be taken but can be duplicated if the first sample is unusable. It is recommended that the saliva sample be collected at Visit 2.

- The PGx sample is labelled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The saliva sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the saliva sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or a set of studies) of FF/VI Inhalation Powder has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to FF/VI Inhalation Powder.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research and has had a sample taken for PGx research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options:

- Retain the sample for PGx research
- Destroy the PGx sample

If a subject withdraws consent for PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Pharmacogenetics Analyses

Pharmacogenetics Analyses

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to FF/VI Inhalation Powder. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any saliva being taken for PGx research.

Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarize the PGx research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

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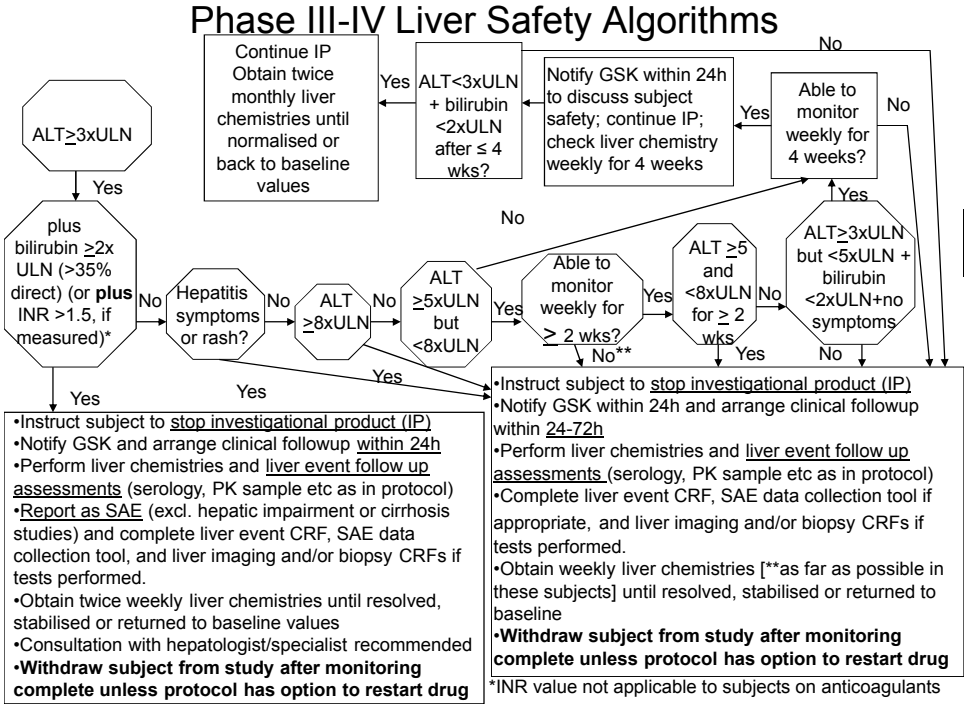
11.3. Appendix 3: Country Specific Requirements

11.4. Appendix 4: Liver Chemistry Stopping and Followup Criteria



11.5. Appendix 5: Protocol Changes

This amendment applies to all study centers participating in HZC102972

Rationale

This protocol amendment is being implemented to revise and clarify exclusion criteria concerning participation in pulmonary rehabilitation programs; clarify the description of DEXA procedures and clinical labs; correction of typographical errors.

Section - Study Design

Original Text:

The target enrolment across approximately 40 study centres is approximately 400 randomized subjects, to achieve approximately 280 who complete the 156-week treatment period.

Amended Text:

The target enrolment across approximately 40 study centres is approximately 280 randomized subjects, to achieve approximately 224 who complete the 156-week treatment period.

Section 4.2. Inclusion Criteria - #6

Original Text:

Severity of Disease: Subject with a measured pre- and post-albuterol/salbutamol FEV_1/FVC ratio of < 0.70 at Screening (Visit 1).

Amended Text:

Severity of Disease: Subject with a measured post-albuterol/salbutamol FEV_1/FVC ratio of < 0.70 at Screening (Visit 1).

Section 4.3. Exclusion Criteria

Deleted Text (formerly criteria #23):

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. Subjects who are in the maintenance phase of a Pulmonary Rehabilitation Program are not excluded.

Section 4.4. Withdrawal Criteria – 3rd paragraph

Original Text:

Subject compliance with double-blind study medication will be assessed at Visits 2 through 14, by reviewing the dose counter on the NDPI.

Amended Text:

Subject compliance with double-blind study medication will be assessed from Visits 2 through 14, by reviewing the dose counter on the NDPI.

Section 6. Time and Events – Table 3

Original Text:

Collect Double-Blind Medication			X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Amended Text:

Collect albuterol (salbutamol)[14]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Single-Blind Medication		X															
Collect Blinded Medication			X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Section 6. Time and Events – Table 3 Footnotes

Original Text:

1. **Visit 0** and **Visit 1** may occur on the same day.
3. Subjects will be assigned a subject number at the time ICF is signed. The ICF must be signed before any study procedures including drug washout(s).
9. Non-fasting and pre-dose. **Visit 2:** pre-dose lab only completed if any part of Screening lab needs to be repeated

Amended Text:

1. **Visit 0** and **Visit 1** may occur on the same day if the subject does not take or has not taken any protocol excluded medications.
3. Subjects will be assigned a subject number at the time ICF is signed. The ICF must be signed before any study procedures including medication exclusion period(s).
9. Non-fasting and pre-dose. A blood sample for repeat analysis is collected only if any part of Screening lab needs to be repeated. Results of repeat labs should be received prior to Randomization at Visit 2.

Section 6.1. Critical Baseline Assessments and Section 9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Original Text:

The informed consent may be given at the screening visit if the subject does not take or has not taken any protocol excluded medications.

Amended Text:

The pre-screening visit and screening visit may occur on the same day if the subject does not take or has not taken any protocol excluded medications.

Section 6.2.6. COPD Exacerbations and Pneumonias

Added Text:

COPD exacerbations should not be recorded as an adverse event, unless they meet the definition of a Serious Adverse Event. For the purposes of this study, COPD exacerbations will be collected and recorded on the exacerbation log in the eCRF.

Section 6.2.4. Bone Mineral Density – 4th paragraph

Original Text:

<u>DEXA Assessments</u>

- At Screening, any subject with a T score < -1.5 (assessed from the L_1-L_4 regions of the spine or the total hip) will be counseled about the clinical implications of this value.
- At any visit after randomization to double-blind treatment (Visit 2) through Visit 10, any subject with a bone mineral density loss of ≥8% from baseline (assessed from the L_1-L_4 regions of the spine or the total hip) will be counseled about the clinical implications of this value.
- At any visit after 2 years (Visit 10), any subject with a bone mineral density loss of ≥10% from baseline (assessed from the L_1-L_4 regions of the spine or the total hip) will be counseled about the clinical implications of this value.

Amended Text:

Subjects with DEXA results meeting pre-defined criteria for clinically significant bone mineral density loss from the Screening scan or any visit scan after randomization will be counseled about the clinical implications of the scan results.

Section 6.2.16. Laboratory Assessments – 3rd paragraph

Original Text:

a blood sample for repeat analysis of the analyte(s) should be collected pre-dose at Visit 2 (Randomization).

Amended Text:

a blood sample for repeat analysis of the analyte(s) should be collected prior to Visit 2 (Randomization). Results of repeat Screening labs should be received prior to Randomization at Visit 2.

Section 11.1. Appendix 1: Laboratory Assessments – third column

Deleted Text:

Urine pregnancy test (in clinic/home test)[2]

TITLE PAGE

Division: Worldwide Development

Title:	Multi-centre, randomized, double-blind, parallel-group study evaluating the effect of Fluticasone Furoate/ Vilanterol (FF/VI) Inhalation Powder once daily compared with Vilanterol (VI) Inhalation Powder Once Daily on Bone Mineral Density (BMD) in subjects with Chronic Obstructive Pulmonary Disease (COPD)

Compound Number: GW685698+GW642444

Development Phase IV

Effective Date: 07-JAN-2013

Subject: COPD, Bone Mineral Density, Fluticasone Furoate (FF), Vilanterol (VI), Novel Dry Powder Inhaler (NDPI)

Author(s): PPD

SPONSOR SIGNATORY:

PPD

Co PPD PPD D
Directo Development
Respiratory Medicines Discovery and Development
GlaxoSmithKline

24 Jan 2023
Date

SPONSOR INFORMATION PAGE

Clinical Study Identifier:
HZC102972

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

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Sponsor Serious Adverse Events (SAE) Contact Information:

Case Management Group, GCSP –Stockley Park, UK
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Fax: PPD

Regulatory Agency Identifying Number(s): FDA IND Numbers: 077855 and 050703; EudraCT #: 2012-004801-28

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Required Standard Wording:

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

_____ _____

Investigator Signature Date

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
AM	Morning
ANCOVA	Analysis of Covariance
AST	Aspartate Transaminase
AUC	Area Under the Curve
ATS	American Thoracic Society
BMD	Bone Mineral Density
IB	Investigator's Brochure
COPD	Chronic Obstructive Pulmonary Disease
eCRF	Electronic Case Report Form
DEXA	Dual Energy X-ray Absorptiometry
ECG	Electrocardiogram
EISR	Expedited Investigator Safety Report
FEV_1	Forced Expiratory Volume in one Second
FF	Fluticasone Furoate
FF/VI	Fluticasone Furoate/ Vilanterol Inhalation Powder Combination
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
IEC	Independent Ethics Committee
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
ITT	Intent to Treat
IVRS	Interactive Voice Response System
L	Liter
LABA	Long Acting Beta Agonist
LDH	Lactate Dehydrogenase
LSLV	Last Subject Last Visit
LTOT	Long Term Oxygen Therapy
MAOI	Monoamine Oxidase Inhibitor
Mcg	Microgram
MDI	Metered Dose Inhaler
MEDDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MSDS	Material Safety Data Sheet
NDPI	Novel Dry Powder Inhaler
OTC	Over the Counter
PD	Pharmacodynamics
PK	Pharmacokinetics

PEF	Peak Expiratory Flow
PFT	Pulmonary Function Test
PGx	Pharmacogenetics
PM	Evening
PR	Pulse Rate
PRN	As needed
QD	Once Daily
RAMOS	Registration and Medication Ordering System
RAP	Reporting Analysis Plan
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SD	Standard Deviation
SPM	Study Procedures Manual
UC	Urine Cortisol
ULN	Upper Limit of Normal
VI	Vilanterol
WHO	World Health Organization

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None

PROTOCOL SUMMARY

Rationale

Chronic obstructive pulmonary disease (COPD) has been defined as a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. The pulmonary component of COPD is characterized by airflow limitation that is not fully reversible, which is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. COPD is a major cause of poor health, resulting in millions of deaths annually worldwide [GOLD, 2010] and contributing significantly to health care costs and morbidity [Chapman, 2006; Lopez, 2006]. According to the World Health Organization, COPD was the fifth leading cause of death worldwide in 2002 and is estimated to be the third leading cause by 2030 [WHO, 2010].

Currently published guidelines on COPD state that the goals of pharmacologic therapy should be to control symptoms, improve health status and exercise tolerance, and reduce the frequency of COPD exacerbations [GOLD, 2010]. Recent clinical research has indicated that an inhaled corticosteroid (ICS) combined with a long acting β_2-agonist (LABA) is more effective than the individual components in managing stable COPD to reduce exacerbations and improve lung function and health status [Ferguson, 2008; Calverley, 2007; Kardos, 2007].

Although inhaled corticosteroids have demonstrated utility in patients with COPD, there is a potential safety concern with long-term use on bone demineralization. These concerns, for the most part, are derived from the well-documented effects of oral corticosteroids on bone density and fracture, however the actual effects of inhaled corticosteroids are not clear and require further study.

Study HZC102972 will prospectively assess the effects of 3 years (156 weeks) exposure to fluticasone furoate/vilanterol (FF/VI) versus VI on bone mineral density in adult subjects with COPD at approximately 40 centers.

Objective(s)

The primary objective of this study is to evaluate the effect of the inhaled corticosteroid FF on bone mineral density (BMD) assessed at the total hip by comparing FF/VI treatment with VI treatment in subjects with moderate COPD.

A secondary objective is to evaluate the effect of the inhaled corticosteroid FF on bone mineral density by gender by comparing FF/VI treatment with VI treatment in subjects with moderate COPD.

Another secondary objective is to evaluate the effect of FF on bone mineral density as assessed at the lumbar spine (L1-L4) by comparing FF/VI treatment with VI treatment in subjects with moderate COPD.

Study Design

This is a multi-center, randomized, double-blind, parallel-group study. The FF/VI inhalation powder once daily and VI inhalation powder once daily will be evaluated in subjects with COPD over 156 weeks. Subjects will sign the informed consent form (ICF) at Visit 0 and will be assigned a subject identifier. See Table 3 for further details. Subjects who meet all study inclusion and none of the exclusion criteria will begin a 14 to 21 day single-blind run-in period following Visit 1. Baseline BMD measurements will be collected between Visits 1 and 2. At Visit 2, eligible subjects will be randomized to double-blind study medication and entered into a 156-week treatment period. Randomisation will be stratified based upon gender. During the treatment period, clinic visits will occur every 3 months. BMD determined by dual-energy x-ray absorptiometry (DEXA) scans will be conducted every 6 months following randomization. A safety Follow-up Visit 15 will occur 7 days after the last treatment study day as a telephone contact. Subjects will be prescribed appropriate COPD therapy at the end of Treatment Visit 14 if required. There are no plans to provide the study drug for compassionate use following study completion.

The target enrolment across approximately 40 study centres is approximately 400 randomized subjects, to achieve approximately 280 who complete the 156-week treatment period. The total duration of subject participation will be approximately 159 to 160 weeks.

Study Endpoints/Assessments

Primary

- BMD measured at the total hip

Secondary

- BMD measurements by gender
- BMD measured at the lumbar spine (L1-L4)

Other

- Adverse Event reporting
- Serious Adverse Event reporting
- Incidence of fractures
- Incidence of pneumonias
- COPD exacerbations

1. INTRODUCTION

1.1. Background

COPD has been defined as a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. The pulmonary component of COPD is characterized by airflow limitation that is not fully reversible, which is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. COPD is a major cause of poor health, resulting in millions of deaths annually worldwide [GOLD, 2010] and contributing significantly to health care costs and morbidity [Chapman, 2006; Lopez, 2006]. According to the World Health Organization, COPD was the fifth leading cause of death worldwide in 2002 and is estimated to be the third leading cause by 2030 [WHO, 2010].

Currently published guidelines on COPD state that the goals of pharmacologic therapy should be to control symptoms, improve health status and exercise tolerance, and reduce the frequency of COPD exacerbations [GOLD, 2010]. Recent clinical research has indicated that an inhaled corticosteroid (ICS) combined with a long acting β_2-agonist (LABA) is more effective than the individual components in managing stable COPD to reduce exacerbations and improve lung function and health status [Ferguson, 2008; Calverley, 2007; Kardos, 2007].

Bronchodilators are considered key to the symptomatic management of COPD and current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend the use of long-acting inhaled bronchodilators in moderate to very severe COPD, because they are more efficacious and more convenient to use than short-acting bronchodilators. The benefits of bronchodilators include not only the control of symptoms but improvements in lung function, hyperinflation, exercise performance, and health status.

Inhaled corticosteroids are considered the most effective anti-inflammatory treatments for all severities of COPD. The benefits of ICS may include control of COPD symptoms, improvement in lung function, decrease in airway hyper-responsiveness and improvement in health status and reduction in exacerbations.

1.2. Rationale

Although inhaled corticosteroids have demonstrated utility in patients with COPD, there is a potential safety concern with long-term use of ICS on bone demineralization. These concerns, for the most part, are derived from the well-documented effects of oral corticosteroids on bone density and fracture, however the actual effects of inhaled corticosteroids are not clear and require further study.

Study HZC102972 will prospectively assess the effects of 3 years (156 weeks) exposure to versus VI on bone mineral density in adult subjects with chronic obstructive pulmonary disease (COPD) at approximately 40 centers.

2. OBJECTIVE(S)

The primary objective of this study is to evaluate the effect of the inhaled corticosteroid FF on bone mineral density assessed at the total hip by comparing FF/VI treatment with VI treatment in subjects with moderate COPD.

A secondary objective is to evaluate the effect of the inhaled corticosteroid Fluticasone Furoate (FF) on bone mineral density by gender by comparing FF/VI treatment with VI treatment in subjects with moderate COPD.

Another secondary objective is to evaluate the effect of FF on bone mineral density as assessed at the lumbar spine (L1-L4) by comparing FF/VI treatment with VI treatment in subjects with moderate COPD.

3. INVESTIGATIONAL PLAN

3.1. Study Design

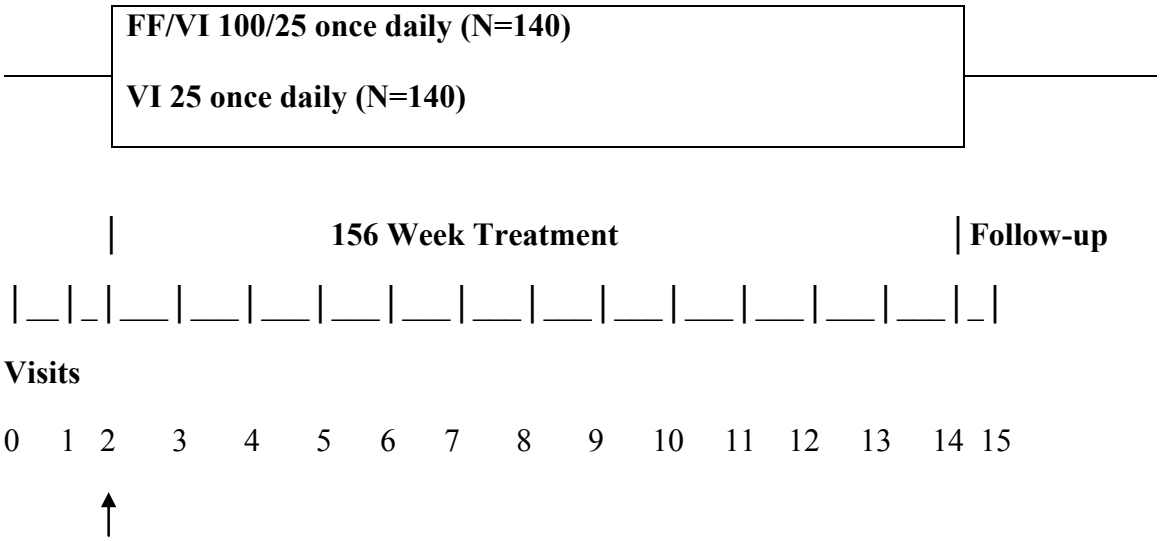
Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

This is a multi-center, randomized, double-blind, parallel-group study. The FF/VI inhalation powder once daily and VI inhalation powder once daily will be evaluated in subjects with COPD over 156 weeks. Subjects will sign the ICF at Visit 0 and will be assigned a subject identifier. See Table 3 for further details. Subjects who meet all study inclusion and none of the exclusion criteria will begin a 14 to 21 day single-blind run-in period following Visit 1. Baseline BMD measurements will be collected between Visits 1 and 2. At Visit 2, eligible subjects will be randomized to double-blind study medication and entered into a 156-week treatment period. Randomisation will be stratified based upon gender. During the treatment period, clinic visits will occur every 3 months. BMD DEXA scans will be conducted every 6 months following randomization. A safety Follow-up Visit 15 will occur 7 days after the last treatment study day as a telephone contact. Subjects will be prescribed appropriate COPD therapy at the end of Treatment Visit 14 if required. There are no plans to provide the study drug for compassionate use following study completion.

Systemic corticosteroid therapies will not be allowed during the run-in period. Subjects may take courses of systemic corticosteroids, where necessary, for treatment of a COPD exacerbation during the double-blind treatment period.

3.1.1. Study Schematic



3.2. Discussion of Design

The purpose of this study is primarily to assess the long-term safety effects of the FF component of the FF/VI inhalation powder on bone mineral density when administered to subjects with COPD over 156 weeks. The American Thoracic Society (ATS)/European Respiratory Society definition of COPD defines the subject population that will be included in this study [Celli, 2004]. BMD at the total hip was chosen as the primary endpoint due to the important morbidity/mortality implications of hip fractures. BMD at the lumbar spine (L1-L4) will be measured and assessed as a secondary endpoint.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

Approximately 400 male and female subjects will be screened to randomize approximately 280 subjects, to obtain at least 224 who complete 156 weeks of treatment. Approximately 40 centres in multiple countries will be required to recruit for the study.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB.

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. **Informed consent:** Subjects must give their signed and dated written informed consent to participate.

2. **Gender:** Male or female subjects. Female subjects must be post-menopausal or using a highly effective method for avoidance of pregnancy. The decision to include or exclude women of childbearing potential may be made at the discretion of the investigator in accordance with local practice in relation to adequate contraception.

3. **Age:** ≥ 40 years of age at Screening (Visit 1)

4. **COPD diagnosis:** Subjects with a clinical history of COPD in accordance with the following definition by the American Thoracic Society/European Respiratory Society [Celli, 2004]: COPD is a preventable and treatable disease characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.

5. **Tobacco use:** Subjects with a current or prior history of ≥10 pack-years of cigarette smoking at screening (Visit 1). Former smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Number of pack years = (number of cigarettes per day/20) x number of years smoked

   Note: Pipe and/or cigar use cannot be used to calculate pack year history.

6. **Severity of Disease:** Subject with a measured pre- and post-albuterol/salbutamol FEV_1/FVC ratio of < 0.70 at Screening (Visit 1). Subjects with a measured post-albuterol/salbutamol 50% ≤ FEV_1 ≤ 70% of predicted normal values calculated using NHANES III reference equations [Hankinson, 1999] at Screening (Visit 1).

7. **Native Hip:** Have at least one evaluable native hip.

4.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

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

1. **Pregnancy:** Women who are pregnant or lactating or are planning on becoming pregnant during the study.

2. **Asthma:** Subjects with a current diagnosis of asthma. (Subjects with a prior history of asthma are eligible if they have a current diagnosis of COPD).

3. **α1-antitrypsin deficiency:** Subjects with α-1 antitrypsin deficiency as the underlying cause of COPD.

4. **Other respiratory disorders:** Subjects with tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases.

5. **Lung resection or transplantation:** Subjects with lung volume reduction surgery within the 12 months prior to Screening Visit 1 or having had a lung transplant.

6. **Chest X-ray:** Subjects with a chest X-ray (or CT scan) that revealed evidence of clinically significant abnormalities not believed to be due to the presence of COPD. A chest X-ray should be taken at Screening Visit 1 if a chest X-ray or CT scan is not available within 12 months prior to Visit 1.

7. **Poorly controlled COPD:** Subjects with poorly controlled COPD, defined as the occurrence of the following in the 12 weeks prior to Screening Visit 1: Acute worsening of COPD that is managed by the subject with corticosteroids or antibiotics or that requires treatment prescribed by a physician or requires hospitalization.

8. **Moderate or severe COPD exacerbation or lower respiratory tract infection:** Subjects with 2 or more moderate or severe COPD exacerbations and/or a lower respiratory tract infection (including pneumonia) within the 12 months prior to Screening Visit 1 or experience a moderate or severe COPD exacerbation and/or a lower respiratory infection (including pneumonia) during the Run-In period.

   NOTE: A moderate COPD exacerbation is defined as requiring systemic corticosteroids and/or antibiotics. A severe COPD exacerbation is defined as requiring hospitalization.

9. **Abnormal clinically significant laboratory finding:** Subjects who have an abnormal, clinically significant finding in any liver chemistry, biochemical, or haematology tests at Screening Visit 1 or upon repeat prior to randomization.

10. **Abnormal and clinically significant 12-lead ECG:** Subjects who have an abnormal, clinically significant ECG finding at Screening Visit 1.

11. **Non-Compliance during Run-In Period**: Failure to demonstrate adequate compliance with run-in medication (< 80% compliant), the ability to withhold COPD medications, and to keep clinic visit appointments.

12. **Bone disorders/conditions:** Subjects with historical or current evidence of bone cancer, severe scoliosis, rheumatoid arthritis, metabolic bone diseases (other than osteoporosis) including hyper-or hypo-parathyroidism, Paget's disease of bone, osteomalacia, or osteogenesis imperfecta. Removal of vertebrae between L1 and L4 of the lumbar spine and/or presence of metal implants or devices, such as plates, rods, or screws in the lumbar spine and/or hip.

13. **Immobility:** Wheel chair bound or paraplegic.

14. **Low vitamin D:** Previously known low-serum 25-hydroxy vitamin D concentration (less than 10ng [25nmoles] per liter).

15. **Other diseases/abnormalities:** Serious, uncontrolled disease (including serious psychological disorders) likely to interfere with the study within the 3-year study.

16. **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.

17. **Drug/food allergy:** Subjects with a history of hypersensitivity to any of the study medications (e.g. beta-agonists, corticosteroid) or components of the inhalation powder (e.g. lactose, magnesium stearate). In addition, patients with a history of severe milk protein allergy that, in the opinion of the study physician, contraindicates the subject's participation will also be excluded.

18. **Drug/alcohol abuse:** Subjects with a known or suspected history of alcohol or drug abuse within the last 2 years.

19. **Prohibited medications prior to spirometry at Visit 1:** Subjects who are medically unable to withhold the following medications prior to spirometry testing at Visit 1:

Medication	**No use within the following time intervals prior to Visit 1 Spirometry Testing**
Inhaled corticosteroids	48 hours
Inhaled ICS/LABA combination products	48 hours
Long-acting anticholinergics (e.g., tiotropium)	48 hours
Theophylline preparations	48 hours
Oral leukotriene inhibitors (zafirlukast, montelukast, zileuton)	48 hours
Oral PDE-4 inhibitors (e.g. roflumilast)	48 hours
Oral beta-agonists Long-acting Short-acting	 48 hours 12 hours
Inhaled long acting $beta_2$-agonist (LABA) - Indacaterol	48 hours
Other inhaled LABAs (e.g., salmeterol)	24 hours
Inhaled sodium cromoglycate or nedocromil sodium	24 hours
Ipratropium/ albuterol (salbutamol) combination product	4 hours
Inhaled short-acting $beta_2$-agonists	4 hours
Short-acting anti-cholinergics (e.g., ipratropium bromide)	4 hours

20. **Additional medication:** Use of the following medications within the following time intervals prior to Visit 1 or during the study (unless otherwise specified):

Medication	**No use within the following time intervals prior to Screening Visit 1 or thereafter at any time during the study (unless otherwise specified)**
Depot corticosteroids	12 weeks
Systemic, Oral, parenteral, intra-articular corticosteroids[1]	30 days
Any other investigational drug	30 days or 5 half lives whichever is longer.

1. Subjects may take courses of systemic corticosteroids, where necessary, for treatment of an exacerbation during the double-blind treatment period.

21. **COPD medications:** Use of inhaled corticosteroids (ICS), long-acting beta$_2$-agonists (LABA), or ICS/LABA combination products (other than the study-provided double-blind study medication) at Visit 2 (Randomization) or during the double-blind treatment period.

22. **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.

23. **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. Subjects who are in the maintenance phase of a Pulmonary Rehabilitation Program are not excluded.

24. **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.

25. **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

26. **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.

4.4. Withdrawal Criteria

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue a subject from this study at any time. Every effort should be made by the investigator to keep the subject in the study.

The primary reason for subject withdrawal will be recorded in the electronic Case Report Form (eCRF). Primary reasons for withdrawal will be categorised as:

- adverse event
- withdrew consent
- lost to follow-up
- protocol deviation
- lack of efficacy
- subject reached protocol-defined stopping criteria
- study closed/terminated
- investigator discretion

Subject compliance with double-blind study medication will be assessed at Visits 2 through 14, by reviewing the dose counter on the NDPI. Subjects must be ≥80% to ≤120% compliant on taking study medication between each pair of on-treatment visits. Subjects who fall outside this range should be re-educated on treatment compliance by their site. This re-education should be documented in the subject's source document. If the double-blind study medication is prematurely discontinued during the course of study or medication compliance repeatedly falls outside of acceptable ranges, the study sponsor/site monitor must be contacted to discuss subject eligibility for continued participation in the study.

A subject will also be withdrawn from the study, in consultation with the medical monitor and principal investigator, if any of the following stopping criteria are met:

- **Liver Chemistry**: Meets any of the liver chemistry stopping criteria as defined in Section 6.2.7.
- **Pregnancy:** Positive pregnancy test
- **Laboratory Measurements:** Demonstrate a clinically important change in a laboratory parameter(s).

If a subject is withdrawn due to an exacerbation, the exacerbation section and SAE section, if applicable, of the eCRF should be completed and the subject should be followed until resolution of exacerbation.

If a subject is withdrawn due to pneumonia, the AE/SAE section and the pneumonia/chest x-ray section of the eCRF should be completed and the subject should be followed until clinical resolution of the pneumonia.

4.5. Pre-Screen Failures and Screening Failures

A subject will be assigned a subject number at the time the informed consent is signed.

A subject who is assigned a subject number but does not have Visit 1 will be considered a pre-screen failure.

Any subject who performs a Visit 1 procedure but does not continue in the study beyond Visit 1 or any subject who completes Visit 1 and enters the run-in period, but is subsequently found to be ineligible for the study (e.g. exclusionary laboratory, ECG, or spirometry findings) conducted prior to randomization to the study treatment medication (Visit 2), is classified as a 'screen failure'.

The study interactive voice response system (IVRS) will be contacted to report pre-screen failures. The following information will be collected for subjects who are pre-screen failures:

- Subject number
- Date of ICF signature
- Demographic information including race, age and gender
- Details of COPD medications within 30 days of Visit 0
- Details of COPD exacerbation (yes/no status), if applicable
- Serious Adverse Event information, if applicable, only for an SAE considered as related to study participation (e.g. study treatment, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication
- Investigator signature page

IVRS will be contacted to report screen failures, In addition to the information above, the following information will be collected for screen failures:

- Date of screening visit
- Reason for screen failure (screening failure and inclusion/exclusion criteria)

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

GSK Clinical Trials Supplies will provide the investigational products for use in this study. All blinded study medication will be delivered via the NDPI. At each dispensing each subject will receive one NDPI for once-daily administration. The contents of each treatment are described in Table 1 and Table 2

The NDPI provides a total of 30 doses (60 blisters), with each actuation comprising the contents of one blister from each of the two internal foil strips simultaneously. The

NDPIs containing randomized treatment and dummy medication (placebo) will appear identical on the outside to the subject (and his/her caregiver) and the Investigator.

All subjects will receive supplemental albuterol/salbutamol (MDI and/or nebules) to be used on an as-needed basis throughout the study; for all sites this medication will be sourced locally where possible.

Following the 14 to 21 day, Run-In period, eligible subjects will be randomized (1:1) to one of the following two possible treatments, administered each morning for 156 weeks:

- FF/VI Inhalation Powder 100/25mcg QD
- VI Inhalation Powder 25mcg QD

Randomization in each treatment group will be stratified (1:1) according to gender.

A description of the investigational treatments is provided below:

Table 1 Description of FF/VI Inhalation Powder Novel Dry Powder Inhaler (NDPI)

Formulation	**First strip**: Fluticasone Furoate blended with lactose	**Second strip**: Vilanterol micronised drug (as the 'M' salt triphenylacetate) blended with lactose and magnesium stearate[1]
Dosage Form	Novel dry powder inhaler with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	100mcg per blister	25mcg per blister
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	Inhaled

1. Magnesium stearate 1% w/w of total drug product

Table 2 Description of VI Inhalation Powder Novel Dry Powder Inhaler (NDPI)

Formulation	**First strip**: lactose	**Second strip**: Vilanterol micronised drug (as the 'M' salt triphenylacetate) blended with lactose and magnesium stearate[1]
Dosage Form	NDPI with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	N/A	25mcg per blister
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	Inhaled

1. Magnesium stearate 1% w/w of total drug product

The contents of the label will be in accordance with all applicable regulatory requirements. Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

Adequate precautions must be taken to avoid direct contact with the investigational product. The occupational hazards and recommended handling procedures are provided in the Material Safety Data Sheet (MSDS).

5.1.1. Storage

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the investigational product will be limited to the investigator and authorized site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

The NDPIs are packaged in a foil overwrap with enclosed desiccant. The foil overwrap must not be opened until immediately prior to use. Once the foil overwrap has been opened the NDPI has a 30 day in-use shelf life.

5.1.2. Study Drug Return

At the end of the study, all study-supplied study medication (used and unused) will be destroyed following local standard operating procedures, except where it is suspected that the NDPI or NDPI packaging is defective. The NDPI and packaging should be returned to GSK.

Details for both destruction and return of study medication are found in the SPM.

In addition, any study inhaler that fails to function properly must be identified to GSK personnel for return to GSK for testing. Details of the failure will be documented in the eCRF. The subject should return the NDPI to the clinic as soon as possible and avoid missing any doses if possible. The site should then call IVRS and obtain a new treatment pack number for this subject and dispense a new study medication kit from the site's investigational product supply as instructed by RAMOS, an Interactive Voice Response System (IVRS).

5.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule. Once a randomization number has been assigned to a subject, the same number cannot be reassigned to any other subject in the study.

Subjects will be stratified based on gender.

Subjects will be site-based randomized using RAMOS, an Interactive Voice Response System (IVRS). This is a telephone based system that will be used by the investigator or designee to register the subject (initially at Visit 0, and subsequently at each study visit), randomize the subject and provide medication assignment information. Details on how to use RAMOS to register and randomize subjects is provided in the SPM.

Following the 14-21 day, Run-In period, eligible subjects will be randomized (1:1) to one of the following 2 possible treatments, administered as one inhalation each morning and evening for 156 weeks:

- Fluticasone Furoate /Vilanterol 100/25mcg once daily
- Vilanterol 25mcg once daily

5.3. Blinding

Study Medication taken during the 156-week treatment period will be double-blind. Neither the subject nor the study physician will know which study medication the subject is receiving.

The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. Whenever possible, the investigator must first discuss options with the GSK Medical Monitor or appropriate GSK study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the investigator must notify GSK as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to clinical investigators in accordance with local regulations and/or GSK policy.

Subjects will be withdrawn if the treatment code becomes unblinded. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.

5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

5.5. Treatment Compliance

An initial supply of albuterol (salbutamol), a short-acting, $beta_2$-agonist, will be provided to each subject to use as needed for symptomatic relief of COPD symptoms during both the Run-in and Treatment Periods. The subject's use of albuterol (salbutamol) will be assessed at each clinic visit and additional albuterol (salbutamol) will be dispensed to the subject as needed.

Subject compliance with the single-blind placebo NDPI during Run-In will be assessed at Visit 2 by reviewing the dose counter on the NDPI.

Subject compliance with double-blind study medication will be assessed at each treatment visit (from Visits 3 - Visit 14) and any unscheduled visit where study drug is returned by reviewing the dose counter on the NDPI. Subjects must be ≥80% to ≤120% compliant on taking study medication between each pair of on-treatment visits. Subjects who fall outside this range should be re-educated on treatment compliance by their site. This re-education should be documented in the subject's source document. If the double-blind study medication is prematurely discontinued during the course of study or medication compliance repeatedly falls outside of acceptable ranges, the study sponsor/site monitor must be contacted to discuss subject eligibility for continued participation in the study.

5.6. Concomitant Medications and Non-Drug Therapies

All COPD medications taken within 30 days prior to Visit 0 and during the run-in period will be recorded in the eCRF. All COPD and non-COPD concomitant medications taken during the study will be recorded in the eCRF. The minimum requirement includes, but is not limited to name of the medications, and the dates of the administration.

Note: Care is advised when co-administering with strong CYP 3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for an increased systemic exposure to both fluticasone furoate and vilanterol, which could lead to an increase in the potential for adverse reactions.

5.6.1. Permitted Medications and Non-Drug Therapies

The following medications are permitted during the Screening and Treatment periods:

COPD Medications

- Study supplied albuterol/salbutamol (MDI or nebules) for symptomatic relief during the Run-In and Double-Blind Treatment period
- Mucolytics at constant dosage
- Oxygen for intermittent use or PRN therapy ≤ 12 hours per day is allowed. (Subjects requiring LTOT or nocturnal oxygen therapy required for greater than 12 hours a day are excluded from the study.)
- Theophyllines (long and short-acting)
- Short-acting anti-cholinergic agents
- Long-acting anti-cholinergic agents
- Short-acting beta2-agonists; i.e. albuterol
- Beta2-agonist-anti-cholinergic combinations; i.e. Combivent
- Subjects may take courses of systemic corticosteroids, where necessary, for treatment of an exacerbation.

Non-COPD Medications

- Cardioselective beta-blockers (stable dose) and ophthalmic beta-blockers. (Administer with caution as they may block bronchodilatory effects of beta-agonists and produce severe bronchospasm).
- Care is advised when co-administering with strong CYP 3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for an increased systemic exposure to both fluticasone furoate and vilanterol, which could lead to an increase in the potential for adverse reactions.
- Antihistamines and nasal decongestants
- Over-the-counter (OTC) cough suppressants (for short term treatment ≤7days)
- Intranasal sodium cromoglycate or nedocromil sodium
- Intranasal corticosteroids, provided the subject is on a stable daily dose for at least 4 weeks prior to Visit 1 and remains on this dose throughout the study
- Topical (≤1 % hydrocortisone in strength) or ophthalmic corticosteroids
- Influenza and/or pneumonia vaccination
- Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). Administer with caution as they may potentiate the effects of beta-agonists on the vascular system.
- Diuretics. Caution is advised in the co-administration of beta-agonists with nonpotassium sparing diuretics.
- Treatment(s) for smoking cessation
- All medications for other disorders as long as the dose remains constant wherever possible.

5.6.2. Prohibited Medications and Non-Drug Therapies

Medications prohibited at specific time intervals prior to Screening Visit 1 and at any time during the study are identified in Section 4.3 Exclusion Criteria.

If a subject's current medication is going to be changed in order to participate in the study, then consent must be obtained prior to any medication change and the subject will be required to return to the clinic to complete the Screening Visit 1 once the protocol specified time period has been completed.

5.7. Treatment after the End of the Study

At the end of the treatment period (Visit 14 or Early Withdrawal), subjects can resume conventional COPD therapy as prescribed by the Investigator. There are no plans to provide the study drug for compassionate use following study completion.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition whether or not GSK is providing specific post study treatment.

5.8. Treatment of Study Treatment Overdose

An overdose is defined as a dose greater than what is instructed (see Section 5.1), which results in clinical signs and symptoms. In the event of an overdose of study medication, the investigator should use clinical judgement in treating the overdose and contact the study medical monitor. GSK is not recommending specific treatment guidelines for overdose and toxicity management. The investigator should refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug(s) being used in this study. Such documents may include, but not be limited to, the approved product labeling for albuterol (salbutamol), and the IB or equivalent document provided by GSK for double blind medications.

6. STUDY ASSESSMENTS AND PROCEDURES

The Time and Events Table is provided in Table 3. All study assessments should be conducted by the investigator or his/her qualified designee. Please refer to the SPM for a suggested order of assessments.

Table 3 Time and Events Table

			Double-Blind Treatment period														
Visit Number	**0 Pre-screen[1]**	**1 Screen-ing[2]**	**2 Random-ization**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Early With-draw**	**15 Follow -up**
			Day 1	13 wks ±14 Days	26 wks ±14 Days	39 wks ±14 Days	52 wks ±14 Days	65 wks ±14 Days	78 wks ±14 Days	91 wks ±14 Days	104 wks ±14 Days	117 wks ±14 Days	130 wks ±14 Days	143 wks ±14 Days	156 wks ±14 Days		Visit 14/EW + 7±2 Days
Assessments																	
Informed consent[3]	X																
PGx Consent & Sampling[4]			X														
Demography	X																
Medical History		X															
Physical Exam		X					X				X				X	X	
Spirometry Testing		X	X		X		X		X		X		X		X	X	
Reversibility Testing		X															
Smoking history/ smoking status		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Smoking cessation counseling		X					X				X				X	X	
Register visit on IVRS[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments																	
BMD DEXA scans[6]		X			X		X		X		X		X		X	X	
Oropharyngeal examination[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chest X-ray[8]		X															
Lab Tests[9] / Serum Pregnancy Test[10]		X															

			Double-Blind Treatment period														
Visit Number	**0 Pre-screen[1]**	**1 Screen-ing[2]**	**2 Random-ization**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Early With-draw**	**15 Follow -up**
			Day 1	13 wks ±14 Days	26 wks ±14 Days	39 wks ±14 Days	52 wks ±14 Days	65 wks ±14 Days	78 wks ±14 Days	91 wks ±14 Days	104 wks ±14 Days	117 wks ±14 Days	130 wks ±14 Days	143 wks ±14 Days	156 wks ±14 Days		Visit 14/EW + 7±2 Days
12-lead ECG & Rhythm Strip		X															
Exacerbation Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment[11]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event Assessment[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Diary		X	X	X	X	X	X	X	X	X	X	X	X	X			
Collect/Review Diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medication Assessments																	
Concurrent Medication Assessment[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense albuterol (salbutamol)[14]		X	X	X	X	X	X	X	X	X	X	X	X	X			
Dispense Double-Blind Medication		X	X	X	X	X	X	X	X	X	X	X	X	X			
Collect Double-Blind Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Other Assessment																	
Discharge from Study[15]															X	X	

1. **Visit 0** and **Visit 1** may occur on the same day.
2. Following Screening **Visit 1**, subjects enter a 14 to 21 day single-blind run-in period
3. Subjects will be assigned a subject number at the time ICF is signed. The ICF must be signed before any study procedures including drug washout(s).
4. Saliva (2ml) sample is collected in the DNA self-collection kit. This should ideally be taken as soon after randomization (Visit 2) as possible, but may be taken at any other visit after randomization if necessary. PGx consent must be signed prior to PGx sampling.
5. A telephone based IVRS system (RAMOS) which will be used by the investigator or designate to register the subject, randomize the subject and provide medication assignment information.
6. Baseline BMD measurements will be collected between **Visit 1** and **Visit 2**.
7. If evidence of infection, culture swab may be taken and appropriate therapy should be instituted at Investigator discretion. Subjects with culture-positive infection may continue in the study on appropriate anti-infective treatment at Investigator discretion.
8. Chest X-ray must be taken if a Chest X-ray or CT scan is not available within the 12 months preceding **Visit 1**. Chest x-rays will be requested for suspected cases of pneumonia.
9. Non-fasting and pre-dose. **Visit 2:** pre-dose lab only completed if any part of Screening lab needs to be repeated
10. Females of child-bearing potential only
11. Adverse events are to be collected from the start of blinded study medication (Visit 2) until the follow-up phone contact.
12. Serious adverse events are to be collected from the start of study drug (Visit 2) until the follow-up phone contact. However, any SAEs assessed as related to study participation will be recorded from the time subjects sign informed consent.
13. All COPD medications taken within 30 days prior to **Visit 0** will be collected.
14. Collect and re-dispense as needed after **Visit 1**.
15. Discharge from study on appropriate therapy.

6.1. Critical Baseline Assessments

No study related procedures may be performed until the informed consent form document has been signed by the subject. A pre-screening visit may be required in order to administer the informed consent before any changes are made to the subject's current medication regimen. Selection and modification of subject's medications prior to study participation is based on the physician's judgment according to sound medical practice, principles, and each subject's needs. A subject's treatment must not be changed merely for the purpose of enabling the subject's participation in the study. The informed consent may be given at the screening visit if the subject does not take or has not taken any protocol excluded medications. During the pre-screening visit (Visit 0), each subject will have the following demographic information collected:

- Demographic history (including gender, ethnic origin, date of birth)

During Screening Visit 1, each subject will undergo the following assessments**:**

- Medical history (including COPD and smoking history)
- Cardiovascular medical history/risk factors will be assessed at baseline.
- Inclusion/Exclusion criteria assessment
- Concomitant medication review
- ECG and rhythm strip
- Spirometry with reversibility testing
- Physical exam (including vital signs)
- Laboratory assessments (including chemistry, hematology, hepatitis, and pregnancy)

See Section 4.5 for information regarding Screening Failures.

6.2. Safety

6.2.1. Primary Endpoint

- BMD measured at the total hip

6.2.2. Secondary Endpoints

- BMD measured at the lumbar spine (L1-L4)
- BMD measurements by gender

6.2.3. Other Endpoints

- Adverse Event reporting
- Serious Adverse Event reporting
- Incidence of fractures

- Incidence of pneumonias
- COPD exacerbations

6.2.4. Bone Mineral Density

Effects on the skeletal system will be assessed by measuring bone mineral density (BMD) using dual energy x-ray absorptiometry (DEXA) with established methodology. DEXA measurements of the total hip and the L_1-L_4 regions of the spine will be completed at baseline, 26 weeks, 52 weeks, 78 weeks, 104 weeks, 130 weeks, and 156 weeks or end of study treatment.

All DEXA scans will be conducted by qualified technicians and sent electronically for centralized analysis. Quality assurance and calibration of DEXA equipment and densitometric measurements will be monitored by this facility to control for site-to-site variability in BMD measurements.

Acceptable DEXA measurements must be conducted prior to the first dose of randomized study medication.

DEXA Assessments

- At Screening, any subject with a T score < -1.5 (assessed from the L_1-L_4 regions of the spine or the total hip) will be counseled about the clinical implications of this value.
- At any visit after randomization to double-blind treatment (Visit 2) through Visit 10, any subject with a bone mineral density loss of ≥8% from baseline (assessed from the L_1-L_4 regions of the spine or the total hip) will be counseled about the clinical implications of this value.
- At any visit after 2 years (Visit 10), any subject with a bone mineral density loss of ≥10% from baseline (assessed from the L_1-L_4 regions of the spine or the total hip) will be counseled about the clinical implications of this value.

6.2.5. Fractures

For any fractures that occur after the initiation of the double-blind study drug, the location of the fracture, and whether it is considered traumatic or non-traumatic must be recorded on the Fractures page of the eCRF. Severity of a fracture should be determined by the Investigator. Details regarding the information to be captured for fractures will be provided in the SPM.

6.2.6. COPD Exacerbations and Pneumonias

For the purpose of this study, exacerbation of COPD is defined by a worsening of symptoms requiring additional treatment as follows:

- A mild COPD exacerbation: managed by subject with increased use of prn medications
- A moderate COPD exacerbation: requires treatment with antibiotics and/or systemic corticosteroids
- A severe COPD exacerbation: requires hospitalization

Any subject experiencing worsening of symptoms should:

- Contact his/her study investigator and/or research coordinator immediately, and report to the study clinic as required
- If the subject is unable to contact his/her study investigator and/or research coordinator, they should contact their primary care physician (or other health care practitioner as required) and contact their study site as soon as possible
- If the subject seeks emergent/acute care for worsening respiratory symptoms, he/she should inform the caring Health Care Provider (HCP) to contact the investigator as soon as possible.

Subjects with presence of worsening respiratory symptoms will be classified by the Investigator as having:

- A mild/moderate/severe COPD exacerbation and/or pneumonia

OR

- A lower respiratory tract infection (LRTI) [i.e. other than pneumonia]
- Background variability of COPD
- A non-respiratory related disease
- Other respiratory related disease

The time period for collection of COPD exacerbations will begin from the time of Visit 2 (Randomization) and will end when the 7±2day Follow-up period has been completed.

Exacerbations that meet the definition of an SAE, will be recorded on the appropriate eCRF section and should be reported to GSK for all subjects regardless of whether or not they are randomized to blinded study medication.

Subjects are excluded from participating if any of the following apply:

- They have poorly controlled COPD, defined as the occurrence of the following in the 12 weeks prior to Screening Visit 1: Acute worsening of COPD that is managed by the subject with corticosteroids or antibiotics or that requires treatment prescribed by a physician or requires hospitalization.

- They have 2 or more moderate or severe COPD exacerbations and/or a lower respiratory tract infection (including pneumonia) within the 12 months prior to Screening Visit 1 or experience a moderate or severe COPD exacerbation and/or a lower respiratory infection (including pneumonia) during the Run-In period.

The dates of onset and resolution of each COPD exacerbation should be based on when the Investigator and/or subject determines that the COPD symptoms initially started and then returned to pre-exacerbation levels.

If an exacerbation begins as mild, but becomes moderate or severe or begins as moderate and becomes severe, the exacerbation should be captured as one exacerbation and classified by its highest level of severity.

For the purpose of this study, pneumonia is defined as new auscultatory findings compatible with parenchymal lung infection and/or radiographic evidence of parenchymal/air space disease. All suspected cases of pneumonia are encouraged to be confirmed radiographically within 48 hours of diagnosis. All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable). Information regarding chest X-ray-confirmed cases of pneumonia will be recorded in the eCRF. Details regarding the information to be captured for pneumonias will be provided in the SPM.

Definitions for COPD exacerbations and pneumonia are given above. If, based upon these criteria, a subject's symptoms do not fulfill the diagnosis of an exacerbation and/or pneumonia, then the investigator should use his/her clinical judgment to assess the subject's symptoms (including increased volume of sputum production and/or change in the sputum color) for a diagnosis of LRTI (e.g. acute bronchitis), background variability of COPD, a non-respiratory related disease or other respiratory related disease.

Investigator judgment should be used in deciding whether to report the signs and symptoms (and/or determined diagnosis) as an AE/SAE in the eCRF. Medication(s) used to treat a COPD exacerbation and/or pneumonia are to be recorded in the eCRF.

6.2.7. Liver chemistry stopping and follow up criteria

Phase III-IV liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

Phase III-IV liver chemistry stopping criteria 1-5 are defined below and in Appendix 4:

1. ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT ≥ 3xULN **and** INR>1.5, if INR measured)

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT ≥ 8xULN.

3. ALT ≥ 5xULN but <8 xULN persists for ≥2 weeks

4. ALT ≥ 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

5. ALT ≥ 5xULN but <8 xULN and cannot be monitored weekly for ≥2 weeks

When any of the liver chemistry stopping criteria 1-5 is met, do the following:

- **Immediately** withdraw investigational product for that subject
- Report the event to GSK **within 24 hours** of learning its occurrence
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN **and** INR>1.5, if INR measured); INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Withdraw the subject from the study after completion of the liver chemistry monitoring (unless further safety follow up is required).
- Do not restart investigational product.

In addition, for criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values

For criteria 2, 3, 4 and 5:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (see below)

- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Subjects with ALT ≥5xULN and <8xULN which exhibit a decrease to ALT x≥3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks:

- Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss subject safety
- Can continue investigational product
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

For criteria 1-5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Cytomegalovirus IgM antibody;
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
  - Hepatitis E IgM antibody
- Blood sample for PK analysis, obtained within 72 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN.
- Obtain complete blood count with differential to assess eosinophilia.

- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form.

The following are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China.**
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. **NOTE**: if hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) – as outlined in: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793/.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

6.2.8. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of double-blind Investigational Product and until the follow up contact.

COPD exacerbations should not be recorded as an adverse event, unless they meet the definition of a Serious Adverse Event. For the purposes of this study, COPD exacerbations will be collected and recorded on the COPD exacerbation log in the eCRF. The time period for collection of COPD exacerbations will begin from the time of Visit 2 (Randomization) and will end when the 7-day Follow-up period has been completed.

The investigators and site staff should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD receiving fluticasone furoate/vilanterol include current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m^2 and patients with an FEV_1<50% predicted. For all suspected cases of pneumonia, Investigators are encouraged to confirm the diagnosis (this includes obtaining a chest x-ray) and to initiate appropriate therapy as promptly as possible. All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable).

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate AE/SAE CRF page will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

6.2.8.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

6.2.8.2. Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not

required and the threshold value stated will not apply to patients receiving anticoagulants).

NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

6.2.9. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

6.2.10. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thrombosis
- Deep Venous Thrombosis
- Revascularization

This information should be recorded within one week of when the AE/SAE(s) are first reported.

6.2.11. Death Events

In addition, all deaths, whether or not they are considered SAEs, will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.

This information should be recorded within one week of when the death is first reported.

6.2.12. Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

6.2.13. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of study treatment and until the follow up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.2.14.

6.2.14. Prompt Reporting of Serious Adverse Events and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool "CV events" and/or "death" data collection tool(s) if applicable	24 hours	Updated "SAE" data collection tool "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	2 weeks	"Pregnancy Notification Form"	2 weeks	"Pregnancy Follow-up Form"
Non-serious adverse events related to study treatment	5 calendar days	"Adverse Reaction" data collection tool	2 weeks	Updated "Adverse Reaction" data collection tool
Liver chemistry abnormalities for Phase I to IV:				
ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) (or ALT≥3xULN **and** INR>1.5, if INR measured)[1]	24 hours[2]	"SAE" data collection tool. "Liver Event CRF" and "Liver Imaging" and/or "Liver Biopsy" CRFs, if applicable[3]	24 hours	Updated "SAE" data collection tool/"Liver Event" Documents[3]
Remaining liver chemistry abnormalities Phase III to IV:				
ALT≥8xULN; ALT≥3xULN with hepatitis or rash or ≥3xULN and <5xULN that persists≥4 weeks	24 hours[2]	"Liver Event" Documents (defined above) [3]	24 hours	Updated "Liver Event" Documents[3]
ALT≥5xULN plus bilirubin <2xULN	24 hours[2]	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks[3]	24 hours	Updated "Liver Event" Documents, if applicable[3]
ALT≥5xULN and bilirubin <2xULN that persists ≥2 weeks	24 hours[2]	"Liver Event" Documents (defined above) [3]	24 hours	Updated "Liver Event" Documents[3]

ALT≥3xULN and <5x ULN and bilirubin <2xULN	24 hours[2]	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[3]	24 hours	Updated "Liver Event" Documents, if applicable[3]

1. INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants.
2. GSK must be contacted at onset of liver chemistry elevations to discuss subject safety
3. Liver Event Documents (i.e., "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible.

The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

6.2.14.1. Regulatory reporting requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

6.2.15. SpirometryTesting

Lung function will be measured by spirometry at Visits 1, 2, 4, 6, 8, 10, 12, and 14, or at Early Withdrawal using site available spirometry equipment that meets or exceeds the minimum performance recommendations of the ATS/ERS [Miller, 2005]. For Visits 2 onward, FEV_1 will be measured prior to administration of morning study medication.

For each observation, at least 3 valid (with no more than 8) efforts will be obtained using ATS/ERS guidelines. The largest FEV_1 and FVC from the 3 acceptable efforts should be

recorded, even if they do not come from the same effort. Acceptable spirometry efforts should have a satisfactory start of test and end of test (i.e. a plateau in the volume-time curve) and be free from artifacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons [Miller, 2005]. The subject's position during spirometry measurements (sitting or standing) should remain constant for the duration of the study.

A post-albuterol (salbutamol) FEV_1/FVC ratio of < 0.70 and predicted normal value of $50\% \leq FEV_1 \leq 70\%$ is required at Screening Visit 1.

All predicted values will be taken from Hankinson [Hankinson, 1999].

The investigator will retain a printed copy of the spirometry data in the subject's source documents.

6.2.15.1. Reversibility Testing

At Visit 1, reversibility to albuterol (salbutamol) will be assessed. To determine reversibility, the subject will self-administer 4 puffs (360mcg) of albuterol (salbutamol) without the use of a spacer or holding chamber. Triplicate spirometry efforts will be performed immediately pre-albuterol (salbutamol) and within 30 minutes post-albuterol (salbutamol). The highest FEV_1 from three valid forced expiratory curves will be used to determine reversibility.

Reversibility is defined as an increase in FEV_1 of ≥12% and ≥200mL following administration of albuterol (salbutamol). Non-reversible is defined as a post-albuterol (salbutamol) increase in FEV_1 of <200mL or a ≥200mL increase that is <12% from pre-albuterol (salbutamol) FEV_1.

6.2.16. Laboratory Assessments

Routine, **non-fasting** clinical laboratory (hematology and biochemistry), will be performed in all subjects at the Screening Visit 1.

For women of childbearing potential, a serum pregnancy test will be included in the laboratory panel collected at Visit 1 if applicable.

At the discretion of the investigator, additional samples may be taken for safety reasons. If the subject has an abnormal laboratory finding for any analyte from the Screening Visit laboratory panel, which in the opinion of the Investigator does not preclude the subject from participating in the study, but for which the Investigator feels warrants treatment/correction with a non-excluded medication(s) (e.g., calcium supplement for hypocalcemia), a blood sample for repeat analysis of the analyte(s) should be collected pre-dose at Visit 2 (Randomization)

All protocol required laboratory assessments, as defined in Appendix 1 must be performed by the central laboratory. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled

with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the central laboratory. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

6.2.17. Oropharyngeal Examination

Oropharyngeal examinations for clinical evidence of infection (i.e., Candida albicans) will be performed at each study visit as shown in the Time and Events Table. If there is evidence of infection, a culture swab may be taken and appropriate therapy should be instituted at the discretion of the Investigator. Subjects with culture-positive infection may continue in the study on appropriate anti-infective treatment at the discretion of the Investigator. The results of these assessments, and any relative pharmacotherapy, will be recorded in the subject's clinic notes and in the eCRF. After randomization, all culture positive results must be reported as adverse events.

6.2.18. Diary Card - Medical Problems/Medications Taken

Subjects will be instructed to record any medical problems they may have experienced and any medications used to treat those medical problems in their diaries from Screening (Visit 1) through the Follow-up Phone Contact.

Subjects will be instructed on how to complete the diary and will be asked to return completed diaries at each clinic visit. The study coordinator must review the diary at each clinic visit and will inquire about the diary data during the Follow-up Phone Contact as well. If the subject does not mention an event which is recorded on the diary, he/she should be questioned for further information in order to determine if there was the occurrence of an AE. Any confirmed AE and/or concurrent medication will be entered into the eCRF.

6.2.19. 12-lead ECG Assessment

A single 12-lead ECG and rhythm strip will be recorded prior to spirometry at the Screening Visit 1.

All ECG measurements will be performed with the subject resting in a supine position for approximately 5 minutes before each reading, which should be carried out after measurement of vital signs and before spirometry.

The investigator, a designated sub-investigator, or other appropriately trained site personnel, will be responsible for performing the 12-lead ECG recording on each study visit, if applicable. The investigator must provide his/her dated signature on the original paper tracing, attesting to the authenticity of the ECG machine interpretation.

6.2.20. Smoking Cessation Counselling

During the Screening Visit 1, 6, 10, and 14 or EW visit (if necessary), subjects will be given smoking cessation counselling, which includes advice regarding the following:

- the health effects that smoking may cause.
- the health benefits that may result if they stop smoking.
- if they do not feel capable of discontinuing smoking that their primary care physician may be able to discuss anti-smoking strategies with them.
- that they may discontinue smoking at any time during the study and will not have to be withdrawn from the study if they do so.

6.3. Pharmacogenetic Research

Information regarding pharmacogenetic research is included in Appendix 2. The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments. In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

7. DATA MANAGEMENT

For this study subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK and combined with data (e.g. laboratory data, diary data) provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug. An appropriate medical dictionary that covers all approved drugs in the region will be referenced. eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

The null hypothesis for the primary measure is that the change in BMD assessed at the total hip is worse for the FF/VI combination product arm compared with the VI arm. The alternative hypothesis that the change in BMD assessed at the total hip is not worse for the FF/VI arm compared with the VI arm.

This is also the null and alternative hypothesis for the secondary measure of BMD assessed at the L1-L4 lumbar spine.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

This study will evaluate non-inferiority in both males and females separately as key secondary measures. 56 subjects per gender per treatment would provide 80% power to demonstrate non-inferiority by comparing the lower boundary of a two-sided 95% confidence interval on the treatment difference to -1%/year assuming a true treatment difference of -0.3%/year. In study SCO40041, approximately 20% of subjects did not provide post-baseline data, therefore 70 subjects per gender per treatment will be randomized (280 total subjects). Randomization will be stratified by gender.

For the primary evaluation of BMD for the total hip, males and females will be combined, and will have >90% power to demonstrate non-inferiority by comparing the lower boundary of a two-sided 95% confidence interval on the treatment difference to -1%/year assuming a true treatment difference of -0.3%/year.

8.2.2. Sample Size Sensitivity

The following table presents the power of the study under different circumstances in terms of the standard deviation and the observed treatment difference in change from baseline in bone mineral density for the total hip.

	True Treatment Difference between FF/VI and VI		
SD	**-0.2%/yr**	**-0.3%/yr**	**-0.4%/yr**
1.3%/yr	>99%	99%	96%
1.4%/yr	>99%	**98%**	94%
1.5%/yr	>99%	97%	91%

8.2.3. Sample Size Re-estimation

No sample size re-estimation is planned for this study.

8.3. Data Analysis Considerations

8.3.1. Analysis Populations

All Subjects Enrolled Population: This population will consist of all subjects, for whom a record exists on the study database, including screen failures and any subject who was not screened but signed the informed consent form. This population will be used for reporting subject disposition, reasons for withdrawal prior to randomisation, and inclusion, exclusion and randomisation criteria deviations and SAEs for non-randomised subjects.

(Modified) Intent-to-Treat (ITT) Population: This population will consist of all subjects who are randomised and receive at least one dose of study drug. The ITT Population will be the primary population for all analyses of safety and efficacy measures.

8.3.2. Analysis Data Sets

The bone mineral density data will comprise the primary data set of interest. Details of derived data in analysis datasets to be created will be provided in the Reporting and Analysis Plan (RAP).

8.3.3. Treatment Comparisons

8.3.3.1. Primary Comparisons of Interest

BMD measured for the total hip will be summarized by visit and as change from baseline at each visit for raw values, percent changes from baseline, t-scores, and z-scores. The percent change from baseline in BMD for the total hip will be the primary endpoint, and analyzed using a repeated measures model with terms for treatment, time, time by treatment, baseline BMD, baseline BMI and gender. Contrasts will be formed using the time by treatment variable to provide 95% confidence intervals for the treatment difference with the unit of percent change per year. The 95% confidence interval will be compared to a lower bound of -1%/year in order to assess clinical non-inferiority. Any additional covariates for the model, along with other details, including model inclusion and exclusion criteria for those covariates, will be determined a priori in a detailed Reporting and Analysis Plan (RAP) that will be completed prior to unblinding of the study.

The percent change from baseline in BMD at the L1-L4 region of the spine will also by summarized and analyzed in the same manner as the BMD data for the total hip.

8.3.4. Interim Analysis

No interim analysis is planned for this study.

8.3.5. Key Elements of Analysis Plan

8.3.5.1. Efficacy Analyses

No efficacy analyses are planned for this study

8.3.5.2. Safety Analyses

8.3.5.2.1. Extent of Exposure

The extent of exposure to study drug will be summarized by treatment group.

8.3.5.2.2. Adverse Events (AEs)

AEs will be coded using the standard GSK dictionary, Medical Dictionary for Regulatory Activities (MedDRA), and grouped by body system. AEs occurring pre-treatment, during active treatment and post-treatment will be summarized separately. The number and percentage of subjects experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be presented for each treatment group.

Separate summaries will be provided for all AEs, drug related AEs, SAEs, and for AEs leading to withdrawal.

8.3.5.2.3. Deaths and SAEs

All SAEs will be listed by treatment group. Deaths and SAEs will be documented in case narrative format.

8.3.5.2.4. Fractures

The number and percent of patients experiencing a bone fracture during the study will be summarized.

8.3.5.2.5. COPD Exacerbations and Pneumonias

The number of moderate or severe COPD exacerbations and the percent of patients experiencing moderate or severe COPD exacerbations will be summarized.

8.3.5.3. Pharmacogenetic Analyses

See Appendix 2: Pharmacogenetic Research for details about the Pharmacogenetics Analysis Plan.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

No study related procedures may be performed until the informed consent form document has been signed by the subject. A pre-screening visit may be required in order to administer the informed consent before any changes are made to the subject's current medication regimen. The informed consent may be given at Screening (Visit 1) if the subject does not take or has not taken any protocol excluded medications.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., PGx assessments described in Appendix 2, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the

conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

9.5. Study and Site Closure

Upon completion or termination of the study, the GSK monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

9.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last subject's last visit (LSLV) [this applies to each data analysis phase for studies with multiple phases, e.g., primary analysis, follow up analysis etc]. In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

9.8. Independent Data Monitoring Committee (IDMC)

There is no IDMC in this study.

10. REFERENCES

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11. APPENDICES

11.1. Appendix 1: Laboratory Assessments

Refer to the Time and Events Table 3 for information regarding the timing of laboratory tests.

CHEMISTRY	HEMATOLOGY	OTHER
Albumin	Hemoglobin	Hepatitis B surface antigen[1]
Alkaline phosphatase	Hematocrit	Hepatitis C virus antibody[1]
Alanine amino-transferase (ALAT or SGPT)	Platelet count	Urine pregnancy test (in clinic/home test)[2]
Aspartate amino-transferase (ASAT or SGOT)	WBC count	Fungal culture of oral mucosa (if visual evidence of candidiasis)
Bilirubin, direct	Neutrophils, absolute	hCG qualitative (serum pregnancy)[2]
Bilirubin, indirect	Neutrophils, segs (%)	
Bilirubin, total	Neutrophils, bands (%)	
Calcium	Basophils (%)	
Chloride	Eosinophils (%)	
CO_2 content/Bicarbonate	Eosinophils , absolute	
Creatinine	Lymphocytes (%)	
Creatine phosphokinase (CPK), total	Monocytes (%)	
Gamma glutamyl transferase (GGT)		
Glucose		
Phosphorus		
Potassium		
Protein, total serum		
Sodium		
Urea nitrogen (BUN)		
Uric Acid		

1. Assessed at Visit 1 (Screening) only, result is not exclusionary
2. Only females of child-bearing potential; refer to Time and Events Table for specific visit information

11.2. Appendix 2: Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	HLA-B* 5701	Carriage of the HLA-B*5701 variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective HLA-B*5701 screening and exclusion of HLA-B*5701 positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective HLA-B*5701 screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. HLA-B*5701 screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia Chung, 2010; Ferrell, 2008	HLA-B*1502	Independent studies indicated that patients carrying HLA-B*1502 are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis and that this marker is prevalent in some populations, particularly with Asian ancestry. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	UGT1A1*28	Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular UGT1A1 gene variation might be too high for another patient without this variation, raising the risk of certain side-effects, that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the UGT1A1*28 variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to FF/VI Inhalation Powder.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to FF/VI Inhalation Powder. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with FF/VI Inhalation Powder, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Relationship between genetic variants and the pharmacokinetics and/or pharmacodynamics of investigational product
- Relationship between genetic variants and safety and/or tolerability of investigational product
- Relationship between genetic variants and efficacy of investigational product

Study Population

Any subject who is enrolled in the clinical study, can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

Saliva samples can be taken for Deoxyribonucleic acid (DNA) extraction and used in PGx assessments.

No additional whole blood samples will be necessary for the PGx analysis. Saliva (2mL) is collected into the DNA self-collection kit. A single sample will be taken but can be duplicated if the first sample is unusable. It is recommended that the saliva sample be collected at Visit 2.

- The PGx sample is labelled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The saliva sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the saliva sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or a set of studies) of FF/VI Inhalation Powder has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to FF/VI Inhalation Powder.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research and has had a sample taken for PGx research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options:

- Retain the sample for PGx research
- Destroy the PGx sample

If a subject withdraws consent for PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Pharmacogenetics Analyses

Pharmacogenetics Analyses

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to FF/VI Inhalation Powder. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. A detailed description of the analysis

to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any saliva being taken for PGx research.

Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarize the PGx research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

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11.3. Appendix 3: Country Specific Requirements

11.4. Appendix 4: Liver Chemistry Stopping and Followup Criteria