Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk

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on behalf of the SUMMIT Investigators

Online supplement containing:

Protocol with Amendments

Reporting and Analysis Plan

List of Participating Centers and Investigators

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number HZC113782

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 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 Address:	
Investigator Phone Number:	

Investigator Signature	Date

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LIST OF ABBREVIATIONS

AE	Adverse Event
AM	Morning
BP	Blood Pressure
BMI	Body Mass Index
CAT	COPD Assessment Test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
ATS	American Thoracic Society
eCRF	Electronic Case Report Form
EQ-5D	EuroQol 5D
FCS	Fluticasone/Salmeterol Combination Product
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in One Second
FF	Fluticasone furoate
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
IB	Investigators Brochure
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent to Treat
IUD	Intrauterine Device
IVRS	Interactive Voice Response System
LABA	Long Acting Beta Agonist
LFQ	Lung Function Questionnaire
LTOT	Long Term Oxygen Therapy
MSDS	Material Safety Data Sheet
mcg	Microgram
MDI	Metered Dose Inhaler
MIU	Million International Units
mL	Milliliter
mmHg	Millimeter of Mercury
MMRC	Modified Medical Research Council Qusetionnaire
NDA	New Drug Application
NDPI	Novel Dry Powder Inhaler
PEF	Peak Expiratory Flow
PFT	Pulmonary Function Test
PGx	Pharmacogenetics
PWV	Pulse Wave Velocity
QD	Once Daily

QoL	Quality of Life
RAP	Reporting Analysis Plan
SAE	Serious Adverse Event
SDV	Source Document Verification
SGRQ-C	St. George's Respiratory Questionnaire – COPD Questionnaire
SPM	Study Procedures Manual
VI	Vilanterol

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PROTOCOL SUMMARY

Rationale

Chronic obstructive pulmonary disease (COPD) is increasingly being recognized as having significant systemic manifestations that are associated with increased morbidity and mortality [Agusti, 2005]. The extrapulmonary manifestations that have been noted include, but are not limited to skeletal muscle dysfunction [Agusti, 2002], nutritional depletion [Schols, 1993], osteoporosis/osteopenia [Bolton, 2004] and cardiovascular co-morbidities. Risk factors leading to these extrapulmonary co-morbidities are multifactorial; however, multiple studies have demonstrated that these conditions are often associated with elevated inflammatory markers in the systemic circulation [Eid, 2001; Ginaldi, 2005].

In particular, several prospective studies have reported an association between impaired pulmonary function and cardiovascular morbidity and mortality [Tockman, 1995; Weiss, 1995; Hole, 1996] even after adjusting for accepted cardiovascular risk factors. In fact, epidemiological data suggests that patients with COPD are at a greater risk for cardiovascular disease compared with age and gender-matched controls without COPD [Curkendall, 2006]. Systemic inflammation has been proposed as having a potential role in explaining the association between COPD and increased cardiovascular disease risk [Sin, 2003]. Furthermore, more patients with mild-moderate COPD die from lung cancer and cardiovascular diseases such as coronary artery disease and stroke than from the respiratory effects of COPD [Anthonisen, 2005; Mannino, 2006; Calverley, 2007]. The mechanism(s) underlying this association is/are currently unknown despite the known role of cigarette smoking in the pathogenesis of both cardiovascular and chronic obstructive pulmonary diseases. Importantly, inflammation in the small airways has been established as the initial event in the pathogenesis of COPD [Hogg, 1968]; of which the magnitude is related to the degree of airflow obstruction [Hogg, 2004], and recent studies suggest that systemic inflammation in COPD may promote atherosclerosis [Sevenoaks, 2006].

Atherosclerosis leads to structural changes (e.g. elastin fragmentation and degeneration, increased collagen) in the wall of the aorta and medium-sized arteries and functional changes (resulting from elevated pressures), resulting in decreased elasticity and increased stiffness [Avolio, 1983; Safar, 1999; Lakatta, 2003]. This arterial stiffness can be assessed non-invasively by measuring the pulse wave velocity. In particular, aortic stiffness has been shown to be an independent predictor of all-cause and cardiovascular morbidity and mortality in hypertensive patients [Laurent, 2001; Boutouyrie, 2002; Laurent, 2003], as well as a predictor of cardiovascular events in well-functioning septuagenarians [Sutton-Tyrrell, 2005], apparently healthy elderly subjects [Mattace Raso, 2006] and a general at-large Danish population aged 40-70 years [Hansen, 2006] .

To what extent these types of data may apply to patients with COPD is of increasing interest. Zureik and colleagues demonstrated that carotid-femoral PWV was significantly and negatively associated with the spirometric parameter forced expired volume in second (FEV_1); for each 2.5 m/s increase in PWV, FEV_1 decreased by 195.2 ±50.1 ml

[Zureik, 2001]. Moreover, Sabit and coworkers compared PWV in COPD patients with healthy smokers and ex-smokers who were free of cardiovascular disease [Sabit, 2007]. PWV was greater in patients, and as in the study by Zureik, was inversely related to FEV_1. In addition, by multiple regression analysis, the circulating cytokine interleukin-6 (IL-6) was a strong predictor of PWV in this study. Increased PWV and elevated serum C-reactive protein (CRP) have also been demonstrated in COPD patients compared with controls matched for age and smoking history [Mills, 2008]. These latter findings may be important as the acute phase reactant CRP is related to and is a predictor of cardiovascular risk [Ridker, 2004] and IL-6 is a regulator of CRP production and secretion [Li, 1996; Zhang, 1996]. Finally, in a cross-sectional study McAllister et al demonstrated that emphysema severity, as assessed by quantitative high-resolution computerized tomography, is independently associated with arterial stiffness [McAllister, 2007]. These observations raise the potential of a possible link between the pulmonary and systemic inflammation observed in COPD, with progression of atherosclerosis and the increased cardiovascular morbidity and mortality that has been observed.

Despite this potential link between the pathogenetic mechanisms involved in COPD and atherosclerotic cardiovascular disease, there are no currently approved therapies for COPD patients that have clearly shown an additional beneficial effect in such patients with particular cardiovascular comorbidities. The TOwards a Revolution in COPD Health (TORCH) study assessed the impact of the inhaled corticosteroid fluticasone propionate (FP) in combination with the long-acting beta agonist, salmeterol (SAL), in reducing all-cause mortality [Calverley, 2007]. TORCH demonstrated a 17.5% reduction on all-cause mortality with salmeterol-fluticasone propionate combination (SFC) compared with placebo (HR=0.825, 95% CI (0.681, 1.002), p=0.052) in the entire COPD population with disease severity from moderate to very severe. A post hoc analysis of the data restricted to those subjects with an FEV1 ≥50% predicted with an apparent history of cardiovascular co-morbidities (defined as use at baseline of β-blockers, angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), HMG CoA reductase inhibitors (i.e. statins) or a prior MI recorded at baseline) demonstrated a 49% reduction in the risk of dying within 96 weeks for the comparison of SFC with placebo. These *post hoc* data suggest the possibility of an ICS/LABA combination product to be of substantial benefit in COPD subjects with less severe airflow obstruction yet with increased cardiovascular risk.

The mechanism by which SFC appears to be associated with a greater reduction in mortality in these less severe COPD subjects with concomitant cardiovascular comorbidities is speculative at present, but could potentially in part be related to a lessening of the degree of inflammation in the systemic circulation [Sin, 2004], potential plaque stabilization and/or amelioration of arterial stiffness.

ICS/LABA combinations that are currently available require twice daily administration. A once daily ICS/LABA combination has the potential to improve patient compliance and as a result, overall disease management

The purpose of this study is to prospectively evaluate the effect of the once daily ICS/LABA combination Fluticasone Furoate (FF)/Vilanterol (VI) inhalation powder on survival in subjects with moderate COPD (≥50 and ≤70 % predicted FEV_1) and a history of or at increased risk for cardiovascular disease.

Objective(s)

Primary

The primary objective of this study is to prospectively evaluate the effect of Fluticasone Furoate (FF)/Vilanterol (VI) inhalation powder 100/25mcg QD compared with placebo on survival in subjects with moderate COPD (≥50 and ≤70 % predicted FEV_1) and a history of, or at increased risk for cardiovascular disease.

Secondary

Secondary objectives are:

- To evaluate the effect of FF/VI compared with placebo on the rate of decline in FEV_1
- To evaluate the effect of FF/VI compared with placebo on a cardiovascular composite endpoint comprised of on-treatment CV death, myocardial infarction, stroke, unstable angina and TIA

Other objectives are:

- To evaluate the following treatment comparisons on all primary, secondary, other and exploratory endpoints:

  FF/VI compared with FF

  FF/VI compared with VI

  FF compared with placebo

  VI compared with placebo
- To evaluate the effect of FF/VI compared with placebo on moderate/severe COPD exacerbations
- To evaluate the effect of FF/VI compared with placebo on COPD related mortality
- To evaluate the effect of FF/VI compared with placebo on arterial stiffness in a subset of subjects
- To evaluate the effect of FF/VI compared with placebo on health-related quality of life measured with the SGRQ-C in a subset of subjects
- To evaluate quality-adjusted life years (QALYs) by treatment group using health status data collected from EuroQol Questionnaire (EQ-5D) in a subset of subjects

- To evaluate the impact of FF/VI compared with placebo on healthcare resource utilisation (measured by number of days hospitalized for COPD)
- To evaluate the impact of FF/VI compared with placebo on the number of cardiovascular procedures (ie angioplasty or revascularization)
- To evaluate the effect of FF/VI compared with placebo on change from baseline in FEV_1
- To evaluate the effect of FF/VI compared with placebo on change from baseline in FVC

Exploratory objectives are:

- To evaluate the effect of FF/VI compared with placebo on COPD health status in a subset of subjects using the COPD Assessment Tool (CAT)
- To examine the molecular profiles of blood samples to identify factors that may influence biological and clinical responses to FF/VI compared with placebo and/or associated with the development or progression of COPD or medically related conditions in a subset of subjects
- To examine the predictive ability of a comparative index to predict mortality

Study Design

This is a randomized, double-blind, parallel-group, multi-center, placebo-controlled study to evaluate the long term efficacy and safety of FF/VI Inhalation powder 100/25mcg QD, FF Inhalation powder 100mcg QD and VI Inhalation powder 25mcg QD when administered via the Novel Dry Powder Inhaler. Once daily dosing will occur in the morning (with the exception of the first treatment visit).

The target enrolment is approximately 16,000 randomized subjects at approximately 1600 study centers globally. Based on current assumptions of the event rate, the total duration of subject participation will be approximately between 15 and 44 months, consisting of a 4-10 day run-in period, variable treatment period and 1-week follow-up period.

Subjects will be randomized to treatment after a 4-10 day run-in period. Prior to the Run-in period, subjects will discontinue use of COPD medications as listed in Section 4.3.

Study Endpoints/Assessments

Efficacy

Primary Efficacy Endpoint

- Time to death from any cause

Secondary Efficacy Endpoints

- Rate of decline in FEV_1

- Time to CV event

Other Efficacy Endpoints

- Annual rate of and time to moderate/severe COPD exacerbations
- COPD related death (based on CEC adjudication)
- QoL using the St George's Respiratory Questionnaire-COPD.
- Health status using the EuroQol Questionnaire (EQ-5D)
- Health Care Resource Utilization
- PWV
- Cardiovascular procedures
- Change from baseline in FEV_1
- Change from baseline in FVC

Exploratory Endpoints

- Health status using the CAT
- Biomarkers
- Clinical laboratory tests

Safety

- Incidence of adverse events
- Oropharyngeal examinations

1. INTRODUCTION

1.1. Background

Chronic obstructive pulmonary disease (COPD) is increasingly being recognized as having significant systemic manifestations that are associated with increased morbidity and mortality [Agusti, 2005]. The extrapulmonary manifestations that have been noted include, but are not limited to skeletal muscle dysfunction [Agusti, 2002] nutritional depletion [Schols, 1993], osteoporosis/osteopenia [Bolton, 2004],and cardiovascular co-morbidities. Risk factors leading to these extrapulmonary co-morbidities are multifactorial; however, multiple studies have demonstrated that these conditions are associated with elevated inflammatory markers in the systemic circulation [Eid, 2001; Ginaldi, 2005].

Moreover, several prospective studies have reported an association between impaired pulmonary function and cardiovascular morbidity and mortality [Tockman, 1995; Weiss, 1995; Hole, 1996] even after adjusting for accepted cardiovascular risk factors. In fact, epidemiological data suggests that patients with COPD are at a greater risk for cardiovascular disease compared with age and gender-matched controls without COPD [Curkendall, 2006]. Systemic inflammation has been proposed as having a potential role in explaining the association between COPD and increased cardiovascular disease risk [Sin, 2003]. Furthermore, more patients with mild-moderate COPD die from lung cancer and cardiovascular diseases such as coronary artery disease and stroke than from the respiratory effects of COPD [Anthonisen, 2005; Mannino, 2006; Calverley, 2007]. The mechanism(s) underlying this association is/are currently unknown despite the known role of cigarette smoking in the pathogenesis of both cardiovascular and chronic obstructive pulmonary diseases. Importantly, inflammation in the small airways has been established as the initial event in the pathogenesis of COPD [Hogg, 1968] of which the magnitude is related to the degree of airflow obstruction [Hogg, 2004], and recent studies suggest that systemic inflammation in COPD may promote atherosclerosis [Sevenoaks, 2006].

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1.2. Rationale

Despite this potential link between the pathogenetic mechanisms involved in COPD and atherosclerotic cardiovascular disease, there are no currently approved therapies for COPD patients that have clearly shown an additional beneficial effect in such patients with particular cardiovascular comorbidities. The TOwards a Revolution in COPD Health (TORCH) study assessed the impact of the inhaled corticosteroid fluticasone propionate (FP) in combination with the long-acting beta agonist, salmeterol (SAL), in reducing all-cause mortality [Calverley, 2007]. TORCH demonstrated a 17.5% reduction on all-cause mortality with salmeterol-fluticasone propionate combination (SFC) compared with placebo (HR=0.825, 95% CI (0.681, 1.002), p=0.052) in the entire COPD population with disease severity form moderate to very severe. A *post hoc* analysis of the data restricted to those subjects with an FEV_1 ≥50% predicted with an apparent history of cardiovascular co-morbidities (defined as use at baseline of β-blockers, angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), HMG CoA reductase inhibitors (i.e. statins) or a prior MI recorded at baseline) demonstrated a 49% reduction in the risk of dying within 96 weeks for the comparison of SFC with placebo. These *post hoc* data suggest the possibility of an ICS/LABA combination product to be of substantial benefit in COPD subjects with less severe airflow obstruction yet with increased cardiovascular risk.

The mechanism by which SFC appears to be associated with a greater reduction in mortality in these less severe COPD subjects with concomitant cardiovascular comorbidities is speculative at present, but could potentially in part be related to a lessening of the degree of inflammation in the systemic circulation [Sin, 2004], potential plaque stabilization and/or amelioration of arterial stiffness.

ICS/LABA combinations that are currently available require twice daily administration. A once daily ICS/LABA combination has the potential to improve patient compliance and as a result, overall disease management.

The purpose of this study is to prospectively evaluate the effect of the once daily ICS/LABA combination Fluticasone Furoate (FF)/Vilanterol (VI) on survival in subjects with moderate COPD (≥50 and ≤70 % predicted FEV_1) and a history of, or at increased risk for cardiovascular disease.

2. OBJECTIVE(S)

2.1. Primary Objective

The primary objective of this study is to prospectively evaluate the effect of Fluticasone Furoate (FF)/Vilanterol (VI) inhalation powder 100/25mcg QD compared with placebo on survival in subjects with moderate COPD (≥50 and ≤70 % predicted FEV_1) and a history of, or at increased risk for developing, cardiovascular disease.

2.2. Secondary Objectives

- To evaluate the effect of FF/VI compared with placebo on the rate of decline in FEV_1
- To evaluate the effect of FF/VI compared with placebo on a cardiovascular composite endpoint comprised of on-treatment CV death, myocardial infarction, stroke, unstable angina and TIA.

2.3. Other Objectives

- To evaluate the following treatment comparisons on all primary, secondary, other and exploratory endpoints:

  FF/VI compared with FF

  FF/VI compared with VI

  FF compared with placebo

  VI compared with placebo
- To evaluate the effect of FF/VI compared with placebo on moderate/severe COPD exacerbations
- To evaluate the effect of FF/VI compared with placebo on COPD-related mortality
- To evaluate the effect of FF/VI compared with placebo on arterial stiffness in a subset of subjects
- To evaluate the effect of FF/VI compared with placebo on health-related quality of life measured with the SGRQ-C in a subset of subjects
- To evaluate quality-adjusted life years (QALYs) by treatment group using health status data collected from EuroQol Questionnaire (EQ-5D) in a subset of subjects
- To evaluate the impact of FF/VI compared with placebo on healthcare resource utilisation (measured by number of days hospitalized for COPD)

- To evaluate the impact of FF/VI compared with placebo on the number of cardiovascular procedures (ie angioplasty or revascularization)
- To evaluate the effect of FF/VI compared with placebo on change from baseline in FEV_1
- To evaluate the effect of FF/VI compared with placebo on change from baseline in FVC

2.4. Exploratory Objectives

- To evaluate the effect of FF/VI compared with placebo on COPD health status in a subset of subjects using the COPD Assessment Tool (CAT) in a subset of subjects
- To examine the molecular profiles of blood samples to identify factors that may influence biological and clinical responses to FF/VI compared with placebo and/or associated with the development or progression of COPD or medically related conditions in a subset of subjects
- To investigate a composite index to predict mortality

3. INVESTIGATIONAL PLAN

3.1. Study Design

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 randomized, double-blind, parallel-group, multi-center study evaluating FF/VI 100/25mcg, each component individually, and placebo. The target enrolment is approximately 16,000 randomized subjects at approximately 1600 study centers globally. Based on current assumptions of the event rate, the total duration of subject participation will be approximately between 15 and 44 months, consisting of a 4-10 day run-in period, variable treatment period, and 1-week follow-up period.

Subjects will be randomized to treatment after a 4-10 day run-in period. Prior to run-in, subjects will discontinue use of previous COPD medications except for short-acting bronchodilators and theophyllines. Clinic visits will occur at screening, randomization, 4 weeks and then every 12 weeks until the study has reached the required number of events. A safety follow-up phone contact will occur 1 week after completing either randomized treatment or an early withdrawal of investigational product.

Following the run-in period, eligible subjects will be randomized (1:1:1:1) to one of the following double-blind treatment groups. All treatments will be delivered via the Novel Dry Powder Inhaler (NDPI) once daily in the AM during the treatment period (with the possible exception of the randomization visit):

- FF/VI 100mcg/25mcg QD
- FF 100mcg QD
- VI 25mcg QD
- placebo QD

Each NDPI will contain 30 doses of study medication. Subjects will be instructed to administer medication once daily in the morning for the duration of the treatment period. Each subject should be advised to adhere to this dosing regimen throughout the study. In addition, each subject will be instructed on the proper use of the NDPI. Subjects will self-administer their first dose of blinded study drug in the clinic at the end of Visit 2. There are no plans to provide the study drug for compassionate use following study completion.

3.2. Discussion of Design

The design of this study (i.e., randomized, double-blind, placebo-controlled, parallel-group) is well established to evaluate the efficacy and safety of an investigational drug.

A placebo arm is included in this study to allow for a quantitative assessment of FF/VI Inhalation Powder 100/25mcg and the individual components compared with an inactive control.

ICS Dose Selection

GSK is currently investigating FF/VI at three strengths: 50/25 mcg, 100/25mcg, and 200/25mcg. GSK believes that the lowest effective dose of FF will be 100mcg in patients with COPD. This was based on the dose-ranging studies in patients with asthma demonstrating substantial efficacy with FF 100mcg and near maximal efficacy with FF 200mcg. While FF 50mcg demonstrated some level of efficacy (less than that with the 100 and 200mcg doses), we believe this will be the less effective/no effect dose in COPD based on the fact that patients with COPD have greater airflow obstruction and are less responsive to the effects of inhaled corticosteroids. GSK intends to investigate only one dose of the combination product in the proposed study. To date, the safety profiles for all 3 doses of FF are similar and with no unexpected findings.

LABA Dose Selection

The B2C111045 study was a multi-centre, randomised, double-blind, placebo-controlled parallel group, dose-ranging study evaluating the dose response, efficacy and safety of five doses of GW642444M (3mcg, 6.25 mcg, 12.5 mcg, 25mcg and 50 mcg), administered once daily in the morning, over a 28day treatment period in 602 subjects with COPD. The primary endpoint was the mean change from baseline in clinic visit

trough (pre-bronchodilator and pre-dose) FEV_1 at the end of the 28-day treatment period. The trough FEV_1 was defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Day 28. All doses were well tolerated. However, as the differences between the 25 and 50mcg doses were not considered to be clinically relevant, the 25mcg is felt to be an optimal dose to assess in the combination for this study. VI has been well tolerated in clinical studies to date with typical beta-agonists effects observed at high doses. There was no observed association of any side-effects with VI at the proposed clinical dose of 25 mcg.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

Approximately 16,000 male and female outpatient subjects will be randomized. All randomized subjects are considered evaluable. Approximately 1,600 centers in multiple countries will participate in the study.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the investigational product that may impact subject eligibility is provided in the IB/IB supplement(s) and other pertinent documents.

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

1. **Type of subject:** outpatient.
2. **Informed consent**: Subjects must give their signed and dated written informed consent to participate.
3. **Gender**: Male or female. 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.
4. **Age**: ≥40 and ≤ 80 years of age at Screening (Visit 1).
5. **Tobacco use**: Subjects with a current or prior history of ≥10 pack-years of cigarette smoking at screening (Visit 1). Previous smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1.
6. **Airflow Obstruction**:
    - Subjects with a measured post-albuterol/salbutamol FEV1/FVC ratio of ≤0.70 at Screening (Visit 1).
    - Subjects with a measured post-albuterol/salbutamol FEV1 ≥50 and ≤70% of predicted normal values calculated using NHANES III reference equations [Hankinson, 1999; Hankinson, 2010] at Screening (Visit 1).

      Post-bronchodilator spirometry will be performed approximately 15 minutes after the subject has self-administered 4 inhalations (i.e., total 400mcg) of

albuterol/salbutamol via an MDI with a valved-holding chamber. The FEV_1/FVC ratio and FEV_1 percent predicted values will be calculated.

7. **Dyspnea:**

   Subjects must score 2 or higher on the modified Medical Research Council Dyspnea scale (Visit 1)

8. **Cardiovascular disease:**

   For patients >= 40 years of age: any one of the following:

   Established (i.e. by clinical signs or imaging studies) coronary artery disease (CAD)
   Established (i.e. by clinical signs or imaging studies) peripheral arterial disease (PAD)
   Previous stroke
   Previous MI
   Diabetes mellitus with target organ disease

   OR

   For patients >=60 years of age: any 2 of the following:

   Being treated for hypercholesterolemia
   Being treated for hypertension
   Being treated for diabetes mellitus
   Being treated for peripheral arterial disease

4.3. Exclusion Criteria

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

1. **Pregnancy**: Women who are pregnant or lactating.
2. **Asthma**: Subjects with a current diagnosis of asthma. (Subjects with a prior history of asthma are eligible if they also have a current diagnosis of COPD).
3. **α1-antitrypsin deficiency**: Subjects with known α-1 antitrypsin deficiency as the underlying cause of COPD.
4. **Other respiratory disorders**: Subjects with active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, pulmonary 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 or having had a lung transplant.
6. **A moderate/severe COPD exacerbation** that has not resolved at least 14 days prior to Visit 1 and at least 30 days following the last dose of oral corticosteroids (if applicable).
7. **Current severe heart failure** (New York Heart Association class IV). Subjects will also be excluded if they have a known ejection fraction of <30% or if they have an implantable cardioverter defibrillator (ICD).

8. **Other diseases/abnormalities:** Any life-threatening condition with life expectancy <3 years, other than vascular disease or COPD, that might prevent the subject from completing the study.
9. **End stage chronic renal disease:** Subjects will be excluded if on renal replacement therapy (hemodialysis or peritoneal).
10. **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.
11. **Drug/alcohol abuse:** Subjects with a known or suspected history of alcohol or drug abuse within the last 2 years.
12. **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.
13. **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 or the potential compliance to study procedures.
14. **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.
15. **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 or thereafter at any time during the study (unless otherwise specified)
Inhaled Long acting beta-agonists (LABA)	48 hours
ICS/LABA combination products	48 hours
Inhaled corticosteroids	48 hours
Tiotropium	1 week*
Systemic, Oral, parenteral, intra-articular corticosteroids	30 days (oral and systemic corticosteroids may be used to treat COPD exacerbations during the study)
Cytochrome P450 3A4 strong inhibitors including but not limited to antiretrovirals (protease inhibitors) (e.g.Indinavir, Nelfinavir, Ritonavir, Saquinavir); Imidazole and Triazole anti-fungals (e.g. Ketaconazole, Itraconazole); Clarithromycin, Telithromycin, and Nefazodone	6 weeks Grapefruit is allowed up to Visit 1, then limited to no more than one glass of grapefruit juice (250 mL/ 8 ounces) or one grapefruit per day
Any other investigational drug	30 days or 5 half lives whichever is longer.

* See Section 5.6.2 for information regarding Tiotropium use during the study

Note regarding appropriate patient selection:

Potential subjects should not be withdrawn from medications necessary for their disease management solely for the purpose of enrolling in this study. Patients who are currently controlled on short acting medications or who can adequately be managed with short-acting inhaled medications and oral therapies (including theophylline or roflumilast) based on physician opinion are the appropriate patients for this study.

4.4. Randomization Criteria

Any subject who experiences a moderate/severe COPD exacerbation (a COPD exacerbation requiring treatment with antibiotics and/or systemic corticosteroids or requiring hospitalization) or pneumonia during the run-in period must not be randomized.

4.5. Withdrawal Criteria

Once a subject is randomized to investigational product, the subject's vital status will be tracked for the duration of the study. Subjects may choose to discontinue use of investigational product at any time but full accountability at the end of the study is required for all subjects.

4.5.1. Withdrawal from Investigational Product

A subject may voluntarily discontinue investigational product at any time. The investigator may also, at his or her discretion, discontinue a subject from receiving investigational product at any time. Every effort should be made by the investigator to keep the subject in the study. Subjects who are withdrawn from investigational product will not be replaced.

The primary reason for subject withdrawal from investigational product will be recorded in the eCRF. Primary reasons for withdrawal will be categorized as:

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

COPD exacerbation will be a sub-reason for withdrawal under lack of efficacy. Specific regard should be given to distinguishing withdrawals due to an adverse event and lack of efficacy.

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

- **Liver Chemistry:** Meets any of the following Liver chemistry stopping criteria as defined in Section 6.3.1.

4.5.2. Screen Failures

A subject who has at least one study procedure performed in addition to signing a consent form, and is assigned a subject identifier but is NOT randomized is classified as a screen failure. The IVRS system used to track study enrolment will be notified and the following information on subjects who are not randomized must be collected in the eCRF:

- Date screened
- Subject identification number
- Demography (race, age, and gender)
- Reason subject failed Screening
- Any Serious Adverse Events (SAEs) related to study procedures or GlaxoSmithKline (GSK) concomitant medications that occurred after signing the informed consent. Any fatal event should also be recorded.

A subject who is classified as a screen failure cannot be re-screened.

4.5.3. Run-in failures

A subject who has had all screening procedures performed (in addition to signing a consent form), is assigned a subject identifier, and is dispensed rescue albuterol/salbutamol, but is NOT randomized is classified as a Run-in failure. The IVRS system will be notified and the following information on subjects who fail Run-in must be collected in the eCRF:

- Date screened
- Subject identification number
- Demography (race, age, and gender)
- Reason subject failed Run-in
- Any Serious Adverse Events (SAEs) related to study procedures or GlaxoSmithKline (GSK) concomitant medications that occurred after signing the informed consent. Any fatal event should also be recorded.

Subjects who experience a COPD exacerbation and/or pneumonia during the Run-in period will be excluded from participating in the study.

A subject who is classified as a Run-in failure cannot be re-screened.

5. STUDY TREATMENTS

5.1. Investigational Product and Reference Therapy

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).

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.

5.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomisation schedule. The randomisation schedule will be generated using the GSK validated randomization software RANDALL. A separate randomisation schedule will be produced for each country. For those countries participating in the Arterial Stiffness sub-study two schedules will be produced for each country, one for the sites participating, and one for the sites not participating. This is to help ensure balance of treatment groups within the sub-study.

Following the run-in period, eligible subjects will be randomized (1:1:1:1) to one of the following double-blind treatment groups with the NDPI once daily in the AM for the duration of the treatment period:

- FF/VI 100mcg/25mcg QD
- FF 100mcg QD
- VI 25mcg QD
- placebo QD

Assignment of subject number

At Visit 1, a unique Subject Number will be assigned to any subject who has at least one Visit 1 procedure performed, other than informed consent. The unique Subject Number will be used to identify individual subjects during the course of the study.

Assignment of treatment number

At Visit 2 (end of run-in/randomisation visit), subjects meeting the eligibility criteria will be assigned to study treatment following a telephone call to the IVRS, in accordance with the computer generated randomisation schedule. Once a randomisation number has been assigned to a subject, it cannot be reassigned to any other subject in the study.

During this call, the IVRS will confirm the Subject Number and provide two additional types of numbers:

- A treatment pack number will be provided that identifies the double-blind medication that should be dispensed to the subject from the investigator's inventory (container number).
- A randomisation number will be assigned from a randomisation schedule created by GlaxoSmithKline.
- For subsequent visits when study medication is to be dispensed, a telephone call must be made to the IVRS for the next treatment pack number(s) to be assigned from the investigator's inventory

5.3. Blinding

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.

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 GSK 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

Subject compliance with double-blind study medication will be assessed at Visits 3 through End of study/Early Withdrawal by reviewing the dose counter on the NDPI. Subjects who are not compliant (<80%) with study drug administration should be counselled on appropriate dosing of study drug.

5.6. Concomitant Medications and Non-Drug Therapies

5.6.1. Permitted Medications and Non-Drug Therapies

The following medications are permitted during the study:

- Study-supplied albuterol/salbutamol (MDI or nebules)
- Ipratropium/Combivent
- Theophyllines and roflumilast
- Oral corticosteroids and antibiotics for the short term treatment of COPD exacerbations
- Mucolytics

- Oxygen
- Antihistamines and nasal decongestants
- OTC cough suppressants
- Intranasal cromolyns or nedocromil
- Intranasal, ophthalmic and topical corticosteroids
- Antibiotics for short term treatment of acute non-respiratory tract infections and for the treatment of pneumonia and COPD exacerbations.
- Influenza and pneumonia vaccines
- Tricyclic antidepressants and Monamine oxidase inhibitors (MOAs). (Administer with caution as they may potentiate the effects of beta-agonists on the vascular system.)
- Diuretics. (Caution is advised in the coadminstration of beta-agonists with nonpotassium –sparing diuretics).
- Smoking cessation medications
- Cardioselective Beta-blockers and ophthalmic beta-blockers. (Administer with caution as they may block bronchodilatory effects of beta-agonists and produce severe bronchospasm.) Noncardioselective beta-blockers (eg carvedilol) may also be used if deemed appropriate by the PI.
- All medications for other disorders as long as the dose remains constant wherever possible.

5.6.2. Prohibited Medications and Non-Drug Therapies

Tiotropium use will not be permitted at baseline. However, if during the double-blind treatment phase a subject experiences a severe COPD exacerbation (i.e requiring hospitalization) and requires additional treatment or experiences multiple moderate exacerbations, Tiotropium may be added. GSK medical monitor should be contacted for any other situation where the PI believes addition of Tiotropium is required. The same criteria apply to use of any new LAMA, PDE IV inhibitor or anti-inflammatory approved for COPD during the course of the study.

Use of any inhaled corticosteroid (ICS) or long acting beta-agonist (LABA) while on double-blind treatment is not permitted.

5.7. Treatment after the End of the Study

At the end of treatment with Investigational Product, subjects will be prescribed appropriate COPD therapy if required. There are no plans to provide the study medication for compassionate use following study completion.

5.8. Treatment of Investigational Product Overdose

An overdose is defined as a dose greater than what is instructed (Section 5.2) that results in clinical signs and symptoms. In the event of an overdose of study medication, the investigator should use clinical judgment in treating the overdose and contact the study medical monitor. GlaxoSmithKline (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 labelling and/or IB for albuterol/salbutamol, and the IB or equivalent document provided by GSK for double blind study medications.

6. STUDY ASSESSMENTS AND PROCEDURES

The Time and Events Table is provided in Table 1. All study assessments should be conducted by the investigator or his/her qualified designee unless otherwise specified in the protocol or SPM. Please refer to the SPM for a suggested order of assessments.

Subjects will self-administer their first dose of double-blind study medication in the clinic at the end of Visit 2.

Table 1 Time and Events Table

Pre-Randomization Assessments:

Procedures	Screening	Baseline Visit[1]
Written Informed Consent	X	
Demography & Medical History	X	
COPD & Exacerbation History	X	
Inclusion/Exclusion Criteria	X	
Concomitant Medication Assessment	X	X
Smoking Status/history	X	X
Smoking Cessation Counselling		X
Randomization Criteria		X
Lung Function Questionnaire (LFQ)[4]	X[4]	
Vital signs	X	X
Physical Exam	X	
Oropharyngeal Exam		X
Blood Sample (10ml)[5]		X[5]
Spirometry –pre and post albuterol/salbutamol	X	
Spirometry - post albuterol/salbutamol		X
Modified Medical Research Council Questionnaire (MMRC)	X	
Subject Questionnaires[2]		X[2]
Adverse Events	X	X
SphygmoCor Assessments[3]		X[3]

Procedures	Screening	Baseline Visit[1]
Dispense Rescue Albuterol/Salbutamol	X	
Dispense diary card	X	X
Register Visit in IVRS	X	X
Pregnancy test	X	
Dispense IP		X

1. All Baseline assessments must be obtained prior to randomization
2. SGRQ-C, CAT and EQ-5D in a subset of ~4,000 subjects primarily in EU, Canada and Australia
3. In a subset of ~1400 subjects
4. Optional (for use as screening tool)
5. Subjects in US only , details in SPM

Post-Randomization Assessments:

Procedures					End of study treatment	Follow-up[3]
						Phone Contact
	Month 1	Month 3 (±14)[1] PLUS every 3 months	Month 6 (±14) PLUS every 6 months	Month 12 (±14) PLUS every 12 months		7±2 days after last dose of study drug
Concomitant Medication Assessment		X			X	X
Spirometry – post albuterol/salbutamol (FEV1 and FVC)		X			X	
Exacerbation Assessment		X			X	
Survival Assessment		X			X	
Subject Questionnaires[4]		X[4]	X[4]		X	
Adverse Event Assessment		X			X	X
Smoking Status		X			X	
Oropharyngeal exam		X			X	
Vital signs		X			X	
Blood Sample		X[5]				
Pregnancy Test			X		X	
SphygmoCor Assessments[2]				X[2]	X	
Dispense diary Card		X				
Dispense Investigational Product.	X	X				
Assess Investigational Product Compliance		X			X	
Collect Investigational Product	X	X			X	
Dispense Rescue	X	X				

Procedures					End of study treatment	Follow-up[3]
						Phone Contact
	Month 1	Month 3 (±14)[1] PLUS every 3 months	Month 6 (±14) PLUS every 6 months	Month 12 (±14) PLUS every 12 months		7±2 days after last dose of study drug
Albuterol/Salbutamol						
Collect/check Rescue Albuterol/Salbutamol	X	X			X	
Register Visit in IVRS		X			X	X

1. Visits will continue at the specified intervals until the end of the study which will be determined by reaching approximately 1000 deaths.
2. In a subset of ~1400 subjects- to be done annually, details in SPM
3. The Follow-up Visit is scheduled to occur 7 ± 2 days after the last dose of IP.
4. SGRQ-C, CAT and EQ-5D in a subset of ~4,000 subjects - these will be done during the first year at 3 months and 6 months and then every 6 months for the duration of the treatment period
5. Only at initial 3 month Visit – subjects in US only

6.1. Critical Baseline Assessments

No study related procedures may be performed until the informed consent form document has been reviewed with and signed by the subject. A pre-screening visit may be required in order to administer and discuss the informed consent before any changes are made to the subject's current medication regimen. Washout of any prohibited medication, which is done only if deemed appropriate by the Investigator in discussion with the subject, **MUST NOT OCCUR prior to the informed consent being discussed and signed**. The informed consent may be administered and discussed at the screening visit if the subject does not take or has not taken any protocol excluded medications. During the screening visit (Visit 1) or randomization visit (Visit 2), each subject will undergo the following assessments (refer to Table 1 for specific visit for each assessment)**:**

- Demographic history (including gender, ethnic origin, date of birth, height and weight)
- Medical history (including COPD, cardiovascular and smoking history)
- Exacerbation assessment (history of COPD exacerbations that required antibiotics and/or oral corticosteroids or hospitalization in the past 12 months)
- Inclusion/Exclusion criteria assessment (including LFQ if being used)
- MMRC
- Concomitant medication review
- Spirometry with reversibility testing
- Physical exam (including vital signs)

- Baseline questionnaires in a subset: SGRQ-C, CAT and EQ-5D
- Baseline PWV in a subset

6.2. Efficacy

6.2.1. Primary Efficacy Endpoint

- Time to death from any cause

6.2.2. Secondary Efficacy Endpoints

- Rate of decline in FEV_1
- Time to CV event

6.2.3. Other Efficacy Endpoints

- Annual rate of and time to moderate/severe COPD exacerbations
- COPD-related death (based on CEC adjudication)
- QoL using the St George's Respiratory Questionnaire-COPD.
- Health status using the EuroQol Questionnaire (EQ-5D)
- Health Care Resource Utilization
- PWV
- Cardiovascular procedures
- Change from baseline in FEV_1
- Change from baseline in FVC

6.2.4. Exploratory Endpoints

- Health status using the CAT
- Biomarkers

6.2.5. Survival Status

The primary endpoint is all cause mortality, therefore the survival status of each subject will be recorded at every Visit.

In the case of any subject who prematurely withdraws from Investigational Product, survival status will be captured at 3-monthly intervals by means of phone calls or other forms of contact.

All deaths occurring after randomization until the end of the study should be reported as SAEs within 24 hours (Section 6.3.8) of PI becoming aware of event.

Accurate assignment of cause of death is essential and will be done as follows:

The investigator will assign a cause of death based on contact with the attending physician (where possible), details given on the death certificate, autopsy findings (if any) and any other available clinical evidence. The investigator will enter the results into the eCRF.

Categorization of cause of death will also been done centrally by a Clinical Endpoint Committee (CEC) who will review the eCRF data and additional information available (eg details given on the death certificate, autopsy findings, and any other available clinical evidence). The categorization of cause of death assigned by the CEC will be the primary basis for all analyses for cause of death or specific cause of death.

6.2.6. Spirometry and Reversibility Testing

6.2.6.1. Spirometry

A secondary endpoint is rate of decline in FEV1. In order to assess this, spirometry will be performed at every clinic visit and will be performed using equipment that meets or exceeds the minimum performance recommendations of the ATS [Sin, 2003]. All sites will use their own equipment. At least 3 valid spirometry efforts should be attempted (with no more than 8) using the ATS guidelines [Sin, 2003]. Spirometry will be performed at screening (Visit 1), randomization (Visit 2), and at each 3-monthly treatment visit. A post-albuterol/salbutamol FEV_1 ≥50 and ≤70% of predicted normal and an FEV_1/FVC ratio of ≤0.70 are required at Visit 1 (Screening).Values will be calculated using NHANES III reference equations [Hankinson, 1999; Hankinson, 2010].

The Visit 1 spirometry must be performed:

- Between 6:00AM and 10:00AM
- After withholding morning dose of scheduled COPD medications as indicated in the exclusion criteria
- After inhalation of 4 puffs of albuterol via a metered dose inhaler with a spacer/holding chamber

On or after Visit 2 (randomization), FEV1 can be done at any time of day but should be consistent (± 2 hour window based on time from first post baseline visit) between visits for each subject and no later than 2pm

Details regarding the spirometric procedures are provided in the SPM.

6.2.6.2. Reversibility

Subjects' reversibility will be assessed at Visit 1 (Screening). To determine reversibility, the subject will self-administer 4 inhalations of albuterol/salbutamol via metered dose inhaler (MDI) with a spacer/holding chamber following pre-dose spirometry. Triplicate spirometry efforts will be performed after approximately 10-15 minutes, and the highest FEV_1 from three valid forced expiratory curves will be used to determine reversibility.

- Details regarding the spirometric procedures are provided in the SPM.

6.2.7. Cardiovascular Composite Endpoint

A secondary endpoint is a composite of specific cardiovascular events which includes on treatment CV death, unstable angina, myocardial infarction, stroke and transient ischemic events. Unstable angina is included in the composite as it is an entity under acute coronary syndromes, can be objectively defined, and is a harbinger of acute myocardial infarctions. Similarly, transient ischemic attacks will be included in this composite, only if the resultant neurological deficit is verified on examination by a health-care provider, as this event can also be viewed as a prelude to a stroke.

- On treatment cardiovascular mortality which has been agreed by the clinical endpoint committee (CEC).

Cardiovascular event due to one of the following which has been agreed by the CEC:

- A stroke or transient ischemic event (objectively confirmed by a health-care professional) defined as a focal neurological deficit of presumed vascular origin (including retinal infarction).
- A myocardial infarction (based on the Universal definition [Thygesen, 2007])
- Diagnosis of unstable angina defined by:

Ischemic chest discomfort that occurs at rest with at least 1 episode lasting ≥10 minutes and is accompanied by new or presumably new ST segment deviation (transient (<20 minutes) elevation ≥ 0.1mV or dynamic horizontal/ downsloping depression ≥ 0.05mV)) in at least 2 contiguous leads without diagnostic biochemical changes in cardiac enzymes (serum troponin I or T or creatine kinase-MB).

As with all deaths, data on events which make up the CV composite endpoint will be collected for the duration of the study (including both on and off Investigational Product).

6.2.8. COPD exacerbations and Pneumonia

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 their study investigator and/or research coordinator immediately, and report to the study clinic as required

- If the subject is unable to contact their 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 PI as having:

- A mild/moderate/severe 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
- 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. Confirmed diagnoses of pneumonia must be recorded as adverse events in the eCRF.

Definitions for COPD exacerbations and pneumonia are given above. If, based on these criteria, a subject's symptoms do not fulfill the diagnosis of an exacerbation and/or pneumonia, then the investigator should use their 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. Refer to Section 6.3.2.1 and Section 6.3.2.2 for definitions of AE and SAE, respectively.

The dates of onset and resolution of each 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.

6.3. Safety

- Incidence of adverse events
- Vital sign measurements (per guidelines in SPM)

6.3.1. Liver chemistry stopping and follow up criteria

With the exception of US sites which are participating in the biomarker and/or genetics assessments, there are no regular laboratory tests required by this protocol. If, however, while a subject is receiving Investigational Product, lab tests are conducted, any abnormal liver chemistry findings must treated as outlined below:

Phase III-IV liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event etiology.

Phase III-IV liver chemistry stopping criteria 1-5 are defined below:

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, study drug should be discontinued 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 the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, 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
- 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, study drug should be discontinued 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** (unless further safety follow up is required) after completion of the liver chemistry monitoring as described below.
- Do not re-challenge with 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 (if subject resides outside the US or Canada, or has travelled outside US or Canada in past 3 months);

- 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.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

6.3.2. 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.

6.3.2.1. 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 investigational product 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 investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE).

“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

6.3.2.2. 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.

6.3.3. 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.

6.3.4. Disease-Related Events and/or Disease-Related Outcomes Not Subject to Expedited Reporting

The following events are considered secondary efficacy endpoints for this study and will be reported as AEs or SAEs (based on criteria in Section 6.3.2) but will not be subject to expedited reporting regardless of the "expectedness" or "relatedness" of the event:

- MI
- Stroke
- Unstable angina
- TIA

Additionally, any laboratory or ECG abnormalities associated with the diagnosis of individual components of these efficacy endpoints will not be subject to expedited reporting.

The following events are expected in this population and will be reported as AEs or SAEs but will not be subject to expedited reporting regardless of the "expectedness" or "relatedness" of the event:

- COPD exacerbation
- Pneumonia

Additionally, any laboratory or Chest X-ray abnormalities associated with the diagnosis of these events will not be subject to expedited reporting.

6.3.5. 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 investigational product, must be promptly reported to GSK.

6.3.6. Medical Devices

Medical devices are being provided by GSK for use in this study. GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

Medical Device – this is any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
- investigation, replacement or modification of the anatomy or of a physiological process;
- control of conception

and which does not achieve its principle action in or on the human body by pharmacological, immunological or metabolic means, but may be assisted in its function by such means.

Note: if these means fulfill the main purpose of the product, it is a Medicinal Product. The term medical device includes *in vitro* diagnostic (IVD) devices.

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study.

Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that

- An incident associated with a device happened and
- The incident was such that, if it occurred again, it might lead to death or serious deterioration ion health

A serious deterioration in state of health can include:

- A life-threatening illness (a)
- Permanent impairment of body function or permanent damage to a body structure (b)

- A condition necessitating medical or surgical intervention to prevent (a) or (b)
- Any indirect harm as a consequence of an incorrect diagnostic or IVD test results when used within the manufacturer's instructions for use
- Fetal distress, fetal death or any congenital abnormality or birth defects

Incidents include, for example:

- inhalation of an object that has accidentally entered a spacer device and resulted in tracheal obstruction.

Incidents do not include for example:

- medical occurrences associated with metered-dose inhalers that do not fulfill the definition of a medical device (such events will be reported as medicinal product AEs)
- non-serious medical occurrences which have no further safety implications for the subject or the device

Malfunction – A failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer's instructions.

Remedial Action – Any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of a reportable incident. [This includes any amendment to the design to prevent recurrence.]

6.3.7. 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 Investigational Product 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., investigational product, 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. Any fatal SAE occurring between screeing and randomization should be reported. All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.3.8.

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

SAEs, pregnancies, medical device incidents, 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	24 hours	Updated "SAE" data collection tool
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Device Incident	24 hours	"Medical Device Incident Report Form"	24 hours	Updated "Medical Device Incident Report Form"
ALT≥3xULN and Bilirubin≥2xULN (>35% direct) (or ALT≥3xULN and INR>1.5, if INR measured)***	24 hours*	SAE data collection tool. **Liver Event CRF and liver imaging and/or biopsy CRFs if applicable	24 hours	Updated SAE data collection tool. **Updated Liver Event CRF
ALT≥8xULN; ALT≥5xULN with hepatitis or rash or ≥3xULN and <5xULN that persists ≥4 weeks	24 hours*	**Liver event CRF	24 hours	**Updated Liver Event CRF
ALT≥5xULN plus bilirubin <2xULN	24 hours*	**Liver event CRF does not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks	24 hours	
ALT≥5xULN and bilirubin <2xULN that persists ≥2 weeks	24 hours*	**Liver event CRF	24 hours	Updated liver event CRF
ALT≥3xULN and <5x ULN and bilirubin <2xULN	24 hours*	**Liver event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks		

*GSK to be notified at onset of liver chemistry elevations to discuss subject safety.

** Liver event documents should be completed as soon as possible.

*** INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants.

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.

Procedures for documenting, transmitting and follow-up of medical device incidents along with the regulatory reporting requirements for medical devices are provided in the SPM.

6.3.8.1. 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.

6.3.9. Other Safety Outcomes

6.3.9.1. Vital Signs

Vital signs will be performed at all study visits. At Screening (Visit1) vital signs must be taken prior to spirometry. At randomization (Visit 2) and on days of Treatment Visits, vital signs must be performed prior to spirometry. Blood pressure (systolic and diastolic) and pulse rate will be measured in the sitting position after approximately 5 minutes rest. A single set of values will be collected and recorded in the source documentation and eCRF.

6.4. Health Outcomes

St George's Respiratory Questionnaire-Chronic Obstructive Pulmonary Disorder Questionnaire (SGRQ-C)

The SGRQ-C will be completed by a subset of subjects at randomization, at Visit 3 (12 weeks) then every 24 weeks thereafter (see Time and Events schedule) and at the Early Withdraw Visit.

The SGRQ-C is a newly developed version of the well-established SGRQ instrument. This version was developed to reduce the patient burden, reduce missing data and improve the psychometric properties, whilst retaining the established properties of the

instrument. In contrast to the original, it is a COPD specific instrument and has been reduced from the original 50 to 40 items.

EuroQol Questionnaire (EQ-5D)

The EQ-5D questionnaire will be completed by a subset of subjects at randomization, at Visit 3 (12 weeks), then every 24 weeks thereafter (see Time and Events schedule) and at the Early Withdraw Visit.

The EQ-5D is a standardised instrument for use as a measure of health outcome. It is designed for self-completion and is cognitively simple, taking only a few minutes to complete. The EQ-5D is a two-part self-assessment questionnaire. The first part consists of five items covering five dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a three-point Likert scale (1-no problems, 2-moderate problems and 3-extreme problems). Respondents are asked to choose one level that reflects their "own health state today" for each of the five dimensions. Respondents can be then classified into one of 243 distinct health states. The second part is a 20-cm visual analogue scale (EQ-VAS) that has endpoints labelled "best imaginable health state" and "worst imaginable health state "anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health by drawing a line from an anchor box to that point on the EQ-VAS which best represents their own health on that day. EQ-5D health states can be converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. The formula is based on the valuation of EQ-5D health states from general population samples.

COPD Assessment Test (CAT)

The CAT will be completed by a subset of subjects at randomization, Visit 3 (12 weeks), then every 24 weeks thereafter (see Time and Events schedule) and at the Early Withdraw Visit.

The COPD Assessment Test (www.CATestonline.org) is a validated, short and simple patient completed questionnaire which has been developed for use in routine clinical practice to measure the health status of patients with COPD. The CAT is an 8-item questionnaire suitable for completion by all patients diagnosed with COPD. When completing the questionnaire, subjects rate their experience on a 6-point scale, ranging from 0 (maximum impairment) to 5 (no impairment) with a scoring range of 0-40.

Healthcare resource utilisation

Information on the healthcare resources related to hospitalizations for COPD exacerbations will be collected during the study.

6.5. Biomarker(s)

Serum and plasma samples will be collected at the US sites at V2 (pre-dose at randomization visit) and V3 (pre-dose at the 3 month visit). These will be used to

analyze known inflammatory markers (e.g., hsCRP and fibrinogen) and also for measuring a CBC and Chem 7 panel for use in predictive modelling.

Any subject in the US who has given informed consent to participate in the clinical study and has met all of the entry criteria may take part in the biomarker portion of the study. Subject participation in biomarker sample collection is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

6.6. Pharmacogenetics

Information regarding pharmacogenetic research is included in Appendix 1. 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 (i.e., approval of Appendix 1). 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.

Any subject in the US who has given informed consent to participate in the clinical study and has met all of the entry criteria may take part in genotyping. Subject participation in genotyping is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

7. DATA MANAGEMENT

For this study subject data will be entered into a pre-defined electronic case report forms (eCRFs), transmitted electronically to GSK and combined with 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., correcting/resolving 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. Subject initials will not be collected or transmitted to GSK according to GSK policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

The primary efficacy endpoint is time to death from any cause.

The primary analysis will test the following hypotheses:

- Null hypothesis: Hazard ratio for all cause mortality for FF/VI relative to placebo is equal to one. This is equivalent to a reduction in the risk of dying equal to zero, i.e. no difference in time to death between FF/VI and placebo.
- Alternative hypothesis: Hazard ratio for all cause mortality for FF/VI relative to placebo is not equal to one (i.e. two-sided test). This is equivalent to a reduction in the risk of dying not equal to zero, i.e. there is a difference in time to death between FF/VI and placebo.

The study is designed to show superiority of treatment with FF/VI relative to placebo (i.e. hazard ratio less than one, or equivalently, reduction in risk greater than zero) on top of a background of standard care.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

Every effort will be made to obtain mortality status for all subjects who withdraw from study medication. The analysis of the primary endpoint will be performed for the Intent-to-Treat Population, which will include all subjects who have been randomised to treatment, regardless of whether they have discontinued study medication.

This event driven study is designed to have 90% power to detect a 30% reduction in the risk of all-cause mortality (hazard ratio=0.70) on FF/VI compared with placebo at the two-sided 1% significance level. In order to detect this reduction, 478 events (on FF/VI and placebo combined) would be required (using Freedman's formula, [Machin, 1997]).

Note that the possibility of satisfying the stopping rule at the planned interim analysis (see Section 8.3.4) implies that the actual number of deaths in this study may be lower than this upper limit.

Subjects may stop taking study medication, but will continue to be followed up for mortality status. All subjects will be followed until the required total number of events has occurred. Subjects will therefore be followed for a variable length of time. It is assumed that enrolment will start off at 150 subjects per month, building to 600 per month by 6 months. Event Rates have been based on a post-hoc analysis of all-cause mortality in the TORCH study at 96 weeks in a population similar to that intended to be recruited to the present study and assume a placebo event rate of 6.00% by 24 months. A reduction in the hazard of 30% would result in a FF/VI event rate of 4.24% at 24 months. Based on the target of 478 events and under the above recruitment assumptions, 4000 subjects per arm will need to be randomised with a total expected duration of the trial of 44 months with subjects followed for between 14 and 44 months.

It should be noted that the [Schoenfeld, 1981] formula for determining the number of events gives a slightly smaller number of events required for 90% power (468). However to be conservative, the Freedman formula has been used, which results in 478 events needed.

The effects of the components (FF and VI) are expected to be lower than for FF/VI. The study is not powered for comparisons of the components to placebo or for the combination to components . The study will utilise an equal randomisation scheme and so the study will provide as precise an estimate of the magnitude of the mortality effect as is practically achievable for these comparisons.

If the true mortality rates for the components are intermediate between FF/VI and placebo, then it would be expected that by the time there are 478 deaths between the FF/VI and placebo arms there should be a roughly similar number on the component arms combined, which would give a total of 956 on 4 arms. Since this is an event driven study, it is crucial that the study continue long enough to reach 478 events between FF/VI and placebo combined. However, since the study is blinded and the total number of deaths on the 4 arms will be influenced by the component arms it seems prudent to be conservative. This must be balanced against continuing the study for longer than necessary. For these reasons a total number of events of 1000 (between 4 arms) will be used to trigger stopping of the study for the final analysis.

Therefore it is planned that approximately 4000 subjects will be randomised to each of the four treatment arms and the study will continue until a total of 1000 deaths have been reported.

As this is a multi-country trial, in order to ensure balance of treatment arms within each country, separate randomisation schedules will be produced for each country (using permuted blocks).

Given the large number of subjects per treatment, other baseline factors should be fairly balanced, so the randomisation will not be stratified for any other factors. However important prognostic factors will be accounted for in statistical models.

8.2.2. Sample Size Sensitivity

The Table 2 demonstrates the total duration of the study, assuming 4,000 subjects per arm, and various placebo event rates, given that the study does not reach a stopping rule at the interim analysis.

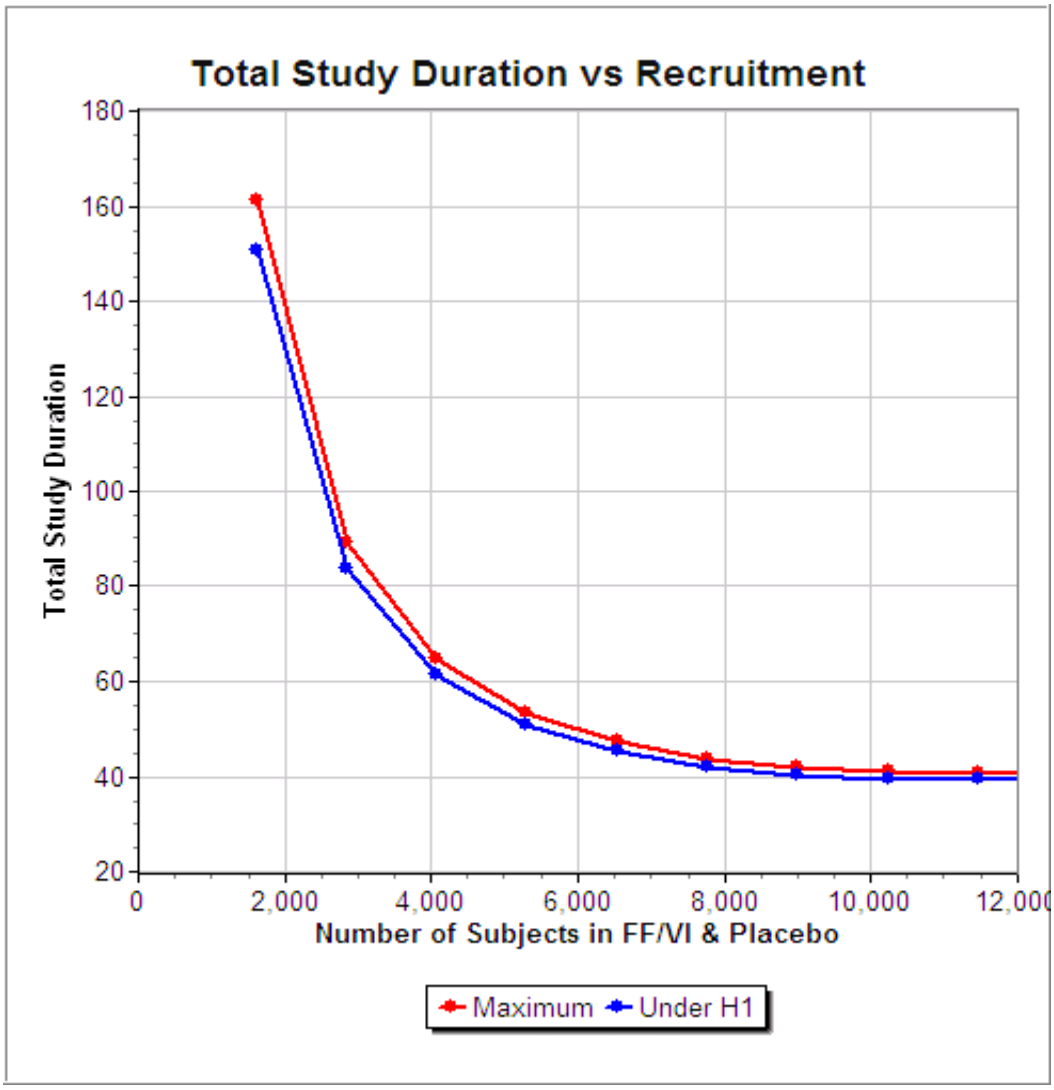
Table 2 Median and Total Study Duration

Placebo Event Rate at 2 years	Total Study Duration (months) (assuming n=4,000 per arm)	Median Duration for Subjects (months)
5%	49	34
6%	44	29
7%	40	25

The Figure 1 shows how changing the number of subjects randomised to the FF/VI and placebo arms affects the total study duration. For example if the number of subjects per arm was 3,000 (recruited in 23 months according to current assumptions) the required

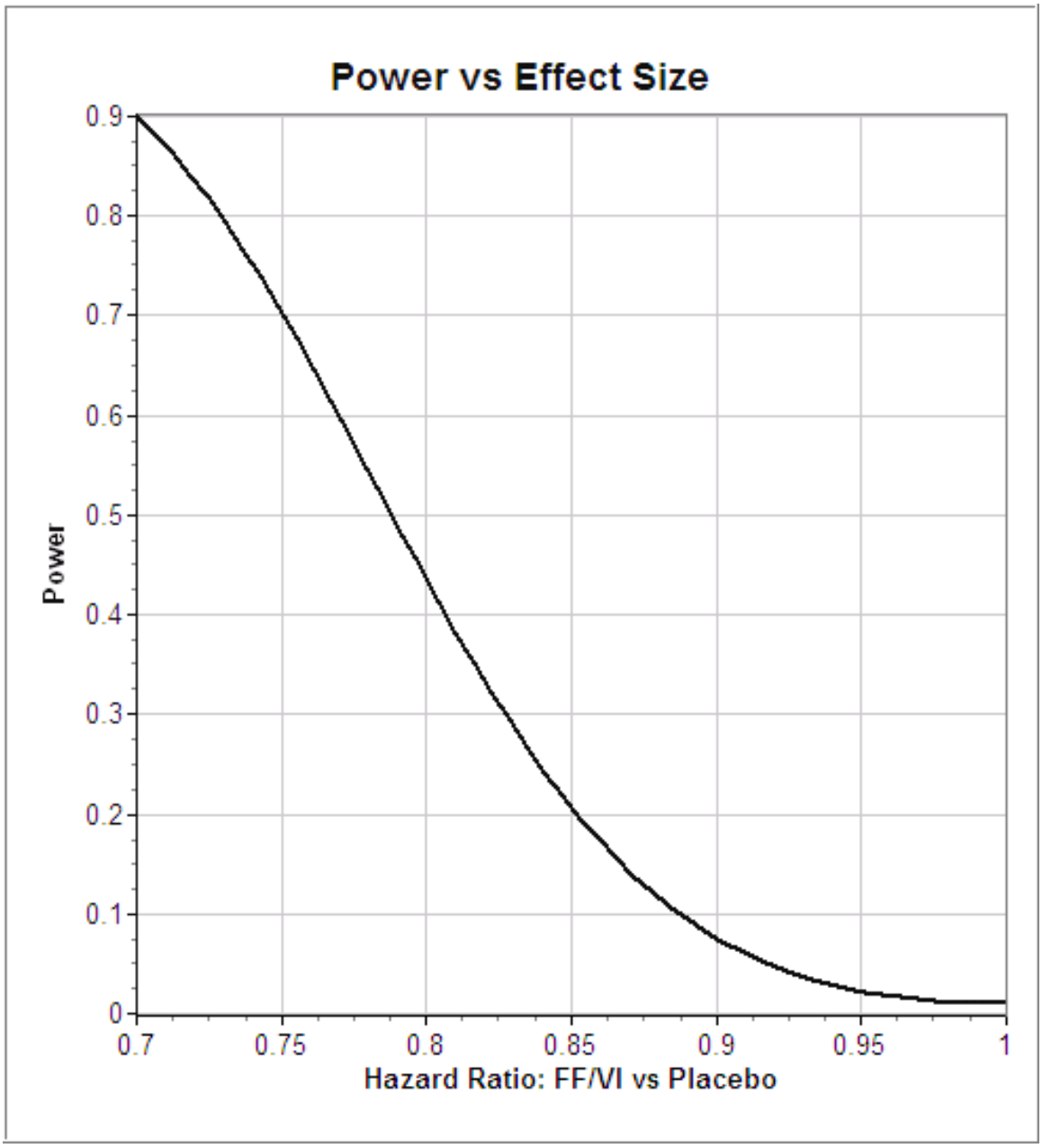
number of events should occur by 50 months (assuming 6% event rate on placebo at 2 years).

Figure 1 Study duration vs number of subjects



The Figure 2 shows the power of the study to detect various effect sizes. For example, if the real reduction in deaths is 25%, i.e. a HR of 0.75, the study as planned would have approximately 70% power to detect this difference.

Figure 2 Power vs Effect size



8.2.3. Sample Size Re-estimation

The event rate will be monitored using data blinded with respect to treatment assignment. If the event rate is lower than anticipated, then Steering Committee and GSK will consider whether the increased duration of follow-up is acceptable or whether to increase the sample size. An increase in sample size is most pragmatically implemented prior to completion of recruitment. If recruitment has already been closed then the duration of the trial may be longer than anticipated. For example, if the combined event rate on FF/VI and placebo at 24 months is only 4.3% (placebo event rate 5%) then the total

expected duration of the trial is estimated to increase to 49 months (if there are 4000 subjects per arm). Under the latter scenario, subjects would therefore be followed for between 30 and 49 months. Alternatively, even if the estimated number of subjects randomised was to be increased to 5,500 per arm (recruited in 40 months) the trial would take 45 months As this is an event driven study, the actual recruitment period will also impact the numbers of subjects and/or duration of follow-up required. For example, if recruitment is very slow and the event rate is quite high, the required number of events may be reached before 4000 subjects per arm are randomised

8.3. Data Analysis Considerations

8.3.1. Analysis Populations

All Subjects Enrolled Population: This population will comprise of all subjects screened and for whom a record exists on the study database and will be used for the tabulation of reasons for withdrawal before randomisation.

Intent-to-Treat (ITT) Population: The ITT Population will consist of all subjects randomised to treatment and who receive at least one dose of study medication. Randomised subjects will be assumed to have received study medication unless definitive evidence to the contrary exists. This will constitute the primary population for all analyses of efficacy measures.

For the primary endpoint of all cause mortality the analysis will include all subjects who have been randomised to treatment, regardless of whether they have discontinued study medication.

For all other efficacy endpoints, with one exception, the analyses will only use on-treatment data. The exception is a sensitivity analysis of the composite CV endpoint which will use events which occurred after the subject discontinued study medication.

Health Outcomes (HO) Population: The HO Population will consist of all subjects in the ITT Population who are included in the substudy of health status measures.

Safety Population: It is expected that the ITT Population will be used for the analyses of safety measures. However if a significant number of patients receive the wrong study medication for the majority of their time on treatment a Safety Population may be defined, where the treatment group a subject is assigned to population may differ from that in the ITT Population.

Arterial Stiffness (AS) Population: The AS Population will consist of all subjects in the ITT Population who are included in the substudy of arterial stiffness.

8.3.2. Analysis Data Sets

Details of the derived data in analysis datasets to be created will be given in the Reporting and Analysis Plan (RAP).

8.3.3. Treatment Comparisons

8.3.3.1. Primary Comparison of Interest

The primary treatment comparison will be FF/VI vs placebo for the primary efficacy endpoint of time to death from any cause (on and off treatment). This analysis will be conducted on the ITT population. The final analysis will be conducted once the required number of events has been reached and the study has been stopped and the survival status of the subjects has been captured.

As a single study will be conducted to seek an indication for all-cause mortality, the study has been powered at the 1% significance level for regulatory purposes. However, all comparisons for the primary, secondary and other endpoints will be performed at the two-sided 5% level. That is, statistical significance will be reached if these are significant at the 5% level.

As there is a single primary treatment comparison and a single primary endpoint, no multiplicity adjustment will be required for the primary efficacy analysis, apart from any adjustment required for the alpha spent at the interim analysis.

8.3.3.2. Other Comparisons of Interest

For the secondary endpoints of rate of decline in FEV_1 and composite CV endpoint the primary comparison of interest is FF/VI vs placebo.

In order to make inferences for pre-defined secondary endpoints while controlling for the overall Type I error, the secondary endpoints will be nested under the primary efficacy endpoint. Multiplicity across these endpoints will be controlled using a closed testing procedure.

The hierarchy will be the primary endpoint followed by the Rate of Lung Function (FEV_1) decline followed by the composite CV endpoint. If significance in this hierarchy is achieved at the two-sided 5% level for the primary endpoint, then the Rate of Lung Function (FEV_1) decline will be tested at the two-sided 5% level. If significance in this is achieved, then the CV endpoint will be tested at the two-sided 5%.

If significance in this hierarchy is not achieved for the primary endpoint, then the tests for the secondary and other efficacy endpoints will be interpreted as descriptive only.

If the primary comparison of FF/VI vs placebo is significant at the 5% level for an endpoint, then inferences for the following treatment comparisons will be carried out for that endpoint:

- VI vs placebo
- FF vs placebo
- FF/VI vs VI
- FF/VI vs FF

These comparisons are to help understand the contribution of the components to the overall treatment effect of the primary FF/VI vs placebo comparison, so no multiple comparison corrections will be considered for these four follow-up comparisons.

8.3.4. Interim Analysis

There have been very few trials comparing long-term treatments for COPD to assess mortality. There is therefore a strong *a priori* desire to obtain a clear and unambiguous result from this trial if possible. Furthermore, in the absence of a substantial body of data on the mortality rates in this population when treated with any of the study drugs, it is desirable to ensure that the study does not stop before sufficient information has been gathered to provide a definitive result. However, it is recognised that there are ethical reasons for stopping the study earlier than anticipated in the events of overwhelming evidence of efficacy or safety.

For these reasons, one formal interim analysis of the time to death from any cause is planned in addition to the final analysis. It is intended that this analysis will be performed when approximately 50% of the total deaths have been observed. The analysis method for this will be the same as to be used in the final analysis i.e. Cox proportional hazards model.

8.3.4.1. Stopping Guidelines

- **FF/VI vs placebo**. In order to have negligible impact on the final significance level, a stopping guideline for efficacy of FF/VI vs placebo will be applied at the interim analysis, using the Haybittle-Peto method using a one sided p-value of 0.00005, (equivalent to a two-sided $p<0.0001$). A one-sided 0.01 p-value will be applied as a non-binding stopping guideline for harm.
- **Other comparisons with placebo**. The study, or a specific treatment arm, may also be stopped prematurely as a result of the interim analysis of the other active treatment arms; in particular, where there is strong evidence that either FF or VI has a strong negative effect on mortality compared with placebo. For the assessment of harm, a non-binding stopping guideline of $p<0.01$ is proposed. This flag would signal further examination of available data by the Independent Data Monitoring Committee (IDMC), with consideration of altering the conduct of or terminating the study.
- **Stopping for safety reasons.** The IDMC will review data periodically throughout the trial. Notwithstanding the formal stopping guidelines described above, the IDMC may recommend that the study, or any treatment arm, should be stopped prematurely on grounds of safety at any time. This may arise where, for example, a review of serious adverse event (SAE) data indicates a substantial deleterious effect of any active treatment arm.

8.3.4.2. Return of data

In order to ensure that the interim analysis of efficacy is based on as complete and accurate data as is possible, vital status will be assessed at approximately 12-weekly intervals in all subjects. Where a subject remains on study treatment, this information will be collected at planned study visits. Where a subject has prematurely discontinued study treatment, this data will be provided by the investigator at approximately 12-weekly intervals from the date of study drug discontinuation.

8.3.4.3. Conduct of interim analyses

An **Independent Data and Monitoring Committee** (IDMC) will monitor progress of the study and ensure that it meets the highest standards of ethics and patient safety. Only the IDMC will be authorized to review unblinded interim efficacy and safety analyses during the trial.

This committee will be formed specifically to oversee trial progression with regards to occurrence of adverse events and to carry out the planned interim analysis. The committee, which will comprise a minimum of 3 people, will include an independent statistician and an independent respiratory clinician with experience in COPD and a cardiologist.

The unblinded interim analysis and periodic safety updates will be performed and delivered to the IDMC by an independent Statistical Data Analysis Centre (SDAC).

The IDMC will give a recommendation to the Steering Committee as to whether the trial should be stopped prematurely following review of the interim results for safety and efficacy. The Steering Committee will, in conjunction with the Sponsor, decide whether to act on this recommendation.

In the event of early stopping due to interim analysis results, the survival status of subjects will be updated by the investigator. Where possible, subjects will be brought to the investigational sites for a final visit. The final analysis will include all data collected up to and including the final visit.

Membership, functions and operating procedures of the Steering Committee, IDMC and other organisational groups for this study will be defined in a separate document. Operating procedures for the IDMC will be established before the first review of unblinded data.

8.3.5. Key Elements of Analysis Plan

Any deviations from the original analysis planned in the protocol, which are agreed prior to finalisation of the RAP will be described in that document.

Hypothesis tests for main effects will use a 2-sided test at the 5% level of significance. Tests for interactions will be 2-sided at the 10% level of significance. If assumptions of the proposed method of analyses are not met, alternative methods of analyses will be used.

As this is a large multi-site, multi-national study, it will be important to investigate any variation in response to treatment by place of recruitment. Such variation may reflect a number of contributory factors including population selection and subject care and management. As most sites are expected to contribute relatively small numbers of subjects, it will not be practical to look in detail at site-to-site differences. Sites will be managed by combining sites within countries, and these countries may then be combined into geographical regions. All amalgamations will be finalized and documented prior to unblinding the treatment codes. These amalgamations will be used wherever region is incorporated into the analysis.

Parametric analyses will include important prognostic variables. Variables which may be important for prognosis in COPD include age, gender, disease severity (as measured by %predicted FEV_1), smoking status, body mass index (BMI) and region. Parametric analyses of primary and some secondary efficacy measures will provide a basis for exploring potential treatment interactions with each of these terms.

8.3.5.1. Efficacy Analyses

8.3.5.1.1. Primary Endpoint

The primary efficacy endpoint of time to all-cause mortality will be analysed using a Cox proportional hazards regression model allowing for important pre-defined covariates which may include, but not be limited to, , baseline %predicted FEV_1, BMI, geographical region and smoking status. The hazard ratio will be derived along with 95% and 99% confidence limits. Cumulative event rates will be calculated using the Kaplan-Meier method.

The proportional hazards assumption will be assessed, with details to be provided in the RAP. If the validity of the proportional hazards assumption is not acceptable, the treatment effect will be assessed using the Log-Rank Test.

The actual survival status of subjects who withdrew from study medication before the study has completed will be included in this analysis, rather than these subjects being censored at the point at which they withdrew. Subjects whose survival status is unknown at the completion of the study will have their event times censored at the timepoint at which they were last known to be alive.

Sensitivity analyses of the primary efficacy endpoint will also be performed to assess the robustness of the primary results, including an "on-treatment" analysis.

Interactions of treatment with subgroups and covariates of specific clinical interest will also be explored; these will be defined in the RAP.

8.3.5.1.2. Secondary Endpoints

Rate of Decline in Lung Function (FEV_1)

The effect of treatment on rate of decline of post-bronchodilator FEV_1 recorded during the treatment period will be analysed using a random coefficients model, including terms

for treatment, time on treatment in years, treatment by time interaction, and appropriate pre-defined covariates.

Composite CV events

For the analysis of time to first on-treatment CV , cumulative event rates will be calculated using the Kaplan-Meier method, and hazard ratios will be calculated using a Cox proportional hazards model, as described for the primary efficacy endpoint. Subjects who withdraw from study medication will be censored at the time of withdrawal - this will be the primary analysis.

A further sensitivity analysis will be performed including CV events captured after the subject discontinued study medication.

8.3.5.1.3. Other Efficacy Analyses

The reporting and analysis of other efficacy endpoints as specified in the protocol will be provided in the RAP.

8.3.5.2. Safety Analyses

AE data will be coded using the standard GSK MedDRA dictionary and medication terms will be coded using the GSK Drug Dictionary.

8.3.5.2.1. Extent of Exposure

IP exposure will be summarized for the duration of exposure.

8.3.5.2.2. Adverse Events (AEs)

AEs will be grouped by body system. AEs occurring pre-treatment, during active treatment and post-treatment will be summarized separately. A summary of the number, percentage, and rate per 1000 subject-years of subjects who report at least one adverse event will be displayed by 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

Deaths and SAEs will also be documented in case narrative format.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov before enrolment of subjects begins.

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

Prior to initiation of a study site, GSK/CRO will obtain approval from the appropriate regulatory agency to conduct the study in accordance with applicable country-specific regulatory requirements, including those required under a US IND.

The study will be conducted in accordance with all applicable regulatory requirements, including an U.S. IND.

The study will be conducted in accordance with Good Clinical Practice (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 approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK/CRO 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.

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK/CRO procedures, 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.

During the study, monitors will 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 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 audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

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 to the Clinical Trials Register 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.

The results summary will be posted to the Clinical Study Register at the time of the first regulatory approval or within 12 months of any decision to terminate development. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 12 months of the first approval or within 12 months of any decision to terminate development. 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. Steering Committee (SC)

This study will be guided by a Steering Committee (SC) consisting of external clinical experts (Pulmonologists and Cardiologists), and clinical/medical/statistical representatives from GSK. The functions of the Steering Committee will include:

- International steering and guidance
- Recruitment review
- Publications and presentations

9.9. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter, which is available upon request.

9.10. Clinical Endpoint Committee (CEC)

A Clinical Endpoint Committee (CEC) will be established to independently review and categorise the cause of death for each subject where a death has been recorded. The CEC will also review the data for the secondary composite endpoint of cardiovascular events.

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11. APPENDICES

11.1. Appendix 1: PGx

Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in different populations. There is increasing evidence that an individual's genetic composition (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 analysis include:

Drug	Disease	Gene	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002]	HLA –B*5701	Individuals with HLA-B*5701 variant may be at increased risk for experiencing hypersensitivity to abacavir. Clinical assays are available for HLA-B*5701 but none has been validated. HLA-B*5701 screening would supplement but never replace abacavir clinical risk management strategies aimed at minimising rare but serious outcomes associated with abacavir hypersensitivity.
Warfarin	Cardiovascular [Neergard, 2006; Wilke, 2005]	CYP2C9	Serious adverse events (SAEs) experienced by some patients on warfarin may be explained by variations in the CYP2C9 gene that influences the degree of anticoagulation achieved.

Drug	Disease	Gene	Outcome
Irinotecan	Cancer [FDA News Release, 2005]	UGT1A1	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. A genetic blood test (Invader UGT1A1 molecular assay) 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 handling or response to Fluticasone Furoate/Vilanterol Inhalation Powder.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a possible genetic relationship to handling or response to Fluticasone Furoate/Vilanterol 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 Fluticasone Furoate/Vilanterol Inhalation Powder that may be attributable to genetic variations of subjects, the following objectives may be investigated:

- 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
- Relationship of genetic variants associated with disease phenotypes, severity and/or progression of COPD

Study Population

Any subject who has given informed consent to participate in the clinical study, has met all the entry criteria for the clinical study, and receives investigational product may take part in the 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. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

Blood samples will be taken for PGx assessments.

In taking blood samples: in addition to any blood samples taken for the clinical study, a whole blood sample (~10ml) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

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 blood 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 blood 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 Fluticasone Furoate/Vilanterol Inhalation Powder has been completed and the study data reviewed.

In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to Fluticasone Furoate/Vilanterol 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 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:

- The sample is retained for PGx research
- Any PGx sample is destroyed.

If a subject withdraws consent from the 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. If the sample has already been processed, it will be destroyed after all steps are complete. GSK will ensure that any data related to the sample will not be analysed. The sample will be destroyed after processing is complete.

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 must complete the appropriate documentation to request sample destruction within 5 days. The sample will be destroyed and documentation sent to the site within 30 working days of receipt of the request for destruction. All documents pertaining to sample destruction must be maintained in the site study records.

Pharmacogenetics Analyses

1. Specific sections of DNA may be selected from areas of the genome (e.g., candidate genes) known to encode the drug target, drug metabolizing enzymes, areas associated with mechanisms underlying adverse events, and those linked to study disease and, thus, linked to drug response.

The candidate genes that may be investigated in this study include the following: the GSK Absorption, Distribution, Metabolism and Excretion genes. These play a central role in drug pharmacokinetics and pharmacodynamics. In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response Fluticasone Furoate/Vilanterol Inhalation Powder. The genes that may code for these proteins may also be studied.

2. By evaluating large numbers of polymorphic markers (e.g., single nucleotide polymorphisms or SNPs) throughout the genome, sets of markers may be identified that correspond to differential drug response.
3. The results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarised as appropriate to the data. In all cases, appropriate statistical methods will be used to analyse the genetic markers in the context of other clinical data. Statistical methods may include, but are not limited to Hardy-Weinberg Equilibrium testing, Comparison of Demographic and Baseline

Characteristics by Genotype, Evaluation of Genotypic Effects, Evaluation of Treatment by Genotype and Gene-Gene Interaction, Linkage Disequilibrium, Multiple Comparison and Multiplicity and/or Power and Sample Size Considerations. Detailed description of the analyses to be conducted will be documented in the Pharmacogenetics Reporting and Analysis Plan.

4. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) located throughout the genome. This approach is often employed when potential genetic effects are not well understood.

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 blood being taken for PGx research.

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

GSK may summarize the cumulative PGx research results in the clinical study report.

In general, GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of the PGx research results that are not known to be relevant to the subject's medical care at the time of the study, because the information generated from PGx studies is preliminary in nature, and the significance and scientific validity of the results are undetermined at such an early stage of research, under any circumstances unless required by law.

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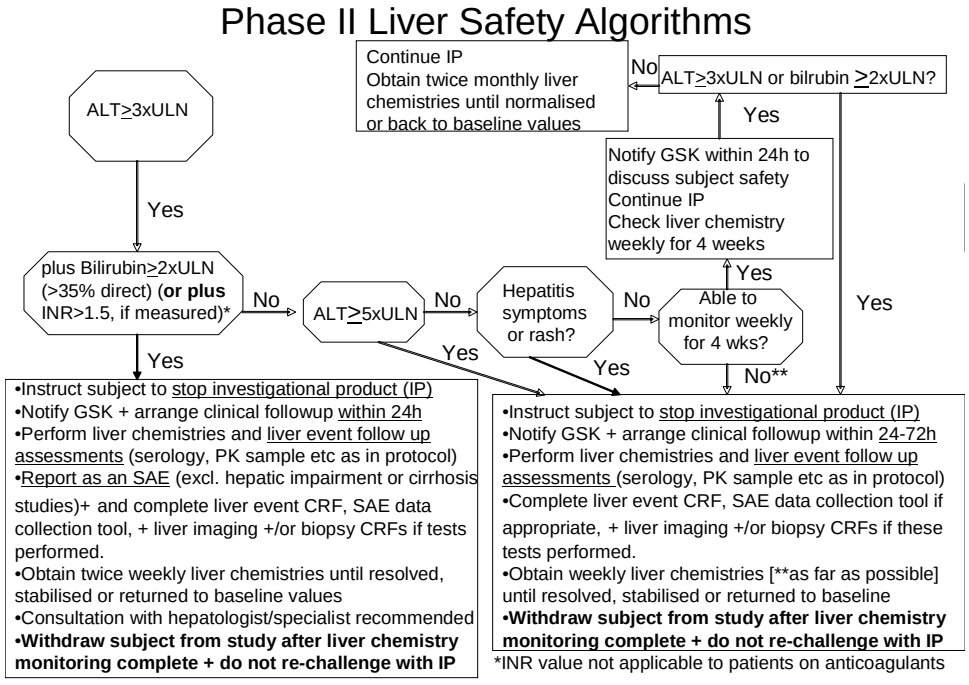
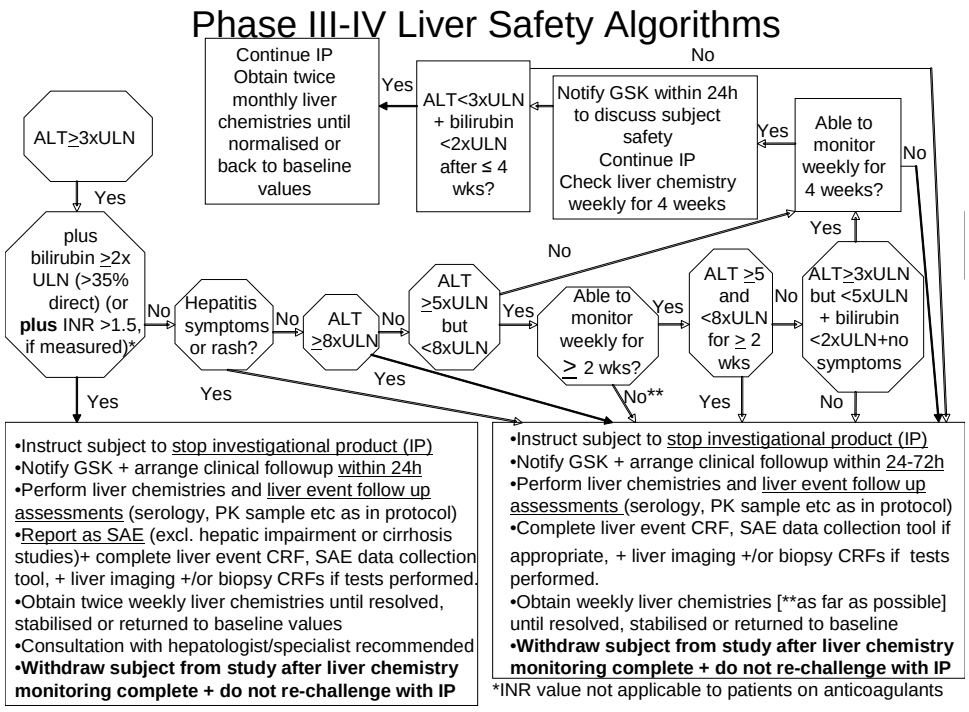
11.2. Appendix 2: Country Specific Requirements

No country specific requirements exist

11.3. Appendix 3: Liver Chemistry Stopping and Followup Criteria





11.4. Appendix 4: Protocol Changes

11.4.1. Protocol Amendment 01

This amendment applies to all study centers participating in HZC113782.

Rationale

This protocol amendment is being implemented to revise exclusion criteria regarding severe heart failure to include subjects with an implantable cardioverter defibrillator (ICD). Clarification was added regarding disease related events/outcomes which will not be subject to expedited reporting. Additional administrative changes and minor clarifications were made.

Section 4.2 Inclusion Criteria - #6

Original text:

Severity of COPD:

- Subjects with a measured post-albuterol/salbutamol FEV1/FVC ratio of ≤0.70 at Screening (Visit 1).
- Subjects with a measured post-albuterol/salbutamol FEV1 ≥50 and ≤70% of predicted normal values calculated using NHANES III reference equations [Hankinson, 1999; Hankinson, 2010] at Screening (Visit 1).

  Post-bronchodilator spirometry will be performed approximately 15 minutes after the subject has self-administered 4 inhalations (i.e., total 400mcg) of albuterol/salbutamol via an MDI with a valved-holding chamber. The FEV_1/FVC ratio and FEV_1 percent predicted values will be calculated.

Amended text:

Airflow Obstruction:

- Subjects with a measured post-albuterol/salbutamol FEV1/FVC ratio of ≤0.70 at Screening (Visit 1).
- Subjects with a measured post-albuterol/salbutamol FEV1 ≥50 and ≤70% of predicted normal values calculated using NHANES III reference equations [Hankinson, 1999; Hankinson, 2010] at Screening (Visit 1).

  Post-bronchodilator spirometry will be performed approximately 15 minutes after the subject has self-administered 4 inhalations (i.e., total 400mcg) of albuterol/salbutamol via an MDI with a valved-holding chamber. The FEV_1/FVC ratio and FEV_1 percent predicted values will be calculated.

Section 4.2 Inclusion Criteria- #7

Original text:

Symptoms of COPD:

Subjects must score 2 or higher on the modified Medical Research Council Dyspnea scale (Visit 1)

Amended text:

Dyspnea:

Subjects must score 2 or higher on the modified Medical Research Council Dyspnea scale (Visit 1)

Section 4.3 Exclusion Criteria - #7

Original text:

Current severe heart failure (New York Heart Association class IV). Subjects will also be excluded if they have a known ejection fraction of <30%.

Amended text:

Current severe heart failure (New York Heart Association class IV). Subjects will also be excluded if they have a known ejection fraction of <30% or if they have an implantable cardioverter defibrillator (ICD).

Section 4.2 Exclusion Criteria - #15

Original text:

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 or thereafter at any time during the study (unless otherwise specified)
Inhaled Long acting beta-agonists (LABA)	48 hours
ICS/LABA combination products	48 hours
Inhaled corticosteroids	48 hours
Tiotropium	1 week*
Systemic, Oral, parenteral, intra-articular corticosteroids	30 days (oral corticosteroids may be used to treat COPD exacerbations during the study)
Cytochrome P450 3A4 strong inhibitors including but not limited to antiretrovirals (protease inhibitors) (e.g.Indinavir, Nelfinavir, Ritonavir,	6 weeks Grapefruit is allowed up to

Medication	No use within the following time intervals prior to Screening or thereafter at any time during the study (unless otherwise specified)
Saquinavir); Imidazole and Triazole anti-fungals (e.g. Ketaconazole, Itraconazole); Clarithromycin, Telithromycin, Amiodarone, and Nefazodone	Visit 1, then limited to no more than one glass of grapefruit juice (250 mL/ 8 ounces) or one grapefruit per day
Any other investigational drug	30 days or 5 half lives whichever is longer.

* See Section 5.6.2 for information regarding Tiotropium use during the study

Amended text:

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 or thereafter at any time during the study (unless otherwise specified)
Inhaled Long acting beta-agonists (LABA)	48 hours
ICS/LABA combination products	48 hours
Inhaled corticosteroids	48 hours
Tiotropium	1 week*
Systemic, Oral, parenteral, intra-articular corticosteroids	30 days (oral and systemic corticosteroids may be used to treat COPD exacerbations during the study)
Cytochrome P450 3A4 strong inhibitors including but not limited to antiretrovirals (protease inhibitors) (e.g.Indinavir, Nelfinavir, Ritonavir, Saquinavir); Imidazole and Triazole anti-fungals (e.g. Ketaconazole, Itraconazole); Clarithromycin, Telithromycin, Amiodarone, and Nefazodone	6 weeks Grapefruit is allowed up to Visit 1, then limited to no more than one glass of grapefruit juice (250 mL/ 8 ounces) or one grapefruit per day
Any other investigational drug	30 days or 5 half lives whichever is longer.

* See Section 5.6.2 for information regarding Tiotropium use during the study

Section 5.6.1 Permitted Medications and Non-Drug Therapies

Original text:

The following medications are permitted during the study:

- Study-supplied albuterol/salbutamol (MDI or nebules)
- Ipratropium/Combivent

- Oral corticosteroids and antibiotics for the short term treatment of COPD exacerbations
- Mucolytics
- Oxygen
- Antihistamines and nasal decongestants
- OTC cough suppressants
- Intranasal cromolyns or nedocromil
- Intranasal, ophthalmic and topical corticosteroids
- Antibiotics for short term treatment of acute non-respiratory tract infections and for the treatment of pneumonia and COPD exacerbations.
- Influenza and pneumonia vaccines
- Tricyclic antidepressants and Monamine oxidase inhibitors (MOAs). (Administer with caution as they may potentiate the effects of beta-agonists on the vascular system.)
- Diuretics. (Caution is advised in the coadminstration of beta-agonists with nonpotassium –sparing diuretics).
- Smoking cessation medications
- Cardioselective Beta-blockers and ophthalmic beta-blockers. (Administer with caution as they may block bronchodilatory effects of beta-agonists and produce severe bronchospasm.)
- All medications for other disorders as long as the dose remains constant wherever possible.

Amended text:

The following medications are permitted during the study:

- Study-supplied albuterol/salbutamol (MDI or nebules)
- Ipratropium/Combivent
- Theophyllines, roflumilast
- Oral and systemic corticosteroids and antibiotics for the short term treatment of COPD exacerbations
- Mucolytics
- Oxygen
- Antihistamines and nasal decongestants
- OTC cough suppressants
- Intranasal cromolyns or nedocromil

- Intranasal, ophthalmic and topical corticosteroids
- Antibiotics for short term treatment of acute non-respiratory tract infections and for the treatment of pneumonia and COPD exacerbations.
- Influenza and pneumonia vaccines
- Tricyclic antidepressants and Monamine oxidase inhibitors (MOAs). (Administer with caution as they may potentiate the effects of beta-agonists on the vascular system.)
- Diuretics. (Caution is advised in the coadminstration of beta-agonists with nonpotassium –sparing diuretics).
- Smoking cessation medications
- Cardioselective Beta-blockers and ophthalmic beta-blockers. (Administer with caution as they may block bronchodilatory effects of beta-agonists and produce severe bronchospasm.)
- All medications for other disorders as long as the dose remains constant wherever possible.

Section 6.2.6.1 Spirometry

Original text:

The Visit 1 spirometry must be performed:

- Between 6:00AM and 10:00AM
- After withholding morning dose of scheduled COPD medications as indicated in the exclusion criteria
- Spirometry at all other treatment visits must be performed:
- After inhalation of 4 puffs of albuterol via a metered dose inhaler with a spacer/holding chamber
- After refraining from exercising for 2 or more hours, smoking for 1 hour, and exposure to cold air for 15 minutes
- After refraining from drinks with high levels of caffeine such as tea and coffee on the morning of all clinic visits
- After Visit 2 (randomization), FEV1 can be done at any time of day but should be consistent (± 2 hour window based on time from first post baseline visit)between visits for each subject

Details regarding the spirometric procedures are provided in the SPM.

Amended text:

The Visit 1 spirometry must be performed:

- Between 6:00AM and 10:00AM
- After withholding morning dose of scheduled COPD medications as indicated in the exclusion criteria
- Spirometry at all other treatment visits must be performed:
- After inhalation of 4 puffs of albuterol via a metered dose inhaler with a spacer/holding chamber

After Visit 2 (randomization), FEV1 can be done at any time of day but should be consistent (± 2 hour window based on time from first post baseline visit) between visits for each subject and no later than 2pm

Details regarding the spirometric procedures are provided in the SPM.

Section 6.2.8 COPD exacerbations and Pnuemonia

Original text:

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 their study investigator and/or research coordinator immediately, and report to the study clinic as required
- If the subject is unable to contact their 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 PI as having:

- A mild/moderate/severe 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
- 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. Confirmed diagnoses of pneumonia must be recorded as adverse events in the eCRF.

Definitions for COPD exacerbations and pneumonia are given above. If, based on these criteria, a subject's symptoms do not fulfill the diagnosis of an exacerbation and/or pneumonia, then the investigator should use their 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. Refer to Section 6.3.2.1 and Section 6.3.2.2 for definitions of AE and SAE, respectively.

Exacerbations should not be recorded in the AE section of the eCRF unless they meet the definition of an SAE. (Pneumonia must be recorded in the AE section of the eCRF and on the exacerbation page of the eCRF.)

The dates of onset and resolution of each 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.

Amended text:

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 their study investigator and/or research coordinator immediately, and report to the study clinic as required

- If the subject is unable to contact their 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 PI as having:

- A mild/moderate/severe 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
- 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. Confirmed diagnoses of pneumonia must be recorded as adverse events in the eCRF.

Definitions for COPD exacerbations and pneumonia are given above. If, based on these criteria, a subject's symptoms do not fulfill the diagnosis of an exacerbation and/or pneumonia, then the investigator should use their 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. Refer to Section 6.3.2.1 and Section 6.3.2.2 for definitions of AE and SAE, respectively.

The dates of onset and resolution of each 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.

New section to be inserted between 6.33 and 6.34

Disease-Related Events and/or Disease-Related Outcomes Not Subject to Expedited Reporting

The following events are considered secondary efficacy endpoints for this study and will be reported as SAEs but will not be subject to expedited reporting regardless of the "expectedness" or "relatedness" of the event:

- MI
- Stroke
- Unstable angina
- TIA

Additionally, any laboratory or ECG abnormalities associated with the diagnosis of individual components of these efficacy endpoints will not be subject to expedited reporting.

The following events are expected in this population and will be reported as SAEs but will not be subject to expedited reporting regardless of the "expectedness" or "relatedness" of the event:

- COPD exacerbation
- Pneumonia

Additionally, any laboratory or Chest X-ray abnormalities associated with the diagnosis of these events will not be subject to expedited reporting.

Section 6.5: Biomarker(s)

Original text:

Serum samples will be collected at the US sites at V2 (pre-dose) and V3 (pre-dose). One tube will be used to analyze 4 known inflammatory markers (hsCRP, PARC, fibrinogen and IL-6), a second tube will be stored for analysis of novel biomarkers emerging from ongoing studies (i.e. ECLIPSE). A third tube will be collected for measuring a CBC and Chem 7 panel for use in predictive modelling.

Any subject in the US who has given informed consent to participate in the clinical study and has met all of the entry criteria may take part in the biomarker portion of the study. Subject participation in biomarker sample collection is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

Amended text:

Serum and plasma samples will be collected at the US sites at V2 (pre-dose) and V3 (pre-dose). These will be used to analyze 4 known inflammatory markers (hsCRP, PARC, fibrinogen and IL-6) and also for measuring a CBC and Chem 7 panel for use in predictive modelling.

Any subject in the US who has given informed consent to participate in the clinical study and has met all of the entry criteria may take part in the biomarker portion of the study. Subject participation in biomarker sample collection is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

Section 6: STUDY ASSESSMENTS AND PROCEDURES

Original text:

Post-Randomization Assessments:

Procedures				End of study treatment	Follow-up[3]
					Phone Contact
	Month 3 (±14)[1] PLUS every 3 months	Month 6 (±14) PLUS every 6 months	Month 12 (±14) PLUS every 12 months		14±2 days after last dose of study drug
Concomitant Medication Assessment	X			X	X
Spirometry (FEV_1)	X			X	
Exacerbation Assessment	X			X	
Survival Assessment	X			X	
Subject Questionnaires[4]	X[4]	X[4]		X	
Adverse Event Assessment[2]	X			X	X
Smoking Status	X			X	
Oropharyngeal exam	X			X	
Vital signs	X			X	
Blood Sample	X[5]				
Pregnancy Test		X		X	
SphygmoCor Assessments[2]			X	X	
Dispense diary Card	X				
Dispense Investigational Product.	X				
Assess Investigational Product Compliance	X			X	
Collect Investigational Product	X			X	
Dispense Rescue Albuterol/Salbutamol	X				

Procedures				End of study treatment	Follow-up[3]
					Phone Contact
	Month 3 (±14)[1] PLUS every 3 months	Month 6 (±14) PLUS every 6 months	Month 12 (±14) PLUS every 12 months		14±2 days after last dose of study drug
Collect/check Rescue Albuterol/Salbutamol	X			X	
Register Visit in IVRS	X			X	X

1. Visits will continue at the specified intervals until the end of the study which will be determined by reaching approximately 1000 deaths.
2. In a subset of ~800 subjects (~200 per treatment group) - to be done annually, details in SPM
3. The Follow-up Visit is scheduled to occur 14 ± 2 days after the last dose of IP.
4. SGRQ-C, CAT and EQ-5D in a subset of ~4,000 subjects - these will be done during the first year at 3 months and 6 months and then every 6 months for the duration of the treatment period
5. Only at initial 3 month Visit

Amended text:

Post-Randomization Assessments:

Procedures				End of study treatment	Follow-up[3]
					Phone Contact
	Month 3 (±14)[1] PLUS every 3 months	Month 6 (±14) PLUS every 6 months	Month 12 (±14) PLUS every 12 months		7±2 days after last dose of study drug
Concomitant Medication Assessment	X			X	X
Spirometry (FEV_1)	X			X	
Exacerbation Assessment	X			X	
Survival Assessment	X			X	
Subject Questionnaires[4]	X[4]	X[4]		X	
Adverse Event Assessment[2]	X			X	X
Smoking Status	X			X	
Oropharyngeal exam	X			X	
Vital signs	X			X	
Blood Sample	X[5]				
Pregnancy Test		X		X	
SphygmoCor Assessments[2]			X	X	
Dispense diary Card	X				
Dispense Investigational Product.	X				

Procedures				End of study treatment	Follow-up[3]
					Phone Contact
	Month 3 (±14)[1] PLUS every 3 months	Month 6 (±14) PLUS every 6 months	Month 12 (±14) PLUS every 12 months		7±2 days after last dose of study drug
Assess Investigational Product Compliance	X			X	
Collect Investigational Product	X			X	
Dispense Rescue Albuterol/Salbutamol	X				
Collect/check Rescue Albuterol/Salbutamol	X			X	
Register Visit in IVRS	X			X	X

1. Visits will continue at the specified intervals until the end of the study which will be determined by reaching approximately 1000 deaths.
2. In a subset of ~800 subjects (~200 per treatment group) - to be done annually, details in SPM
3. The Follow-up Visit is scheduled to occur 7 ± 2 days after the last dose of IP.
4. SGRQ-C, CAT and EQ-5D in a subset of ~4,000 subjects - these will be done during the first year at 3 months and 6 months and then every 6 months for the duration of the treatment period
5. Only at initial 3 month Visit

11.4.2. Protocol Amendment 02

This protocol amendment applies to all study centers participating in HZC113782.

Rationale

This protocol amendment is being implemented to revise the amount of time in the run-in period and correct minor typographical errors.

Study Design

Original text:

The target enrolment is approximately 16,000 randomized subjects at approximately 1000 study centers globally. Based on current assumptions of the event rate, the total duration of subject participation will be approximately between 15 and 44 months, consisting of a 2-7 day run-in period, variable treatment period and 1-week follow-up period.

Subjects will be randomized to treatment after a 2-7 day run-in period. Prior to the Run-in period, subjects will discontinue use of COPD medications as listed in Section 4.3.

Amended text:

The target enrolment is approximately 16,000 randomized subjects at approximately 1100 study centers globally. Based on current assumptions of the event rate, the total duration of subject participation will be approximately between 15 and 44 months, consisting of a 4-10 day run-in period, variable treatment period and 1-week follow-up period.

Subjects will be randomized to treatment after a 4-10 day run-in period. Prior to the Run-in period, subjects will discontinue use of COPD medications as listed in Section 4.3.

Section 3.1 Study Design

Original text:

Based on current assumptions of the event rate, the total duration of subject participation will be approximately between 15 and 44 months, consisting of a 2-7 day run-in period, variable treatment period, and 2-week follow-up period.

Subjects will be randomized to treatment after a 2-7 day run-in period.

Subjects will be randomized to treatment after a 4-10 day run-in period. Prior to run-in, subjects will discontinue use of previous COPD medications except for short-acting bronchodilators and theophyllines. Clinic visits will occur at screening, randomization, and then every 12 weeks until the study has reached the required number of events.

Amended text:

Based on current assumptions of the event rate, the total duration of subject participation will be approximately between 15 and 44 months, consisting of a 4-10 day run-in period, variable treatment period, and 1-week follow-up period.

Subjects will be randomized to treatment after a 4-10 day run-in period.

Subjects will be randomized to treatment after a 4-10 day run-in period. Prior to run-in, subjects will discontinue use of previous COPD medications except for short-acting bronchodilators and theophyllines. Clinic visits will occur at screening, randomization, 4 weeks and then every 12 weeks until the study has reached the required number of events.

Section 6 STUDY ASSESSMENTS AND PROCEDURES

Original text (both pre and post randomization):

2. In a subset of ~800 subjects

Amended text (both pre and post randomization):

2. In a subset of ~1400 subjects

Section 6 STUDY ASSESSMENTS AND PROCEDURES

Original text:

Procedures				End of study treatment	Follow-up[3]
					Phone Contact
	Month 3 (±14)[1] PLUS every 3 months	Month 6 (±14) PLUS every 6 months	Month 12 (±14) PLUS every 12 months		7±2 days after last dose of study drug
Concomitant Medication Assessment	X			X	X
Spirometry (FEV_1)	X			X	
Exacerbation Assessment	X			X	
Survival Assessment	X			X	
Subject Questionnaires[4]	X[4]	X[4]		X	
Adverse Event Assessment[2]	X			X	X
Smoking Status	X			X	
Oropharyngeal exam	X			X	

Procedures				End of study treatment	Follow-up[3]
					Phone Contact
	Month 3 (±14)[1] PLUS every 3 months	Month 6 (±14) PLUS every 6 months	Month 12 (±14) PLUS every 12 months		7±2 days after last dose of study drug
Vital signs	X			X	
Blood Sample	X[5]				
Pregnancy Test		X		X	
SphygmoCor Assessments[2]			X	X	
Dispense diary Card	X				
Dispense Investigational Product.	X				
Assess Investigational Product Compliance	X			X	
Collect Investigational Product	X			X	
Dispense Rescue Albuterol/Salbutamol	X				
Collect/check Rescue Albuterol/Salbutamol	X			X	
Register Visit in IVRS	X			X	X

1. Visits will continue at the specified intervals until the end of the study which will be determined by reaching approximately 1000 deaths.
2. In a subset of ~1400 subjects- to be done annually, details in SPM
3. The Follow-up Visit is scheduled to occur 7 ± 2 days after the last dose of IP.
4. SGRQ-C, CAT and EQ-5D in a subset of ~4,000 subjects - these will be done during the first year at 3 months and 6 months and then every 6 months for the duration of the treatment period
5. Only at initial 3 month Visit

Amended text:

Procedures					End of study treatment	Follow-up[3]
						Phone Contact
	Month 1	Month 3 (±14)[1] PLUS every 3 months	Month 6 (±14) PLUS every 6 months	Month 12 (±14) PLUS every 12 months		7±2 days after last dose of study drug
Concomitant Medication Assessment		X			X	X
Spirometry (FEV_1)		X			X	
Exacerbation Assessment		X			X	

Procedures					End of study treatment	Follow-up[3]
						Phone Contact
	Month 1	Month 3 (±14)[1] PLUS every 3 months	Month 6 (±14) PLUS every 6 months	Month 12 (±14) PLUS every 12 months		7±2 days after last dose of study drug
Survival Assessment		X			X	
Subject Questionnaires[4]		X[4]	X[4]		X	
Adverse Event Assessment[2]		X			X	X
Smoking Status		X			X	
Oropharyngeal exam		X			X	
Vital signs		X			X	
Blood Sample		X[5]				
Pregnancy Test			X		X	
SphygmoCor Assessments[2]				X	X	
Dispense diary Card		X				
Dispense Investigational Product.	X	X				
Assess Investigational Product Compliance		X			X	
Collect Investigational Product	X	X			X	
Dispense Rescue Albuterol/Salbutamol		X				
Collect/check Rescue Albuterol/Salbutamol		X			X	
Register Visit in IVRS		X			X	X

1. Visits will continue at the specified intervals until the end of the study which will be determined by reaching approximately 1000 deaths.
2. In a subset of ~1400 subjects- to be done annually, details in SPM
3. The Follow-up Visit is scheduled to occur 7 ± 2 days after the last dose of IP.
4. SGRQ-C, CAT and EQ-5D in a subset of ~4,000 subjects - these will be done during the first year at 3 months and 6 months and then every 6 months for the duration of the treatment period
5. Only at initial 3 month Visit

Section 6.2.7 Cardiovascular Composite Endpoint

Original text:

Ischemic chest discomfort that occurs at rest with at least 1 episode lasting ≥10 minutes and is accompanied by new or presumably new ST segment deviation (transient (<20 minutes) elevation ≥ 0.1mV or dynamic horizontal/ downsloping depression ≥ 0.05mV)) in at least 2 contiguous leads without diagnostic biochemical changes in cardiac enzymes (serum troponin I or T or creatinine kinase-MB).

Amended text:

Ischemic chest discomfort that occurs at rest with at least 1 episode lasting ≥10 minutes and is accompanied by new or presumably new ST segment deviation (transient (<20 minutes) elevation ≥ 0.1mV or dynamic horizontal/ downsloping depression ≥ 0.05mV)) in at least 2 contiguous leads without diagnostic biochemical changes in cardiac enzymes (serum troponin I or T or creatine kinase-MB).

11.4.3. Protocol Amendment 03

This protocol amendment applies to all study centers participating in HZC113782.

Rationale

This protocol amendment is being implemented to add 2 “other endpoints”, clarify wording regarding washout of prohibited medications and correct other minor errors.

Sponsor Information Page

Original Text:

Clinical Study Identifier: HZC113782

GlaxoSmithKline
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: +44 (0)208 990 9000

GlaxoSmithKline
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: + 001-919-483-2100

*Amended Text**:***

Clinical Study Identifier: HZC113782

GlaxoSmithKline R&D Ltd
980 Great West Road
Brentford, Middelsex, TW8 9GS, UK
Telephone: +44 (0)20 8047 5000

GlaxoSmithKline
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: +44 (0)208 990 9000

GlaxoSmithKline
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: + 001-919-483-2100

Protocol Summary: Objectives

Original text:

Other objectives are:

- To evaluate the following treatment comparisons on all primary, secondary, other and exploratory endpoints:

  FF/VI compared with FF

  FF/VI compared with VI

  FF compared with placebo

  VI compared with placebo
- To evaluate the effect of FF/VI compared with placebo on the rate of moderate/severe COPD exacerbations
- To evaluate the effect of FF/VI compared with placebo on COPD related mortality
- To evaluate the effect of FF/VI compared with placebo on arterial stiffness in a subset of subjects
- To evaluate the effect of FF/VI compared with placebo on health-related quality of life measured with the SGRQ-C in a subset of subjects
- To evaluate quality-adjusted life years (QALYs) by treatment group using health status data collected from EuroQol Questionnaire (EQ-5D) in a subset of subjects
- To evaluate the impact of FF/VI compared with placebo on healthcare resource utilisation (measured by number of days hospitalized for COPD)

Exploratory objectives are:

- To evaluate the effect of FF/VI compared with placebo on COPD health status in a subset of subjects using the COPD Assessment Tool (CAT)
- To examine the molecular profiles of blood, samples to identify factors that may influence biological and clinical responses to FF/VI compared with placebo and/or associated with the development or progression of COPD or medically related conditions
- To examine the predictive ability of a comparative index to predict mortality

Amended text:

Other objectives are:

- To evaluate the following treatment comparisons on all primary, secondary, other and exploratory endpoints:

FF/VI compared with FF

FF/VI compared with VI

FF compared with placebo

VI compared with placebo

- To evaluate the effect of FF/VI compared with placebo on the rate of moderate/severe COPD exacerbations
- To evaluate the effect of FF/VI compared with placebo on COPD related mortality
- To evaluate the effect of FF/VI compared with placebo on arterial stiffness in a subset of subjects
- To evaluate the effect of FF/VI compared with placebo on health-related quality of life measured with the SGRQ-C in a subset of subjects
- To evaluate quality-adjusted life years (QALYs) by treatment group using health status data collected from EuroQol Questionnaire (EQ-5D) in a subset of subjects
- To evaluate the impact of FF/VI compared with placebo on healthcare resource utilisation (measured by number of days hospitalized for COPD)
- To evaluate the impact of FF/VI compared with placebo on the number of cardiovascular procedures (ie angioplasty or revascularization)
- To evaluate the effect of FF/VI compared with placebo on change from baseline in FEV_1
- To evaluate the effect of FF/VI compared with placebo on change from baseline in FVC

Exploratory objectives are:

- To evaluate the effect of FF/VI compared with placebo on COPD health status in a subset of subjects using the COPD Assessment Tool (CAT) in a subset of subjects
- To examine the molecular profiles of blood, samples to identify factors that may influence biological and clinical responses to FF/VI compared with placebo and/or associated with the development or progression of COPD or medically related conditions in a subset of subjects
- To examine the predictive ability of a comparative index to predict mortality

Protocol Summary: Study Endpoints/Assessments

Original text:

Other Efficacy Endpoints

- Annual rate of moderate/severe COPD exacerbations

- Time to COPD related death (based on CEC adjudication)
- QoL using the St George's Respiratory Questionnaire-COPD.
- Health status using the EuroQol Questionnaire (EQ-5D)
- Health Care Resource Utilization
- PWV

Amended text:

Other Efficacy Endpoints

- Annual rate of moderate/severe COPD exacerbations
- Time to COPD related death (based on CEC adjudication)
- QoL using the St George's Respiratory Questionnaire-COPD.
- Health status using the EuroQol Questionnaire (EQ-5D)
- Health Care Resource Utilization
- PWV
- Cardiovascular procedures
- Change from baseline in FEV_1
- Change from baseline in FVC

Protocol Summary: Study Design

Original text:

Study Design

This is a randomized, double-blind, parallel-group, multi-center, placebo-controlled study to evaluate the long term efficacy and safety of FF/VI Inhalation powder 100/25mcg QD, FF Inhalation powder 100mcg QD and VI Inhalation powder 25mcg QD when administered via the Novel Dry Powder Inhaler. Once daily dosing will occur in the morning (with the exception of the first treatment visit).

The target enrolment is approximately 16,000 randomized subjects at approximately 1100 study centers globally. Based on current assumptions of the event rate, the total duration of subject participation will be approximately between 15 and 44 months, consisting of a 4-10 day run-in period, variable treatment period and 1-week follow-up period.

Amended text:

Study Design

This is a randomized, double-blind, parallel-group, multi-center, placebo-controlled study to evaluate the long term efficacy and safety of FF/VI Inhalation powder 100/25mcg QD, FF Inhalation powder 100mcg QD and VI Inhalation powder 25mcg QD when administered via the Novel Dry Powder Inhaler. Once daily dosing will occur in the morning (with the exception of the first treatment visit).

The target enrolment is approximately 16,000 randomized subjects at approximately 1600 study centers globally. Based on current assumptions of the event rate, the total duration of subject participation will be approximately between 15 and 44 months, consisting of a 4-10 day run-in period, variable treatment period and 1-week follow-up period.

Section 2.3 Other Endpoints

Original text:

- To evaluate the following treatment comparisons on all primary, secondary, other and exploratory endpoints:

  FF/VI compared with FF

  FF/VI compared with VI

  FF compared with placebo

  VI compared with placebo
- To evaluate the effect of FF/VI compared with placebo on the rate of moderate/severe COPD exacerbations
- To evaluate the effect of FF/VI compared with placebo on COPD-related mortality
- To evaluate the effect of FF/VI compared with placebo on arterial stiffness in a subset of subjects
- To evaluate the effect of FF/VI compared with placebo on health-related quality of life measured with the SGRQ-C in a subset of subjects
- To evaluate quality-adjusted life years (QALYs) by treatment group using health status data collected from EuroQol Questionnaire (EQ-5D) in a subset of subjects
- To evaluate the impact of FF/VI compared with placebo on healthcare resource utilisation (measured by number of days hospitalized for COPD)

Amended text:

- To evaluate the following treatment comparisons on all primary, secondary, other and exploratory endpoints:

  FF/VI compared with FF

FF/VI compared with VI

FF compared with placebo

VI compared with placebo

- To evaluate the effect of FF/VI compared with placebo on the rate of moderate/severe COPD exacerbations
- To evaluate the effect of FF/VI compared with placebo on COPD-related mortality
- To evaluate the effect of FF/VI compared with placebo on arterial stiffness in a subset of subjects
- To evaluate the effect of FF/VI compared with placebo on health-related quality of life measured with the SGRQ-C in a subset of subjects
- To evaluate quality-adjusted life years (QALYs) by treatment group using health status data collected from EuroQol Questionnaire (EQ-5D) in a subset of subjects
- To evaluate the impact of FF/VI compared with placebo on healthcare resource utilisation (measured by number of days hospitalized for COPD)
- To evaluate the impact of FF/VI compared with placebo on the number of cardiovascular procedures (ie angioplasty or revascularization)
- To evaluate the effect of FF/VI compared with placebo on change from baseline in FEV_1
- To evaluate the effect of FF/VI compared with placebo on change from baseline in FVC

Section 2.4 Exploratory Objectives

Original text:

- To evaluate the effect of FF/VI compared with placebo on COPD health status in a subset of subjects using the COPD Assessment Tool (CAT)
- To examine the molecular profiles of blood samples to identify factors that may influence biological and clinical responses to FF/VI compared with placebo and/or associated with the development or progression of COPD or medically related conditions

Amended text:

- To evaluate the effect of FF/VI compared with placebo on COPD health status in a subset of subjects using the COPD Assessment Tool (CAT)
- To examine the molecular profiles of blood samples to identify factors that may influence biological and clinical responses to FF/VI compared with placebo and/or associated with the development or progression of COPD or medically related conditions in a subset of subjects

Section 3.1 Study Design

Original text:

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 randomized, double-blind, parallel-group, multi-center study evaluating FF/VI 100/25mcg, each component individually, and placebo. The target enrolment is approximately 16,000 randomized subjects at approximately 1100 study centers globally. Based on current assumptions of the event rate, the total duration of subject participation will be approximately between 15 and 44 months, consisting of a 4-10 day run-in period, variable treatment period, and 1-week follow-up period.

Amended text:

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 randomized, double-blind, parallel-group, multi-center study evaluating FF/VI 100/25mcg, each component individually, and placebo. The target enrolment is approximately 16,000 randomized subjects at approximately 1600 study centers globally. Based on current assumptions of the event rate, the total duration of subject participation will be approximately between 15 and 44 months, consisting of a 4-10 day run-in period, variable treatment period, and 1-week follow-up period

Section 4.1 Number of Subjects

Original text:

Approximately 16,000 male and female outpatient subjects will be randomized. All randomized subjects are considered evaluable. Approximately 1,100 centers in multiple countries will participate in the study.

Amended text:

Approximately 16,000 male and female outpatient subjects will be randomized. All randomized subjects are considered evaluable. Approximately 1,600 centers in multiple countries will participate in the study.

Section 4.2 Inclusion Criteria #8

Original text:

Cardiovascular disease:

For patients >= 40 years of age: any one of the following:

Established (i.e. by clinical signs or imaging studies) coronary artery disease (CAD)
Established (i.e. by clinical signs or imaging studies) peripheral vascular disease (PVD)
Previous stroke
Previous MI
Diabetes mellitus with target organ disease

OR

For patients >=60 years of age: any 2 of the following:

Being treated for hypercholesterolemia
Being treated for hypertension
Being treated for diabetes mellitus
Being treated for peripheral vascular disease

Amended text:

Cardiovascular disease:

For patients >= 40 years of age: any one of the following:

Established (i.e. by clinical signs or imaging studies) coronary artery disease (CAD)
Established (i.e. by clinical signs or imaging studies) peripheral arterial disease (PAD)
Previous stroke
Previous MI
Diabetes mellitus with target organ disease

OR

For patients >=60 years of age: any 2 of the following:

Being treated for hypercholesterolemia
Being treated for hypertension
Being treated for diabetes mellitus
Being treated for peripheral arterial disease

Section 4.3 Exclusion Criteria #15

Original text:

Medication	No use within the following time intervals prior to Screening or thereafter at

	any time during the study (unless otherwise specified)
Inhaled Long acting beta-agonists (LABA)	48 hours
ICS/LABA combination products	48 hours
Inhaled corticosteroids	48 hours
Tiotropium	1 week*
Systemic, Oral, parenteral, intra-articular corticosteroids	30 days (oral and systemic corticosteroids may be used to treat COPD exacerbations during the study)
Cytochrome P450 3A4 strong inhibitors including but not limited to antiretrovirals (protease inhibitors) (e.g.Indinavir, Nelfinavir, Ritonavir, Saquinavir); Imidazole and Triazole anti-fungals (e.g. Ketaconazole, Itraconazole); Clarithromycin, Telithromycin, Amiodarone, and Nefazodone	6 weeks Grapefruit is allowed up to Visit 1, then limited to no more than one glass of grapefruit juice (250 mL/ 8 ounces) or one grapefruit per day
Any other investigational drug	30 days or 5 half lives whichever is longer.

* See Section 5.6.2 for information regarding Tiotropium use during the study

Amended text (new note added under table):

Medication	No use within the following time intervals prior to Screening or thereafter at any time during the study (unless otherwise specified)
Inhaled Long acting beta-agonists (LABA)	48 hours
ICS/LABA combination products	48 hours
Inhaled corticosteroids	48 hours
Tiotropium	1 week*
Systemic, Oral, parenteral, intra-articular corticosteroids	30 days (oral and systemic corticosteroids may be used to treat COPD exacerbations during the study)
Cytochrome P450 3A4 strong inhibitors including but not limited to antiretrovirals (protease inhibitors) (e.g.Indinavir, Nelfinavir, Ritonavir, Saquinavir); Imidazole and Triazole anti-fungals (e.g. Ketaconazole, Itraconazole); Clarithromycin, Telithromycin, and Nefazodone	6 weeks Grapefruit is allowed up to Visit 1, then limited to no more than one glass of grapefruit juice (250 mL/ 8 ounces) or one grapefruit per day
Any other investigational drug	30 days or 5 half lives whichever is longer.

* See Section 5.6.2 for information regarding Tiotropium use during the study

Note regarding appropriate patient selection:

Potential subjects should not be withdrawn from medications necessary for their disease management solely for the purpose of enrolling in this study. Patients who are currently controlled on short acting medications or who can adequately be managed with short-acting inhaled medications and oral therapies (including theophylline or roflumilast) based on physician opinion are the appropriate patients for this study.

Section 4.4 Randomization Criteria

Original text:

Any subject who experiences a moderate/severe COPD exacerbation (a COPD exacerbation requiring treatment with antibiotics and/or systemic corticosteroids or requiring hospitalization) during the run-in period must not be randomized.

Amended text:

Any subject who experiences a moderate/severe COPD exacerbation (a COPD exacerbation requiring treatment with antibiotics and/or systemic corticosteroids or requiring hospitalization) or pneumonia during the run-in period must not be randomized.

Section 4.5.1 Withdrawal from Investigational Product

Original text:

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

- **Liver Chemistry:** Meets any of the following Liver chemistry stopping criteria as defined in Section 6.3.1.

Amended text:

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

- **Liver Chemistry:** Meets any of the following Liver chemistry stopping criteria as defined in Section 6.3.1.

Section 4.5.2 Screen Failures

Original text:

A subject who has at least one study procedure performed in addition to signing a consent form, and is assigned a subject identifier but is NOT randomized is classified as a screen failure. The IVRS system used to track study enrolment will be notified and the following information on subjects who are not randomized must be collected in the eCRF:

- Date screened
- Subject identification number
- Demography (race, age, and gender)
- Reason subject failed Screening
- Any Serious Adverse Events (SAEs) related to study procedures or GlaxoSmithKline (GSK) concomitant medications that occurred after signing the informed consent.

A subject who is classified as a screen failure cannot be re-screened.

Amended text:

A subject who has at least one study procedure performed in addition to signing a consent form, and is assigned a subject identifier but is NOT randomized is classified as a screen failure. The IVRS system used to track study enrolment will be notified and the following information on subjects who are not randomized must be collected in the eCRF:

- Date screened
- Subject identification number
- Demography (race, age, and gender)
- Reason subject failed Screening
- Any Serious Adverse Events (SAEs) related to study procedures or GlaxoSmithKline (GSK) concomitant medications that occurred after signing the informed consent. Any fatal event should also be recorded.

A subject who is classified as a screen failure cannot be re-screened.

Section 4.5.3 Run-in failures

Original text:

A subject who has had all screening procedures performed (in addition to signing a consent form), is assigned a subject identifier, and is dispensed rescue albuterol/salbutamol, but is NOT randomized is classified as a Run-in failure. The IVRS system will be notified and the following information on subjects who fail Run-in must be collected in the eCRF:

- Date screened
- Subject identification number
- Demography (race, age, and gender)
- Reason subject failed Run-in
- Any Serious Adverse Events (SAEs) related to study procedures or GlaxoSmithKline (GSK) concomitant medications that occurred after signing the informed consent.

Subjects who experience a COPD exacerbation and/or pneumonia during the Run-in period will be excluded for participating in the study.

A subject who is classified as a Run-in failure cannot be re-screened.

Amended text:

A subject who has had all screening procedures performed (in addition to signing a consent form), is assigned a subject identifier, and is dispensed rescue albuterol/salbutamol, but is NOT randomized is classified as a Run-in failure. The IVRS system will be notified and the following information on subjects who fail Run-in must be collected in the eCRF:

- Date screened
- Subject identification number
- Demography (race, age, and gender)
- Reason subject failed Run-in
- Any Serious Adverse Events (SAEs) related to study procedures or GlaxoSmithKline (GSK) concomitant medications that occurred after signing the informed consent. Any fatal event should also be recorded.

Subjects who experience a COPD exacerbation and/or pneumonia during the Run-in period will be excluded for participating in the study.

A subject who is classified as a Run-in failure cannot be re-screened.

Section 5.6.1 Permitted Medications and Non-Drug Therapies

Original text:

The following medications are permitted during the study:

- Study-supplied albuterol/salbutamol (MDI or nebules)
- Ipratropium/Combivent
- Theophyllines and roflumilast
- Oral corticosteroids and antibiotics for the short term treatment of COPD exacerbations
- Mucolytics
- Oxygen
- Antihistamines and nasal decongestants
- OTC cough suppressants
- Intranasal cromolyns or nedocromil
- Intranasal, ophthalmic and topical corticosteroids
- Antibiotics for short term treatment of acute non-respiratory tract infections and for the treatment of pneumonia and COPD exacerbations.
- Influenza and pneumonia vaccines

- Tricyclic antidepressants and Monamine oxidase inhibitors (MOAs). (Administer with caution as they may potentiate the effects of beta-agonists on the vascular system.)
- Diuretics. (Caution is advised in the coadminstration of beta-agonists with nonpotassium –sparing diuretics).
- Smoking cessation medications
- Cardioselective Beta-blockers and ophthalmic beta-blockers. (Administer with caution as they may block bronchodilatory effects of beta-agonists and produce severe bronchospasm.)
- All medications for other disorders as long as the dose remains constant wherever possible.

Amended text:

The following medications are permitted during the study:

- Study-supplied albuterol/salbutamol (MDI or nebules)
- Ipratropium/Combivent
- Theophyllines and roflumilast
- Oral corticosteroids and antibiotics for the short term treatment of COPD exacerbations
- Mucolytics
- Oxygen
- Antihistamines and nasal decongestants
- OTC cough suppressants
- Intranasal cromolyns or nedocromil
- Intranasal, ophthalmic and topical corticosteroids
- Antibiotics for short term treatment of acute non-respiratory tract infections and for the treatment of pneumonia and COPD exacerbations.
- Influenza and pneumonia vaccines
- Tricyclic antidepressants and Monamine oxidase inhibitors (MOAs). (Administer with caution as they may potentiate the effects of beta-agonists on the vascular system.)
- Diuretics. (Caution is advised in the coadminstration of beta-agonists with nonpotassium –sparing diuretics).
- Smoking cessation medications
- Cardioselective Beta-blockers and ophthalmic beta-blockers. (Administer with caution as they may block bronchodilatory effects of beta-agonists and produce

severe bronchospasm.) Noncardioselective beta-blockers (eg carvedilol) may also be used if deemed appropriate by the PI.

- All medications for other disorders as long as the dose remains constant wherever possible.

Section 6 Study Assessments and Procedures

Original text:

The Time and Events Table is provided in Table 1. All study assessments should be conducted by the investigator or his/her qualified designee unless otherwise specified in the protocol or SPM. Please refer to the SPM for a suggested order of assessments.

Subjects will self-administer their first dose of double-blind study medication in the clinic at the end of Visit 2.

Table 1 Time and Events Table

Pre-Randomization Assessments:

Procedures	Screening	Baseline Visit[1]
Written Informed Consent	X	
Demography & Medical History	X	
COPD & Exacerbation History	X	
Inclusion/Exclusion Criteria	X	
Concomitant Medication Assessment	X	X
Smoking Status/history	X	X
Smoking Cessation Counselling		X
Randomization Criteria		X
Lung Function Questionnaire (LFQ)[4]	X	
Vital signs	X	X
Physical Exam	X	
Oropharyngeal Exam		X
Blood Sample (10ml)		X
Screening Spirometry (including reversibility testing)	X	
Spirometry		X
Modified Medical Research Council Questionnaire (MMRC)	X	
Subject Questionnaires[2]		X
Adverse Events	X	X
SphygmoCor Assessments[3]		X
Dispense Rescue Albuterol/Salbutamol	X	
Dispense diary card	X	X
Register Visit in IVRS	X	X
Pregnancy test	X	
Dispense IP		X

1. All Baseline assessments must be obtained prior to randomization
2. SGRQ-C, CAT and EQ-5D in a subset of ~4,000 subjects primarily in EU, Canada and Australia
3. In a subset of ~1400 subjects
4. Optional (for use as screening tool)

Post-Randomization Assessments:

Procedures					End of study treatment	Follow-up[3]
						Phone Contact
	Month 1	Month 3 (±14)[1] PLUS every 3 months	Month 6 (±14) PLUS every 6 months	Month 12 (±14) PLUS every 12 months		7±2 days after last dose of study drug
Concomitant Medication Assessment		X			X	X
Spirometry (FEV_1)		X			X	
Exacerbation Assessment		X			X	
Survival Assessment		X			X	
Subject Questionnaires[4]		X[4]	X[4]		X	
Adverse Event Assessment[2]		X			X	X
Smoking Status		X			X	
Oropharyngeal exam		X			X	
Vital signs		X			X	
Blood Sample		X[5]				
Pregnancy Test			X		X	
SphygmoCor Assessments[2]				X	X	
Dispense diary Card		X				
Dispense Investigational Product.	X	X				
Assess Investigational Product Compliance		X			X	
Collect Investigational Product	X	X			X	
Dispense Rescue Albuterol/Salbutamol		X				
Collect/check Rescue Albuterol/Salbutamol		X			X	
Register Visit in IVRS		X			X	X

1. Visits will continue at the specified intervals until the end of the study which will be determined by reaching approximately 1000 deaths.
2. In a subset of ~1400 subjects- to be done annually, details in SPM
3. The Follow-up Visit is scheduled to occur 7 ± 2 days after the last dose of IP.
4. SGRQ-C, CAT and EQ-5D in a subset of ~4,000 subjects - these will be done during the first year at 3 months and 6 months and then every 6 months for the duration of the treatment period
5. Only at initial 3 month Visit

Amended text:

The Time and Events Table is provided in Table 1. All study assessments should be conducted by the investigator or his/her qualified designee unless otherwise specified in the protocol or SPM. Please refer to the SPM for a suggested order of assessments.

Subjects will self-administer their first dose of double-blind study medication in the clinic at the end of Visit 2.

Table 1 Time and Events Table

Pre-Randomization Assessments:

Procedures	Screening	Baseline Visit[1]
Written Informed Consent	X	
Demography & Medical History	X	
COPD & Exacerbation History	X	
Inclusion/Exclusion Criteria	X	
Concomitant Medication Assessment	X	X
Smoking Status/history	X	X
Smoking Cessation Counselling		X
Randomization Criteria		X
Lung Function Questionnaire (LFQ)[4]	X[4]	
Vital signs	X	X
Physical Exam	X	
Oropharyngeal Exam		X
Blood Sample (10ml)[5]		X[5]
Spirometry –pre and post albuterol/salbutamol	X	
Spirometry - post albuterol/salbutamol		X
Modified Medical Research Council Questionnaire (MMRC)	X	
Subject Questionnaires[2]		X[2]
Adverse Events	X	X
SphygmoCor Assessments[3]		X[3]
Dispense Rescue Albuterol/Salbutamol	X	
Dispense diary card	X	X
Register Visit in IVRS	X	X
Pregnancy test	X	
Dispense IP		X

1. All Baseline assessments must be obtained prior to randomization
2. SGRQ-C, CAT and EQ-5D in a subset of ~4,000 subjects primarily in EU, Canada and Australia
3. In a subset of ~1400 subjects
4. Optional (for use as screening tool)
5. Subjects in US only , details in SPM

Post-Randomization Assessments:

Procedures					End of study treatment	Follow-up[3]
						Phone Contact
	Month 1	Month 3 (±14)[1] PLUS every 3 months	Month 6 (±14) PLUS every 6 months	Month 12 (±14) PLUS every 12 months		7±2 days after last dose of study drug
Concomitant Medication Assessment		X			X	X
Spirometry – post albuterol/salbutamol (FEV1 and FVC)		X			X	
Exacerbation Assessment		X			X	
Survival Assessment		X			X	
Subject Questionnaires[4]		X[4]	X[4]		X[4]	
Adverse Event Assessment		X			X	X
Smoking Status		X			X	
Oropharyngeal exam		X			X	
Vital signs		X			X	
Blood Sample [5]		X[5]				
Pregnancy Test			X		X	
SphygmoCor Assessments[2]				X[2]	X[2]	
Dispense diary Card		X				
Dispense Investigational Product.	X	X				
Assess Investigational Product Compliance		X			X	
Collect Investigational Product	X	X			X	
Dispense Rescue Albuterol/Salbutamol	X	X				
Collect/check Rescue Albuterol/Salbutamol	X	X			X	
Register Visit in IVRS		X			X	X

1. Visits will continue at the specified intervals until the end of the study which will be determined by reaching approximately 1000 deaths.
2. In a subset of ~1400 subjects- to be done annually, details in SPM
3. The Follow-up Visit is scheduled to occur 7 ± 2 days after the last dose of IP.
4. SGRQ-C, CAT and EQ-5D in a subset of ~4,000 subjects - these will be done during the first year at 3 months and 6 months and then every 6 months for the duration of the treatment period
5. Only at initial 3 month Visit - subjects in US only

Section 6.1 Critical Baseline Assessments

Original text:

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

Amended text:

No study related procedures may be performed until the informed consent form document has been reviewed with and signed by the subject. A pre-screening visit may be required in order to administer and discuss the informed consent before any changes are made to the subject's current medication regimen. Washout of any prohibited medication, which is done only if deemed appropriate by the Investigator in discussion with the subject, **MUST NOT OCCUR prior to the informed consent being discussed and signed**. The informed consent may be administered and discussed at the screening visit if the subject does not take or has not taken any protocol excluded medications.

Section 6.2.6.1 Spirometry

Original text:

A secondary endpoint is rate of decline in FEV1. In order to assess this, spirometry will be performed at every clinic visit and will be performed using equipment that meets or exceeds the minimum performance recommendations of the ATS [Sin, 2003]. All sites will use their own equipment. At least 3 valid spirometry efforts should be attempted (with no more than 8) using the ATS guidelines [Sin, 2003]. Spirometry will be performed at screening (Visit 1), randomization (Visit 2), and at each 3-monthly treatment visit. A post-albuterol/salbutamol FEV_1 ≤70% of predicted normal and an FEV_1/FVC ratio of ≤0.70 are required at Visit 1 (Screening).Values will be calculated using NHANES III reference equations [Hankinson, 1999; Hankinson, 2010].

Amended text:

A secondary endpoint is rate of decline in FEV1. In order to assess this, spirometry will be performed at every clinic visit and will be performed using equipment that meets or exceeds the minimum performance recommendations of the ATS [Sin, 2003]. All sites will use their own equipment. At least 3 valid spirometry efforts should be attempted (with no more than 8) using the ATS guidelines [Sin, 2003]. Spirometry will be performed at screening (Visit 1), randomization (Visit 2), and at each 3-monthly treatment visit. A post-albuterol/salbutamol FEV_1 ≥50 and ≤70% of predicted normal and an FEV_1/FVC ratio of ≤0.70 are required at Visit 1 (Screening).Values will be calculated using NHANES III reference equations [Hankinson, 1999; Hankinson, 2010].

Section 6.2.3 Other Efficacy Endpoints

Original text:

- Annual rate of moderate/severe COPD exacerbations
- Time to COPD-related death (based on CEC adjudication)
- QoL using the St George's Respiratory Questionnaire-COPD.
- Health status using the EuroQol Questionnaire (EQ-5D)
- Health Care Resource Utilization
- PWV

Amended text:

- Annual rate of moderate/severe COPD exacerbations
- Time to COPD-related death (based on CEC adjudication)
- QoL using the St George's Respiratory Questionnaire-COPD.
- Health status using the EuroQol Questionnaire (EQ-5D)
- Health Care Resource Utilization
- PWV
- Cardiovascular procedures
- Change from baseline in FEV_1
- Change from baseline in FVC

Section 6.3.1 Liver Chemistry stopping and follow-up criteria

Original text:

There are no regular laboratory tests required by this protocol. If, however, while a subject is receiving Investigational Product, lab tests are conducted, any abnormal liver chemistry findings must treated as outlined below:

Amended text:

With the exception of US sites which are participating in the biomarker and/or genetics assessments, there are no regular laboratory tests required by this protocol. If, however, while a subject is receiving Investigational Product, lab tests are conducted, any abnormal liver chemistry findings must treated as outlined below:

Section 6.3.4 Disease-Related Events and/or Disease-Related Outcomes Not Subject to Expedited Reporting

Original text:

The following events are considered secondary efficacy endpoints for this study and will be reported as SAEs but will not be subject to expedited reporting regardless of the "expectedness" or "relatedness" of the event:

- MI
- Stroke
- Unstable angina
- TIA

Additionally, any laboratory or ECG abnormalities associated with the diagnosis of individual components of these efficacy endpoints will not be subject to expedited reporting.

The following events are expected in this population and will be reported as SAEs but will not be subject to expedited reporting regardless of the "expectedness" or "relatedness" of the event:

- COPD exacerbation
- Pneumonia

Additionally, any laboratory or Chest X-ray abnormalities associated with the diagnosis of these events will not be subject to expedited reporting.

Amended text:

The following events are considered secondary efficacy endpoints for this study and will be reported as AEs or SAEs (based on criteria in Section 6.3.2) but will not be subject to expedited reporting regardless of the "expectedness" or "relatedness" of the event:

- MI
- Stroke
- Unstable angina
- TIA

Additionally, any laboratory or ECG abnormalities associated with the diagnosis of individual components of these efficacy endpoints will not be subject to expedited reporting.

The following events are expected in this population and will be reported as AEs or SAEs but will not be subject to expedited reporting regardless of the "expectedness" or "relatedness" of the event:

- COPD exacerbation
- Pneumonia

Additionally, any laboratory or Chest X-ray abnormalities associated with the diagnosis of these events will not be subject to expedited reporting.

Section 6.5 Biomarkers

Original text:

Serum and plasma samples will be collected at the US sites at V2 (pre-dose) and V3 (pre-dose). These will be used to analyze 4 known inflammatory markers (hsCRP, PARC, fibrinogen and IL-6) and also for measuring a CBC and Chem 7 panel for use in predictive modelling.

Amended text:

Serum and plasma samples will be collected at the US sites at V2 (pre-dose at randomization visit) and V3 (pre-dose at the 3 month visit). These will be used to analyze 4 known inflammatory markers (hsCRP, PARC, fibrinogen and IL-6) and also for measuring a CBC and Chem 7 panel for use in predictive modelling.

Section 8.3.5.1.2 Secondary Endpoints

Original text:

Rate of Decline in Lung Function (FEV_1)

The effect of treatment on rate of decline of absolute trough FEV_1 recorded during the treatment period will be analysed using a random coefficients model, including terms for treatment, time on treatment in years, treatment by time interaction, and appropriate pre-defined covariates.

Amended text:

Rate of Decline in Lung Function (FEV_1)

The effect of treatment on rate of decline of post-bronchodilator FEV_1 recorded during the treatment period will be analysed using a random coefficients model, including terms for treatment, time on treatment in years, treatment by time interaction, and appropriate pre-defined covariates.

References

2 additional references added:

Machin D, Campbell, MJ, Fayers PM, Pinol APY. Sample size tables for clinical studies second ed. Blackwell 1997; Chapter 9.

Schoenfeld DA (1981). The asymptotic properties of comparative tests for comparing survival distributions. *Biometrika*, 68, 316-9.

11.4.4. Protocol Amendment 04

This protocol amendment applies to sites in Korea only.

Rationale

This amendment is being implemented in Korea to revise the statement about use noncardioselective beta-blockers introduced in Amendment 03.

5.6.1 Permitted Medications and Non-Drug Therapies

The following medications are permitted during the study:

- Cardioselective Beta-blockers and ophthalmic beta-blockers. (Administer with caution as they may block bronchodilatory effects of beta-agonists and produce severe bronchospasm.) Noncardioselective beta-blockers (eg carvedilol) may also be used if deemed appropriate by the PI.

For sites in Korea: The use of noncardioselective beta-blockers is not permitted.

11.4.5. Protocol Amendment 05

This protocol amendment applies to all study centers participating in HZC113782.

Rationale

This amendment is being implemented to revise the Biomarkers to be included as an other endpoint, to add time to first COPD exacerbation and delete time to COPD related death from other endpoint, and update other treatment comparisons of interest.

Title

Original text:

A Clinical Outcomes Study to compare the effect of Fluticasone Furoate/Vilanterol Inhalation Powder 100/25mcg with placebo on Survival in Subjects with moderate Chronic Obstructive Pulmonary Disease (COPD) and a history of or at risk for cardiovascular disease.

Amended text:

A Clinical Outcomes Study to compare the effect of Fluticasone Furoate/Vilanterol Inhalation Powder 100/25mcg with placebo on Survival in Subjects with moderate Chronic Obstructive Pulmonary Disease (COPD) and a history of or at increased risk for cardiovascular disease.

Objectives

Original text:

Other objectives are:

- To evaluate the effect of FF/VI compared with placebo on the rate of moderate/severe COPD exacerbations

Amended text:

Other objectives are:

- To evaluate the effect of FF/VI compared with placebo on moderate/severe COPD exacerbations

Study Endpoints/Assessments

Original text:

Other Efficacy Endpoints

Annual rate of moderate/severe COPD exacerbations

Time to COPD related death (based on CEC adjudication)

Amended text:

Other Efficacy Endpoints

Annual rate of and time to moderate/severe COPD exacerbations

COPD related death (based on CEC adjudication)

Section 2.3 Other Objectives

Original text:

Other objectives are:

- To evaluate the effect of FF/VI compared with placebo on the rate of moderate/severe COPD exacerbations

Amended text:

Other objectives are:

- To evaluate the effect of FF/VI compared with placebo on moderate/severe COPD exacerbations

Section 6.2.3 Other Efficacy Endpoints

Original text:

Annual rate of moderate/severe COPD exacerbations

Time to COPD related death (based on CEC adjudication)

Amended text:

Annual rate of and time to moderate/severe COPD exacerbations

COPD related death (based on CEC adjudication)

Section 6.5 Biomarker(s)

Original text:

Serum and plasma samples will be collected at the US sites at V2 (pre-dose at randomization visit) and V3 (pre-dose at the 3 month visit). These will be used to analyze 4 known inflammatory markers (hsCRP, PARC, fibrinogen and IL-6) and also for measuring a CBC and Chem 7 panel for use in predictive modelling.

Revised text:

Serum and plasma samples will be collected at the US sites at V2 (pre-dose at randomization visit) and V3 (pre-dose at the 3 month visit). These will be used to

analyze known inflammatory markers (e.g., hsCRP and fibrinogen) and also for measuring a CBC and Chem 7 panel for use in predictive modelling.

Section 8.3.3.2 Other Comparisons of Interest

Original text:

There will be interest in the comparison of other treatment groups for all endpoints as follows:

- VI vs placebo
- FF vs placebo
- FF/VI vs VI
- FF/VI vs FF

These comparisons are for interest only, in order to help understand the contribution of the component to the overall treatment effect.

Revised text:

If the primary comparison of FF/VI vs placebo is significant at the 5% level for an endpoint, then inferences for the following treatment comparisons will be carried out for that endpoint:

- VI vs placebo
- FF vs placebo
- FF/VI vs VI
- FF/VI vs FF

These comparisons are to help understand the contribution of the components to the overall treatment effect of the primary FF/VI vs placebo comparison, so no multiple comparison corrections will be considered for these four follow-up comparisons.

Division: World Wide Development
Retention Category: GRS019
Information Type: Reporting and Analysis Plan

Title:	Reporting and Analysis Plan for HZC113782: A Clinical Outcomes Study to compare the effect of Fluticasone Furoate/Vilanterol Inhalation Powder 100/25mcg with placebo on Survival in Subjects with moderate Chronic Obstructive Pulmonary Disease (COPD) and a history of or at increased risk for cardiovascular disease

Compound Number: GW685698+GW642444 (GSK2285997)

Effective Date: 05-JUN-2015

RAP Amendment Number: 01

Description: This document describes the reporting and analysis planned for study HZC113782 for the purpose of the Clinical Study Report.

The study is designed to evaluate the effect of Fluticasone Furoate /Vilanterol Inhalation Powder 100/25mcg versus placebo on survival in subjects with moderate COPD and a history of, or at increased risk for cardiovascular disease. The individual components will be included to assess the contribution of each within the combination. The study is an event based design and will conclude when there have been a total of approximately 1000 primary outcome events of death. This is a randomised, double-blind, parallel-group, multi-centre study. Subjects who meet the eligibility criteria will enter the treatment period and continue treatment until the required number of events have occurred.

Familiarity with the study protocol is assumed.

Subject: COPD, survival, cardiovascular disease, Fluticasone Furoate, Vilanterol, Novel Dry Powder Inhaler

Revision Chronology:

2014N190543_00	29-JAN-2014	Original
2014N190543_01	05-JUN-2015	Amendment No. 01: Multiple minor amendments.

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ABBREVIATIONS

ACM	All Cause Mortality
AE	Adverse Event
ANCOVA	Analysis of Covariance
AS	Arterial Stiffness
ASE	All Subjects Enrolled
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CAT	COPD Assessment Test
CEC	Clinical Endpoint Committee
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CSR	Clinical Study Report
CV	Cardiovascular
CVA	Cerebrovascular accident
DBF	Database Freeze
DBR	Database Release
DM	Diabetes Mellitus
eCRF	Electronic Case Report Form
EQ-5D-3L	EuroQol 5D 3 Level Version
EU	European Union
FDA	Food and Drug Administration
FF	Fluticasone Furoate
FEV1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GSK	GlaxoSmithKline
HO	Health Outcomes
ICD	Implantable Cardioverter Defibrillator
ICU	Intensive Care Unit
ICS	Inhaled Corticosteroid
IDMC	Independent Data Monitoring Committee
IMRS	Intermountain Risk Score
IP	Investigational Product
ITT	Intent-to-Treat - Efficacy
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
L	Litre
LABA	long-acting beta-2-agonist
LAMA	long-acting muscarinic antagonist
Log	logarithm
LRTI	Lower Respiratory Tract Infection
Max.	Maximum
m/sec	Metres per second
Mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocordial Infarction

Min.	Minimum
mL	Millilitre
mMRC score	Modified Medical Council Research score
MMRM	Mixed Models Repeated Measures
N	Number of subjects in the treatment group
N	Number of subjects with non-missing values
NDPI	Novel Dry Powder Inhaler
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
PH	Proportional Hazards
PWV	Pulse Wave Velocity
QALY	Quality-Adjusted Life Years
QD	Once Daily
RAP	Reporting and Analysis Plan
RMC	Respiratory Medication Class
RTSM	Parexel Randomisation and Trial Supply Management System
SAE	Serious Adverse Event
SD	Standard deviation
SE	Standard error
SPM	Study Procedures Manual
Std Err	Standard error
SOC	System Organ Class
SDAC	Statistical Data Analysis Centre
SGRQ-C	St. George's Respiratory Questionnaire – COPD Questionnaire
TIA	Transient Ischemic event
UA	Unstable Angina
VAS	Visual Analogue Scale
VI	Vilanterol

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SAS
S-PLUS
RTSM

1. INTRODUCTION

This Reporting and Analysis Plan (RAP) describes all planned analyses that will be conducted and reported in the Clinical Study Report (CSR) at the end of study HZC113782. The purpose is to evaluate the efficacy and safety of fluticasone furoate (FF)/vilanterol (VI) inhalation powder 100/25mcg QD, FF inhalation powder 100 mcg QD and VI inhalation powder 25 mcg QD versus placebo. This RAP is separate from the RAP already generated for the regular Safety review of the Independent Data Monitoring Committee (IDMC) [GlaxoSmithKline Document Number 2014N190343_00] and the RAP generated for the Interim Analysis by the IDMC [GlaxoSmithKline Document Number 2014N191731_00].

The RAP is based on Section 8 (Data Analysis and Statistical Considerations) of study protocol HZC113782 effective 07-MAY-2015 [GlaxoSmithKline Document Number RM2009/00666/06, Amendment 5. It is intended for use by the Respiratory Statistics and Respiratory Programming Departments of Quantitative Sciences.
All programming will be performed in a HARP environment using SAS Version 9 or a later release and S-Plus Version 8.1 or later release.

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

2.1. Study Objective(s)

Primary

The primary objective of this study is to prospectively evaluate the effect of Fluticasone Furoate (FF)/Vilanterol (VI) inhalation powder 100/25mcg QD compared with placebo on survival in subjects with moderate COPD ($\geq$50 and $\leq$70 % predicted FEV_1) and a history of, or at increased risk for developing, cardiovascular disease.

Secondary

Secondary objectives are:

- To evaluate the effect of FF/VI compared with placebo on the rate of decline in FEV_1
- To evaluate the effect of FF/VI compared with placebo on a cardiovascular composite endpoint comprised of on-treatment CV death, myocardial infarction, stroke, unstable angina and TIA

Other objectives are:

- To evaluate the following treatment comparisons on all primary, secondary, other and exploratory endpoints:

  FF/VI compared with FF

  FF/VI compared with VI

  FF compared with placebo

VI compared with placebo

- To evaluate the effect of FF/VI compared with placebo on moderate/severe COPD exacerbations
- To evaluate the effect of FF/VI compared with placebo on COPD related mortality
- To evaluate the effect of FF/VI compared with placebo on arterial stiffness in a subset of subjects
- To evaluate the effect of FF/VI compared with placebo on health-related quality of life measured with the SGRQ-C in a subset of subjects
- To evaluate quality-adjusted life years (QALYs) by treatment group using health status data collected from EuroQol Questionnaire (EQ-5D-3L) in a subset of subjects
- To evaluate the impact of FF/VI compared with placebo on healthcare resource utilisation (measured by number of days hospitalised for COPD)
- To evaluate the impact of FF/VI compared with placebo on the number of cardiovascular procedures (ie angioplasty or revascularisation)
- To evaluate the effect of FF/VI compared with placebo on change from baseline in FEV_1
- To evaluate the effect of FF/VI compared with placebo on change from baseline in FVC

Exploratory objectives are:

- To evaluate the effect of FF/VI compared with placebo on COPD health status in a subset of subjects using the COPD Assessment Tool (CAT)
- To examine the molecular profiles of blood samples to identify factors that may influence biological and clinical responses to FF/VI compared with placebo and/or associated with the development or progression of COPD or medically related conditions in a subset of subjects
- To investigate a composite index to predict mortality

2.2. Study Endpoint(s)

Efficacy

Primary Efficacy Endpoint

- Time to death from any cause

Secondary Efficacy Endpoints

- Rate of decline in FEV_1
- Time to CV event

Other Efficacy Endpoints

- Annual rate of and time to moderate/severe COPD exacerbations
- COPD related death (based on CEC adjudication)
- QoL using the St George's Respiratory Questionnaire-COPD.
- Health status using the EuroQol Questionnaire (EQ-5D-3L)
- Health Care Resource Utilization
- PWV
- Cardiovascular procedures
- Change from baseline in FEV_1
- Change from baseline in FVC

Exploratory Endpoints

- Health status using the CAT
- Biomarkers
- Clinical laboratory tests

Safety

- Incidence of adverse events
- Oropharyngeal examinations

2.3. Statistical Hypotheses

The primary endpoint is time to death from any cause, both on and off study treatment, for all subjects in the Intent-to-Treat-Efficacy Population. The comparisons of interest for the primary analysis are described in Section 7 (Treatment Comparisons). Inference will be restricted by the step-down multiplicity strategy also described in Section 8.4 (Multiple Comparisons and Multiplicity).

For the primary efficacy endpoint of time to death from any cause the primary analysis will test the following hypotheses:

- Null hypothesis: Hazard ratio for all cause mortality for FF/VI relative to placebo is equal to one. This is equivalent to a reduction in the risk of dying equal to zero, i.e. no difference in time to death between FF/VI and placebo.
- Alternative hypothesis: Hazard ratio for all cause mortality for FF/VI relative to placebo is not equal to one (i.e. two-sided test). This is equivalent to a reduction in the risk of dying not equal to zero, i.e. there is a difference in time to death between FF/VI and placebo.

The study is designed to show superiority of treatment with FF/VI relative to placebo (i.e. hazard ratio less than one, or equivalently, reduction in risk greater than zero) on top of a background of standard care.

For each test on each of the other efficacy endpoints, the null hypothesis is that there is no difference between treatment groups and the alternative hypothesis is there is a difference between treatment groups.

3. STUDY DESIGN

This is a randomised, double-blind, parallel-group, multi-centre study evaluating FF/VI 100/25mcg, each component individually, and placebo. The target enrolment is approximately 16,000 randomised subjects at approximately 1600 study centres globally. Based on current assumptions of the event rate, the total duration of subject participation will be approximately between 15 and 44 months, consisting of a 4-10 day run-in period, variable treatment period, and 1-week follow-up period.

Subjects will be randomised to treatment after a 4-10 day run-in period. Prior to run-in, subjects will discontinue use of previous COPD medications except for short-acting bronchodilators and theophyllines. Clinic visits will occur at screening, randomisation, 4 weeks and then every 12 weeks until the study has reached the required number of events. A safety follow-up phone contact will occur 1 week after completing either randomised treatment or an early withdrawal of investigational product.

Following the run-in period, eligible subjects will be randomised (1:1:1:1) to one of the following double-blind treatment groups. All treatments will be delivered via the Novel Dry Powder Inhaler (NDPI) once daily in the AM during the treatment period (with the possible exception of the randomisation visit):

- FF/VI 100mcg/25mcg QD
- FF 100mcg QD
- VI 25mcg QD
- placebo QD

Each NDPI will contain 30 doses of study medication. Subjects will be instructed to administer medication once daily in the morning for the duration of the treatment period. Each subject should be advised to adhere to this dosing regimen throughout the study. In addition, each subject will be instructed on the proper use of the NDPI. Subjects will self-administer their first dose of blinded study drug in the clinic at the end of Visit 2. There are no plans to provide the study drug for compassionate use following study completion.

Further details can be found in the protocol and the Study Procedures Manual (SPM).

The randomisation code was generated by GlaxoSmithKline (GSK) using RANDALL, a validated computerised system. The Parexel Randomisation and Trial Supply Management System (RTSM), an interactive voice/web recognition system

(IVRS/IWRS), was used by the investigator or designee to register the subject, randomise the subject and receive treatment assignment information.

A separate randomisation schedule was produced for each country. For those countries participating in the Arterial Stiffness sub-study two schedules were produced for each country, one for the sites participating, and one for the sites not participating. This was to help ensure balance of treatment groups within the sub-study.

The schedule of time and events is presented in Table 1.

Table 1 Time and Events Table

Pre-Randomisation Assessments:

Procedures	Screening	Baseline Visit[1]
Written Informed Consent	X	
Demography & Medical History	X	
COPD & Exacerbation History	X	
Inclusion/Exclusion Criteria	X	
Concomitant Medication Assessment	X	X
Smoking Status/history	X	X
Smoking Cessation Counselling		X
Randomisation Criteria		X
Lung Function Questionnaire (LFQ)[4]	X[4]	
Vital signs	X	X
Physical Exam	X	
Oropharyngeal Exam		X
Blood Sample (10ml)[5]		X[5]
Spirometry –pre and post albuterol/salbutamol	X	
Spirometry - post albuterol/salbutamol		X
Modified Medical Research Council Questionnaire (MMRC)	X	
Subject Questionnaires[2]		X[2]
Adverse Events	X	X
SphygmoCor Assessments[3]		X[3]
Dispense Rescue Albuterol/Salbutamol	X	
Dispense diary card	X	X
Register Visit in IVRS	X	X
Pregnancy test	X	
Dispense IP		X

1. All Baseline assessments must be obtained prior to randomisation
2. SGRQ-C, CAT and EQ-5D-3L in a subset of ~4,000 subjects primarily in EU, Canada and Australia
3. In a subset of ~1400 subjects
4. Optional (for use as screening tool)
5. Subjects in US only , details in SPM

Post-Randomisation Assessments:

Procedures					End of study treatment	Follow-up[3]
						Phone Contact
	Month 1	Month 3 (±14)[1] PLUS every 3 months	Month 6 (±14) PLUS every 6 months	Month 12 (±14) PLUS every 12 months		7±2 days after last dose of study drug
Concomitant Medication Assessment		X			X	X
Spirometry – post albuterol/salbutamol (FEV1 and FVC)		X			X	
Exacerbation Assessment		X			X	
Survival Assessment		X			X	
Subject Questionnaires[4]		X[4]	X[4]		X	
Adverse Event Assessment		X			X	X
Smoking Status		X			X	
Oropharyngeal exam		X			X	
Vital signs		X			X	
Blood Sample		X[5]				
Pregnancy Test			X		X	
SphygmoCor Assessments[2]				X[2]	X	
Dispense diary Card		X				
Dispense Investigational Product.	X	X				
Assess Investigational Product Compliance		X			X	
Collect Investigational Product	X	X			X	
Dispense Rescue Albuterol/Salbutamol	X	X				
Collect/check Rescue Albuterol/Salbutamol	X	X			X	
Register Visit in IVRS		X			X	X

1. Visits will continue at the specified intervals until the end of the study which will be determined by reaching approximately 1000 deaths.
2. In a subset of ~1400 subjects- to be done annually, details in SPM
3. The Follow-up Visit is scheduled to occur 7 ± 2 days after the last dose of IP.
4. SGRQ-C, CAT and EQ-5D-3L in a subset of ~4,000 subjects - these will be done during the first year at 3 months and 6 months and then every 6 months for the duration of the treatment period
5. Only at initial 3 month Visit – subjects in US only

4. PLANNED ANALYSES

4.1. Interim Analyses

One formal interim analysis of the time to death from any cause is planned in addition to the final analysis. It is intended that this analysis will be performed when approximately 50% of the total deaths have been observed. The analysis method for this will be the same as to be used in the final analysis i.e. Cox proportional hazards model. This analysis will be performed by an Independent Data Monitoring Committee (IDMC). Full details of this interim analysis are given in a separate RAP [GlaxoSmithKline Document Number 2014N191731_00].

In addition there will be periodic safety reviews where the IDMC will review unblinded serious adverse events (SAEs). Full details of this interim analysis are given in a separate RAP [GlaxoSmithKline Document Number 2014N190343_00].

To preserve the integrity of the study, the results of the interim analysis of efficacy and each interim safety review will only be known to the IDMC. In particular, the study statistician, investigators, and GSK personnel involved in monitoring of the study will not be unblinded until the study completes as planned or is terminated

4.1.1. Stopping Guidelines

- **FF/VI vs placebo**. In order to have negligible impact on the final significance level, a stopping guideline for efficacy of FF/VI vs placebo will be applied at the interim analysis, using the Haybittle-Peto method using a one sided p-value of 0.00005, (equivalent to a two-sided $p<0.0001$). A one-sided 0.01 p-value will be applied as a non-binding stopping guideline for harm.
- **Other comparisons with placebo**. The study, or a specific treatment arm, may also be stopped prematurely as a result of the interim analysis of the other active treatment arms; in particular, where there is strong evidence that either FF or VI has a strong negative effect on mortality compared with placebo. For the assessment of harm, a non-binding stopping guideline of $p<0.01$ is proposed. This flag would signal further examination of available data by the Independent Data Monitoring Committee (IDMC), with consideration of altering the conduct of or terminating the study.
- **Stopping for safety reasons.** The IDMC will review data periodically throughout the trial. Notwithstanding the formal stopping guidelines described above, the IDMC may recommend that the study, or any treatment arm, should be stopped prematurely on grounds of safety at any time. This may arise where, for example, a review of serious adverse event (SAE) data indicates a substantial deleterious effect of any active treatment arm. There will be no impact on the type I error of the study as result of these safety reviews and therefore no statistical adjustment will be made to the final analysis

Further details about the conduct of the interim analyses are given in the protocol.

4.2. Final Analysis

Database release will occur after all subjects have completed all assessments (including assessment of survival status) and the data have been cleaned to a satisfactory level. Unblinding will then be performed and the database will be frozen. After Database Freeze (DBF), the planned analyses will be performed. See Section 10 (Study Population), Section 11 (Efficacy Analyses), Section 12 (Safety Analyses) and Section 13 (Health Outcomes Analyses) for details of all planned analyses.

5. SAMPLE SIZE CONSIDERATIONS

5.1. Sample Size Assumptions

The primary efficacy endpoint is time to death from any cause.

The primary analysis will test the following hypotheses:

- Null hypothesis: Hazard ratio for all cause mortality for FF/VI relative to placebo is equal to one. This is equivalent to a reduction in the risk of dying equal to zero, i.e. no difference in time to death between FF/VI and placebo.
- Alternative hypothesis: Hazard ratio for all cause mortality for FF/VI relative to placebo is not equal to one (i.e. two-sided test). This is equivalent to a reduction in the risk of dying not equal to zero, i.e. there is a difference in time to death between FF/VI and placebo.

The study is designed to show superiority of treatment with FF/VI relative to placebo (i.e. hazard ratio less than one, or equivalently, reduction in risk greater than zero) on top of a background of standard care

Every effort will be made to obtain mortality status for all subjects who withdraw from study medication. The analysis of the primary endpoint will be performed for the Intent-to-Treat-Efficacy Population, which will include all subjects who have been randomised to treatment, regardless of whether they have discontinued study medication.

This event driven study is designed to have 90% power to detect a 30% reduction in the risk of all-cause mortality (hazard ratio=0.70) on FF/VI compared with placebo at the two-sided 1% significance level. In order to detect this reduction, 478 events (on FF/VI and placebo combined) would be required (using Freedman's formula) [Machin et al, 1997].

Note that the possibility of satisfying the stopping rule at the planned interim analysis (see Section 4.1) implies that the actual number of deaths in this study may be lower than this upper limit.

Subjects may stop taking study medication, but will continue to be followed up for mortality status. All subjects will be followed until the required total number of events has occurred. Subjects will therefore be followed for a variable length of time. It is assumed that enrolment will start off at 150 subjects per month, building to 600 per

month by 6 months. Event Rates have been based on a post-hoc analysis of all-cause mortality in the TORCH study at 96 weeks in a population similar to that intended to be recruited to the present study and assume a placebo event rate of 6.00% by 24 months. A reduction in the hazard of 30% would result in a FF/VI event rate of 4.24% at 24 months. Based on the target of 478 events and under the above recruitment assumptions, 4000 subjects per arm will need to be randomised with a total expected duration of the trial of 44 months with subjects followed for between 14 and 44 months.

It should be noted that the Schoenfeld [Schoenfeld, 1981] formula for determining the number of events gives a slightly smaller number of events required for 90% power (468). However to be conservative, the Freedman formula has been used, which results in 478 events needed.

The effects of the components (FF and VI) are expected to be lower than for FF/VI. The study is not powered for comparisons of the components to placebo or for the combination to components . The study will utilise an equal randomisation scheme and so the study will provide as precise an estimate of the magnitude of the mortality effect as is practically achievable for these comparisons.

If the true mortality rates for the components are intermediate between FF/VI and placebo, then it would be expected that by the time there are 478 deaths between the FF/VI and placebo arms there should be a roughly similar number on the component arms combined, which would give a total of 956 on 4 arms. Since this is an event driven study, it is crucial that the study continue long enough to reach 478 events between FF/VI and placebo combined. However, since the study is blinded and the total number of deaths on the 4 arms will be influenced by the component arms it seems prudent to be conservative. This must be balanced against continuing the study for longer than necessary. For these reasons a total number of events of 1000 (between 4 arms) will be used to trigger stopping of the study for the final analysis.

Therefore it is planned that approximately 4000 subjects will be randomised to each of the four treatment arms and the study will continue until a total of 1000 deaths have been reported.

As this is a multi-country trial, in order to ensure balance of treatment arms within each country, separate randomisation schedules will be produced for each country (using permuted blocks).

Given the large number of subjects per treatment, other baseline factors should be fairly balanced, so the randomisation will not be stratified for any other factors. However important prognostic factors will be accounted for in statistical models.

5.2. Sample Size Sensitivity

Details of sample size sensitivity calculations can be found in the study protocol Section 8.2.2 [GlaxoSmithKline Document Number RM2009/00666/06, Amendment 5.

5.3. Sample Size Re-estimation

The event rate will be monitored using data blinded with respect to treatment assignment. If the event rate is lower than anticipated, then Steering Committee and GSK will consider whether the increased duration of follow-up is acceptable or whether to increase the sample size. An increase in sample size is most pragmatically implemented prior to completion of recruitment. If recruitment has already been closed then the duration of the trial may be longer than anticipated. For example, if the combined event rate on FF/VI and placebo at 24 months is only 4.3% (placebo event rate 5%) then the total expected duration of the trial is estimated to increase to 49 months (if there are 4000 subjects per arm). Under the latter scenario, subjects would therefore be followed for between 30 and 49 months. Alternatively, even if the estimated number of subjects randomised was to be increased to 5,500 per arm (recruited in 40 months according to assumptions when the study started) the trial would take 45 months As this is an event driven study, the actual recruitment period will also impact the numbers of subjects and/or duration of follow-up required. For example, if recruitment is very slow and the event rate is quite high, the required number of events may be reached before 4000 subjects per arm are randomised.

It should be noted that at the time of writing this RAP the recruitment was proceeding more slowly than anticipated, implying the duration of the study would be longer than anticipated, and this last scenario was very unlikely to occur (required number of events reached before recruitment stops). The study may finish recruitment with a different number to the 16,000 subjects who are currently planned. However as this is an event-driven study, it is achieving the required number of events which is of primary importance.

6. ANALYSIS POPULATIONS

All Subjects Enrolled (ASE) Population: This population will comprise of all subjects screened and for whom a record exists on the study database and will be used for the tabulation of reasons for withdrawal before randomisation.

Randomised but not treated: This population will be used for Protocol Deviation displays and will include all subjects who were randomised but did not take any dose of study medication.

Screen and Run in Failure Population: This population will comprise all subjects in the All Subjects Enrolled Population who were screen or run-in failures. It will be used for the tabulation of reasons for screen and run-in failure.

Safety Population: The Safety Population will consist of all subjects randomised to treatment and who received at least one dose of study medication. Randomised subjects will be assumed to have received study medication unless definitive evidence to the contrary exists. See Section 9.4.4 for further details.

If any subjects inadvertently received a different treatment for the duration of the study, or were inadvertently given more than one treatment, their data will be assigned to the treatment group to which they took for the majority (i.e. >50%) of the treatment period.

The Safety Population will be used for tables of safety data, listings of adverse events after randomisation, and all relevant listings. Subject accountability, demographic information, and baseline data will also be produced for the Safety Population.

Intent-to-Treat-Efficacy Population: The Intent-to-Treat-Efficacy (ITT) population will consist of all subjects in the Safety Population (i.e. randomised to treatment and who receive at least one dose of study medication), with the exception of subjects recruited at sites that were closed as the result of audit findings or other information that implied the integrity of the data had been compromised. These subjects will be excluded from the ITT population (and all efficacy analyses), and this decision will be formally documented prior to unblinding of the trial.

The ITT Population follows the intention-to-treat principles defined in the ICH Topic E9 guidelines [1998]. Following these principles, if any subjects have inadvertently received a different treatment for the duration of the study, or were inadvertently given more than one treatment, their data will be assigned to the treatment group to which they were originally randomised, irrespective of which treatment they actually took.

This will constitute the primary population for all analyses of efficacy measures.

For the primary endpoint of all cause mortality the analysis will include survival status at study end (see Section 9.4.2) for all subjects who have been randomised to treatment, regardless of whether they have discontinued study medication. That is, both on-treatment and post-treatment deaths will be used.

For all other efficacy endpoints, with one exception, the analyses will only use on-treatment data. The exception is a sensitivity analysis of the CV composite endpoint which will use events which occurred after the subject discontinued study medication.

Health Outcomes (HO) Population: The HO Population will consist of all subjects in the ITT Population who are included in the substudy of health status measures and have at least 1 valid baseline questionnaire value .

Arterial Stiffness (AS) Population: The AS Population will consist of all subjects in the ITT Population who are included in the substudy of arterial stiffness and have at least 1 valid baseline arterial stiffness measurement.

Biomarker Population: The Biomarker Population will consist of all subjects in the ITT Population from US sites who have given informed consent and have provided at least 1 valid baseline biomarker value.

6.1. Analysis Datasets

All reporting and analysis will be performed on datasets of observed data. Sensitivity analyses will also be performed for the FEV_1 data using imputed data as described in Section 11 (Efficacy Analyses).

7. TREATMENT COMPARISONS

7.1. Primary Comparison of Interest

The primary treatment comparison will be FF/VI vs placebo for the primary efficacy endpoint of time to death from any cause (on and off treatment). This analysis will be conducted on the ITT population. The final analysis will be conducted once the required number of events has been reached and the study has been stopped and the survival status of the subjects has been captured.

As a single study will be conducted to seek an indication for all-cause mortality, the study has been powered at the 1% significance level for regulatory purposes. However, all comparisons for the primary, secondary and other endpoints will be performed at the two-sided 5% level. That is, statistical significance will be reached if these are significant at the 5% level.

As there is a single primary treatment comparison and a single primary endpoint, no multiplicity adjustment will be required for the primary efficacy analysis, apart from any adjustment required for the alpha spent at the interim analysis. As the stopping guideline for efficacy of FF/VI vs placebo at the interim analysis will use a one sided p-value of 0.00005, (equivalent to a two-sided $p<0.0001$), this will have negligible impact on the final significance level.

7.2. Other Comparisons of Interest

For the secondary endpoints of rate of decline in FEV_1 and CV composite endpoint the primary comparison of interest is FF/VI vs placebo.

In order to make inferences for pre-defined secondary endpoints while controlling for the overall Type I error, the secondary endpoints will be nested under the primary treatment comparison for the primary efficacy endpoint. Multiplicity across these endpoints will be controlled using a closed testing procedure.

The hierarchy will be the primary endpoint followed by the Rate of Lung Function (FEV_1) decline followed by the CV composite endpoint. If significance in this hierarchy is achieved at the two-sided 5% level for the primary endpoint, then the Rate of Lung Function (FEV_1) decline will be tested at the two-sided 5% level. If significance in this is achieved, then the CV composite endpoint will be tested at the two-sided 5%.

If significance in this hierarchy is not achieved for the primary endpoint, then the tests for the secondary and other efficacy endpoints will be interpreted as descriptive only.

If the primary comparison of FF/VI vs placebo is significant at the 5% level for an endpoint, then inferences for the following treatment comparisons will be carried out for that endpoint:

- FF/VI vs VI
- FF/VI vs FF

- VI vs placebo
- FF vs placebo

These comparisons are to help understand the contribution of the components to the overall treatment effect of the primary FF/VI vs placebo comparison, so no multiple comparisons corrections will be considered for these four follow-up comparisons.

7.3. Data Display Treatment and Other Sub-group Descriptors

In the data displays the treatment will be identified as described in Table 2.

Table 2 Data Display Treatment Descriptors

Treatment Group	Descriptor
Placebo	Placebo
Fluticasone Furoate Inhalation Powder 100mcg	FF 100
Vilanterol Inhalation Powder 25mcg	VI 25
Fluticasone Furoate /Vilanterol Inhalation Powder 100/25mcg	FF/VI 100/25

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

As specified in the protocol, most assessments were scheduled to be collected only up to the end of treatment, therefore except where otherwise specified only baseline and on-treatment data will be used in summaries and analyses.

8.1. Multicentre Studies

As this is a large multi-site, multi-national study, it will be important to investigate any variation in response to treatment by place of recruitment. Such variation may reflect a number of contributory factors including population selection and subject care and management. As most sites are expected to contribute relatively small numbers of subjects, it will not be practical to look in detail at site-to-site differences. Sites will be managed by combining sites within countries, and these countries will then be combined into geographical regions. These country amalgamations will be used wherever region is incorporated into the analysis.

The assignment of investigators to amalgamated countries will be included as a table in the report. All references to ‘region’ in the context of analyses in this RAP will be taken to mean ‘amalgamated countries’. The following table identifies the amalgamations:

Region	Countries
USA	USA
Asia	China, Indonesia, India, Japan, Korea, Malaysia, Philippines, Taiwan, Thailand, Vietnam
Europe 1 (EU)	Austria, Belgium, Bulgaria, Czech Republic, France, Germany, Greece, Hungary, Latvia, Netherlands, Poland, Romania, Slovakia, Spain, UK, Croatia
Europe 2 (Non-EU)	Bosnia and Hertzegovina, Belarus, , Georgia, Israel, Macedonia (Former Yugoslav Republic of), Russian Federation, Serbia, Turkey, Ukraine
Rest of World	Argentina, Australia, Canada, Chile, Columbia, Mexico, , South Africa

Since the writing of the original RAP, there has been some change of designation of sites as Ukranian or Russian. However, we will report based on the original designation. Country is determined by the location of the site, as entered by the site monitor. The SITEID variable will be used to identify and group centres.

For any summaries that include information related to a subject's centre or investigator, the most recent centre and investigator at the time that the database is final will be used.

Region will be considered a fixed effect in analyses. All results will be produced for all regions combined. In addition, summary statistics of demography, screening lung function, primary and secondary endpoints will be produced by region. Interaction with treatment will be explored by fitting a model with an additional treatment by region interaction term.

8.2. Other Strata and Covariates

A separate randomisation schedule was produced for each country. For those countries participating in the Arterial Stiffness sub-study two schedules were produced for each country, one for the sites participating, and one for the sites not participating. This was to help ensure balance of treatment groups within the overall main study and the sub-study. No other stratification variables were used at randomisation. This stratification was implemented for logistical reasons, and neither country nor Arterial Stiffness sub-study participation will be taken into account within the main analysis models, although a sensitivity analysis of the primary endpoint will be performed, including these.

To perform this sensitivity analysis the sites will be grouped as

- US sites participating in the substudy
- US sites not participating in the substudy
- Asia sites participating in the substudy (at the time of writing the RAP there are none of these)

- Asia sites not participating in the substudy
- EU European sites participating in the substudy
- EU European sites not participating in the substudy
- Non-EU European sites participating in the substudy
- Non-EU European sites not participating in the substudy
- Rest of World sites participating in the substudy (at the time of writing the RAP there are none of these)
- Rest of World sites not participating in the substudy

The following variables will be likely to have an important influence on the primary and secondary variables so will be used in parametric models:

- Age
- Gender

These variables will be included in efficacy analyses, where appropriate, as explanatory covariates.

Number of exacerbations reported in the 12 months prior to Screening (0; 1; ≥2) will also be fitted as a covariate in the efficacy analyses of Exacerbations.

Any analyses of change from baseline will also include the baseline value as a covariate. For example the baseline value will also be fitted as a covariate in the efficacy analyses of Health Status measures and arterial stiffness measures.

The protocol specified that baseline % predicted FEV1, BMI, geographical region and smoking status may be included as covariates, however these will not be included in the primary models. This is to reduce the number of covariates in the primary models, as recommended by the European Medicines Agency Guideline on adjustment for baseline covariates [European Medicines Agency, 2013].

8.3. Examination of Subgroups

The following baseline subgroups will be summarised for selected efficacy and safety parameters, to examine whether treatment response differs from that seen in the overall population. The significance of interactions between treatment and these subgroups will also be investigated for exploratory purposes only. These investigations may warrant further data exploration within the subgroups. No formal analysis within subgroups will be performed.

Additional subgroups or covariates of clinical interest may be considered in the future. If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial or if the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup instead.

The subgroups of interest are:

- Smoking status (Current; Former)
- Age (<55; 55-<65; 65-<75; ≥75)
- Cardiovascular disease or risk by age: (40-60 years of age with history of Cardiovascular disease; >=60 years of age with history of Cardiovascular disease; >= 60 years of age with risk of Cardiovascular disease only) (See Section 4.2 of the Protocol for more detail.)
- Gender (Males; Females)
- Ethnic Origin (Hispanic/Latino; not Hispanic/Latino)
- Race (White; Asian; African-American/African Heritage; Other)
- Region (amalgamations as specified in Section 8.1)

The following categories are used only for the summaries of arterial stiffness data:

- Baseline Pulse Wave Velocity (PWV) (<11m/sec; ≥11 m/sec)

Subgroup analyses are designed to evaluate the consistency of the treatment effect; they are descriptive and not inferential.

8.4. Multiple Comparisons and Multiplicity

In order to make inferences for pre-defined secondary endpoints while controlling the overall Type I error, the secondary endpoints will be nested under the primary efficacy endpoint. Multiplicity across these endpoints will be controlled using a closed testing procedure. This is to account for multiplicity across treatment comparisons and key endpoints. Inference for a test in the pre-defined hierarchy is dependent upon statistical significance having been achieved for previous tests in the hierarchy

The hierarchy will be the primary endpoint followed by the Rate of Lung Function (FEV_1) decline followed by the CV composite endpoint. If significance in this hierarchy is achieved at the two-sided 5% level for the primary treatment comparison for the primary endpoint, then the Rate of Lung Function (FEV_1) decline will be tested at the two-sided 5% level for this comparison. If significance in this is achieved, then the CV composite endpoint will be tested at the two-sided 5%.

If significance in this hierarchy is not achieved for the primary endpoint, then the tests for the secondary and other efficacy endpoints will be interpreted as descriptive only.

No adjustment for multiplicity will be made for the other endpoints. These endpoints will be used in a supportive nature to evaluate consistency and further confirmation of efficacy of the treatment groups with respect to All Cause Mortality (ACM).

If the primary comparison of FF/VI vs placebo is significant at the 5% level for an endpoint, then inferences for comparisons of the components to placebo and of the combination to components will be carried out for that endpoint with no correction for multiple comparisons (as described in Section 7.2).

8.5. Genetic Markers

Any genetic analyses will be the subject of a separate analysis plan.

9. DATA HANDLING CONVENTIONS

9.1. Selection of Baseline Values

For purposes of data analyses, the baseline value of a particular type of assessment for a given subject will be defined as the latest assessment on or prior to the date of treatment start. Where a value is missing at the randomisation visit (visit 2) but available at an earlier time point such as screening (visit 1) the last pre-treatment value will be used.

If an assessment is only collected at one pre-treatment visit, the data from this visit will be considered to be baseline.

9.2. Emergency Unblinding

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. If a subject is unblinded in this situation, the subject's data will be included in analyses regardless of unblind status.

9.3. Premature Withdrawal and Missing Data

In this study it is necessary to distinguish between withdrawal from IP and withdrawal from the study. Just because a subject withdraws from IP does not mean they withdraw from the study.

Missing or unavailable data that are required will be queried by Data Management via a Data Clarification Request. In the event that, even after being queried, data are still missing, this will be identified in summaries and analyses of that data item. Any imputation of data performed in specific analyses will be detailed in the relevant section below.

For reporting, a subject will be considered to have completed the study when their final assessment of survival status has been completed at or after the common end date (see Section 9.4.2) or when they die. Mortality data will continue to be collected for subjects who withdraw early from IP and the primary endpoint, time to death from any cause, will use information both on and after withdrawal of IP. Sites also attempt to collect information on cardiovascular events after a subject withdraws from IP. For other endpoints, data from subjects who withdraw prematurely from the study will be included in appropriate analyses where possible. However the protocol does not mandate collection of other efficacy data after withdrawal from IP. In addition, imputation methods may be utilised for specific analysis methods. These will be detailed in the sections to which they are applicable.

Whether a subject withdraws from IP at a scheduled treatment visit, or in between visits, any data collected at a visit will be used in all summaries and analyses wherever possible.

Every effort will be made to gather all available information on subjects prior to GSK stopping the study when the target number of primary endpoints has been achieved. There will be a date at which the database will close and the sites will be unable to enter any further data. At this time point, any subjects who were unable to be contacted will have their data entry end. If GSK is alerted to any data after this time point and prior to unblinding, this data may be described in the clinical study report but will not be included in the database used for analysis purposes.

For efficacy endpoints, missing data is expected to arise mainly from subjects missing complete visits or time points. The amount of occasional missing data for covariates included in the statistical analysis is expected to be minimal. Missing data between two non-missing assessments will be implicitly interpolated; analyses for rate of decline in FEV_1 in Section 11.2.1 (Efficacy Analyses) will address imputation of data missing before the visit at Month 6.

Reasons for withdrawal fall into three broad categories:

- Safety (e.g. subject reached protocol-defined stopping criteria of liver event) – Given the data observed in previous trials with these study treatments, we do not expect to see an increased incidence of specific events leading to withdrawal from the study in the active treatment arms over that seen in the placebo arm. There may be some increased incidence of adverse events in the placebo arm due to sequelae from lack of efficacy (see third bullet). However, it is expected that, in most cases, any change in efficacy related to these reasons for withdrawal would have been captured prior to the subject withdrawing from the study (e.g. a decrease in FEV1), and an assumption of missing at random (MAR) is appropriate for imputation of data post-withdrawal.
- Procedural (e.g. withdrew consent, protocol deviation and site closed) – it is expected that an assumption of MAR is appropriate for imputation of data post-withdrawal. None of the intended analyses require a missing completely at random assumption for validity.
- Lack of efficacy – this is expected to be relatively rare but may demonstrate an imbalance in incidence between the placebo and active treatment groups, with a higher frequency in the placebo arm. The assumption of MAR may not be valid in this case.

The impact of missing data will be investigated as described in Section 11.2.1 (Efficacy Analyses).

9.4. Derived and Transformed Data

9.4.1. Exclusion of Data from Intent-to-Treat- Efficacy Population

All decisions on whether to exclude a subject or a subject's data from analysis will be made prior to breaking the blind.

In general, all data recorded for subjects who were randomised and received at least one dose of study medication will be included in ITT analyses. However certain sites were closed as the result of audit findings or other information that implied the integrity of the

data had been compromised. The subjects at these sites will be excluded from the ITT population (and all efficacy analyses), and this decision will be formally documented prior to unblinding of the trial. However all data collected to the point of site closure will be included in safety analyses, and these subjects will be included in the Safety Population.

9.4.2. Deaths Used in Primary Analysis

A study end date will be determined and documented in advance, when it is forecast that approximately 1000 deaths will have occurred to subjects in the ITT Population. This date will be called a common end date. This common end date will be determined at least one month beforehand. All subjects must have their survival status recorded at or after this date - this will constitute "complete follow-up of survival status" at a common end date. Only deaths which occurred on or before this date will be used in the primary analysis. Subjects who have not died by then, but who are known to be alive on or after the common end date, will be censored at the common end date.

The number of subjects whose survival status is unknown at the common end date is expected to be small, if not zero. These subjects will be censored at the date at which they were last known to be alive.

By determining this common end date in advance, this procedure should minimise any bias in follow-up.

The following method will be used to determine the event and censoring dates to be used in the analysis of time to death.

1. For subjects who die on or before the common end date: the "date of death" on the "Cause of Death" CRF page will be used as the event date; if this is missing then the latest "end date" for any fatal SAE will be used.

2. For subjects who are alive on or after the common end date or have missing survival status at the common end date, the last alive date will be determined as the later of :

- last visit date on the CRF
- "date of contact" on the "Follow-Up Contact (7 days after last dose date)" page of the CRF
- latest "date last confirmed alive" on the "Survival Assessment/Follow-up Contact" page of the CRF

For these subjects the censoring date will be the earlier of the last alive date or the common end date.

9.4.3. Deaths After the Common End date

Sites will start their closeout procedures after the common end date. It is anticipated that it could take 3-4 months for final monitoring to occur, and for the sites to close.

Although deaths will continue to accrue during the closeout period it is not possible to be sure that bias is not introduced during the closeout which could affect the distribution of survival times. For instance sites may be more likely to report deaths that occur during the closeout period, but not report additional last alive dates for subjects who have not died. In addition there may be some logistical or operational procedures which may give rise to some type of systematic reporting, such as systematic closing of some sites before others (e.g. smaller sites before larger sites) which may give rise to unknown biases (if for example there is something different about the subjects at smaller sites compared with those at larger sites). For this reason, any deaths that occur after the pre-determined common end date will not be used in the primary analysis. However these will be summarised and listed.

9.4.4. General

- Randomisation date = Date subject was randomised
- Safety population = A subject is considered to be in safety population if the subject was randomised and either there is evidence that the subject had taken at least one dose of drug or there is insufficient evidence to prove that the subject had not taken any drug. Consequently, for a randomised subject to be included in the safety population they must have either a non-missing treatment start date or an inhaler dispensed from which the drug consumption is either missing or greater than zero.
- Treatment start date = IP start date = Date subject first took IP (if missing for a subject in the Safety Population, the randomisation date)
- Treatment stop date = IP stop date=last date subject took IP=last dose of study medication. If missing for a subject in the Safety Population, then it will be imputed as the last visit at which IP was dispensed plus the number of days of IP taken (if the number of doses taken is not known, then the number of doses dispensed will be used). If it is not possible to calculate this, then the date of the last visit attended will be used. If the subject died before this, then the death date will be used.
- Subjects with an IP stop date prior to the day before the common end date are considered to be prematurely withdrawn from IP, regardless of whether the IP discontinuation page has been filled.
- Subjects who stop taking IP the day before the common end date, on the common end date or after the common end date will only be considered to be prematurely withdrawn from IP if they have completed the IP discontinuation page and the reason is not “study closed/terminated”.
- Extent of exposure to randomised study treatment will be calculated as:

  (IP stop date –IP start date) + 1.
- If a subject received a treatment other than the randomised treatment during the study, the exposure will still be calculated based on IP start and stop dates.
- Subjects who die while on study are considered as having completed the study.
- Only subjects who are lost to follow-up at the common end date are considered not to have completed the study

- Study day = the number of days from treatment start date

  If the treatment start date is missing, the study day will be missing

  If the reference date is missing, the study day will be missing

  If the reference date is less than the treatment start date, then study day = reference date – randomisation date

  If the reference date is equal to or more than the treatment start date, then study day = reference date – randomisation date + 1

- Change from baseline = Post-baseline – Baseline
- Percent change from baseline = 100 x (Post-baseline – Baseline) / Baseline
- End of treatment value = the latest value evaluated on or before either the treatment stop date+1. Missing for subjects not in the safety population.
- Last study contact date = last study contact (clinic or telephone visit) with the subject while on the study
- For purposes of calculation, time will be defined in the following manner according to GSK standard principles:

  1 week = 7 days

  1 month = 30.4375 days

  1 year = 365.25 days

9.4.5. On-Treatment Death

Deaths that occur no more than 7 days after the subject's last dose of study medication will be considered to be "on-treatment" deaths. Deaths which occur greater than 7 days after last dose of study medication will be considered to be "post-treatment" deaths. In particular, deaths which are adjudicated as cardiovascular (CV) will use the same definition, i.e. will be considered to be "on-treatment" CV deaths if they occurred up to and including IP stop date + 7.

9.4.6. Dates for Adjudicated Efficacy Endpoints

Event dates for adjudicated efficacy endpoints are defined as the following based on the dates collected in the CRF:

- Death: date of death
- Myocardial infarction, stroke, unstable angina and TIA

  these need to be reported by the investigator as an adverse event, so the start date of the AE will be used. This will generally be the date of the onset of symptoms (which will generally be earlier than the date of hospitalisation if it occurred).

Fatal CV events may have an AE onset date prior to the date of death. In these situations the date of death will be used in any analysis of deaths, however the AE onset date will be used as the event date in the analysis of time to first CV Composite endpoint.

9.4.7. On-Treatment Cardiovascular Event

Adjudicated CV events of Myocardial Infarction (MI), stroke, Unstable Angina UA and Transient Ischemic event (TIA) will be considered to be "on-treatment" if the start date of the corresponding adverse event occurred no more than 7 days after the subject's last dose of study medication.

9.4.8. On-Treatment Cardiovascular Composite Endpoint

The CV composite endpoint is only comprised of a subject's first CV event. This is comprised of the first event which is adjudicated as on-treatment CV death, on-treatment MI, on-treatment stroke, on-treatment unstable angina or on-treatment TIA.

9.4.9. On or Post-Treatment Cardiovascular Composite Event

Where possible, CV events are also collected after a subject stops IP. The on or post-treatment cardiovascular composite endpoint is comprised of the first event for any subject which is adjudicated as CV death, MI, stroke, unstable angina or TIA, regardless of whether during or post-treatment. This will be summarised.

9.4.10. On-Treatment Revascularisation

During the study it is recorded whether the subject has a cardiovascular revascularisation procedure. A revascularisation will be considered to be "on-treatment" if the procedure date occurred no more than 7 days after the subject's last dose of study medication.

9.4.11. Missing and Partial Values

- Missing AE start dates: Impute the first possible date, whilst avoiding imputing prior to treatment start for potentially treatment emergent adverse events

  If only the day of month is missing, impute the first day of the month unless the treatment start date is in that month (and the AE end date is not before the treatment start date) in which case the treatment start date should be used (e.g. --MAR2012 would impute as 01MAR2012 unless the subject started treatment in March 2012 (and the AE end date was not before the treatment start date) in which case the treatment start date would be used)

  If the month and day of month are missing, impute 01JAN unless the treatment start date is in that year (and the AE end date is not before the treatment start date) in which case the treatment start date should be used (e.g., ----2012 would impute as 01JAN2012 unless the subject started treatment in 2012 (and the AE end date was not before the treatment start date) in which case the treatment start date would be used)

  If the year, month, and day of month are missing, do not impute the date

- Other missing start dates: Impute the first possible date

  If only the day of month is missing, impute the first day of the month (e.g. --MAR2012 would impute as 01MAR2012)

  If the month and day of month are missing, impute 01JAN (e.g., ----2012 would impute as 01JAN2012)

  If the year, month, and day of month are missing, do not impute the date

- Missing stop dates: Impute the last possible date

  If only the day of month is missing, impute to the last day of the month unless the subject died in that month in which case use the date of death (e.g. --MAR2012 would impute as 31MAR2012 unless the subject died in March 2012 in which case the date of death would be used)

  If the month and day of month are missing, impute 31DEC unless the subject died in that year in which case use the date of death (e.g., ----2012 would impute as 31DEC2012 unless the subject died in 2012 in which case the date of death would be used)

  If the year, month, and day of month are missing, do not impute the date

- If the date last smoked for former smokers is missing the following will be imputed:

  If only the day of the month is missing, impute the last day of the month unless this date is after the screening date, in which case the screening date will be used.

  If the month and day are missing, impute as 31DEC unless this date is after the screening date, in which case the screening date will be used.

  If the year, month and day of the month are missing then the screening date will be used.

If an event date for an efficacy analysis of ACM or CV Composite is missing or partial and there is not sufficient information to classify the time period of the event, the event will be classified as occurring on-treatment.

9.4.12. Date of Birth

Only year of birth is collected, not actual day and month of birth, so the date of birth is implicitly imputed as 30 June. However age is also collected, and this will be used for the calculation of predicted FEV_1.

9.4.13. Percentage of Predicted FEV_1

Percent of Predicted FEV_1 = (Observed FEV_1 / Predicted FEV_1) x 100%

Sites were instructed to calculate predicted FEV_1 values using the NHANES III reference equations [Hankinson, 1999; Hankinson, 2010]. However sometimes these calculations were not performed correctly by sites, so will be recalculated by GSK. The formula calculates predicted FEV_1 (L) using the following equation, according to the gender of

the subject, where height is measured to the nearest cm, and age is in whole years attained:

Caucasian Males: Predicted FEV_1 = 0.5536 + (0.00014098 x Height x Height) – (0.01303 x Age) – (0.000172 x Age x Age)

Caucasian Females: Predicted FEV_1 = 0.4333 + (0.00011496 x Height x Height) – (0.00361 x Age) – (0.000194 x Age x Age)

African-American Males: Predicted FEV_1 = 0.3411 + (0.00013194 x Height x Height) – (0.02309 x Age) – (0.0 x Age x Age)

African-American Females: Predicted FEV_1 = 0.3433 + (0.00010846 x Height x Height) – (0.01283 x Age) – (0.000097 x Age x Age)

Mexican-American Males: Predicted FEV_1 = 0.6306 + (0.00015104 x Height x Height) – (0.02928 x Age) – (0.0 x Age x Age)

Mexican-American Females: Predicted FEV_1 = 0.4529 + (0.00012154 x Height x Height) – (0.01178 x Age) – (0.000113 x Age x Age)

If a subject is Asian the predicted value is obtained by multiplying the value for Caucasians by 0.88.

Sites classify the ethnicity of each subject as either Hispanic/Latino or Not Hispanic/Latino. The geographic ancestry is captured as one or more of African American / African Heritage; American Indian or Alaskan Native; Asian - Central / South Asian Heritage; Asian - East Asian Heritage; Asian – Japanese Heritage; Asian - South East Asian Heritage; Native Hawaiian or Other Pacific Islander; White - Arabic / North African Heritage; White - White / Caucasian / European Heritage.

When calculating the predicted FEV_1 the following procedure is to be used:

a. If ethnicity=Hispanic/Latino (regardless of race) then use the Mexican-American equations;

b. If ethnicity is Not Hispanic/Latino and race is African American/African Heritage (alone or with other races) then use the African-American equations;

c. If ethnicity is Not Hispanic/Latino and African American/African Heritage race is not selected at all and race is Asian (alone or with other races) then use the Asian correction of the Caucasian equations;

d. If ethnicity is Not Hispanic/Latino and African American/African Heritage and/or Asian races are not selected at all then use the Caucasian equations.

9.4.14. Absolute Reversibility

Absolute reversibility will be calculated by using the following formula:-

Absolute reversibility = (post-bronchodilator FEV_1 – pre-bronchodilator FEV_1)

9.4.15. Percent Reversibility

Percent reversibility in FEV_1 will be calculated using the following formula:-

Percent Predicted Reversibility =

((post-bronchodilator FEV_1 – pre-bronchodilator FEV_1) / pre-bronchodilator FEV_1) x 100%

9.4.16. Reversibility as Percent of Predicted FEV_1

Reversibility as Percent of Predicted FEV_1 will be calculated using the following formula:-

Reversibility as Percent of Predicted FEV_1 =

((post-bronchodilator FEV_1 – pre-bronchodilator FEV_1) / predicted FEV_1) x 100%

9.4.17. Previous Use of Inhaled Corticosteroids, Long-Acting Beta-2-agonists and Long-Acting Muscarinic Antagonists

At the screening visit, the investigator will record on the CRF whether the subject has taken inhaled corticosteroids and long-acting beta-2-agonists during the previous 12 months, either singly or in combination. The investigator will also record whether the subject has taken Long-Acting Muscarinic Antagonists during the previous 12 months. If the response to this question is missing it will be assumed that it is 'Unknown'.

These variables will be used to derive new variables for previous COPD therapy in the 12 months prior to the study. These will be: ICS and LABA and LAMA; both ICS and LABA; both ICS and LAMA; both LABA and LAMA; ICS only; LABA only; LAMA only; none of the above; unknown.

9.4.18. SGRQ-C Data (Score Derivation and Transformation for Analysis)

The SGRQ-C contains 14 questions grouped into three components (Symptoms, Activity and Impacts).

The Symptoms component consists of all the questions in Part 1 (Questions 1-7). The weights for Questions 1-7 are summed. A single response is required to each item. If multiple responses are given to an item, the weights for the multiple positive responses should be averaged and added to the sum.

The Activity component consists of Questions 9 and 12 in Part 2 of the questionnaire. This will be calculated from the summed weights for the positive responses to items Questions 9 and 12 in Part 2.

The Impacts component consists of Questions 8, 10, 11, 13, 14 in Part 2 of the questionnaire. The weights for all positive responses to items in Questions 10, 11 and 13

are summed together with the responses to the single item that should have been ticked in Questions 8 and 14. In the case of multiple responses to either of these items, the average weight for the item should be calculated.

The Total score is calculated by summing the weights to all the positive responses in each component.

The score for each component will be calculated separately by dividing by the summed weights by the maximum possible weight for that component and multiplying by 100. The SGRQ-C total score will be calculated as the sum of the weights from all the positive items in the questionnaire and dividing by the sum of weights for all items in the questionnaire and multiplying by 100. This calculation is outlined in the developer's guide (St George's Respiratory Questionnaire Manual for COPD Patients, 2008).

Scores for SGRQ-C, calculated as above, will be adjusted as follows to make them directly comparable to those obtained with SGRQ:

Symptoms: SGRQ score = (SGRQ-C x 0.99) + 0.94 units

Activity: SGRQ score = (SGRQ-C x 0.87) + 7.01 units

Impacts: SGRQ score = (SGRQ-C x 0.88) + 2.18 units

Total: SGRQ score = (SGRQ-C x 0.90) + 3.10 units

For Part 1, missed items will be treated as if the answer was negative. A maximum of one missed item is permitted per section.

For Part 2, missed items in Questions 8 and 14 will be treated as if the answer was negative. For the items in Questions 9, 10, 11, 12, 13 all require a response of either ‘True’ or ‘False’. If neither box is ticked, the item should be coded as ‘missing’. The weight for that item should then be removed from the total possible for that component (and the total score). Based on an analysis of the effect of missing data on calculated scores in the original SGRQ, this method will be reliable for handling up to 3 missed items for the Activity component (items in Questions 9 and 12) and up to 5 items for the Impacts component (items in Questions 8, 10, 11, 13, 14).

The baseline SGRQ component and total scores are those recorded at the Randomisation visit (visit 2).

Only questionnaires administered in the same language as that used at baseline will be considered for analyses. Further, any questionnaires administered after a change in language will not be considered, even if the language used is the same as that used at baseline. Scores for questionnaires administered in a language different to that used at baseline or administered after such a change in language will be regarded as missing.

A subject will be considered a ‘responder’ according to his SGRQ total score at each visit if the difference from the baseline score to the visit score was -4 units or lower. A subject will be considered a ‘non-responder’ if the difference from the baseline score to the visit

score was greater than -4 units. In addition, subjects will be classified according to SGRQ total score at each visit as follows:

- Improvement: a difference between visit and baseline of ≤ -4 units.
- No Change: a difference between visit and baseline > -4 units and < 4 units.
- Deterioration: a difference between visit and baseline of ≥ 4 units.

For the classification of responders, subjects with missing SGRQ total scores will be handled as follows: if the final visit containing non-missing data does not provide enough data to calculate the derived variable on which the responder status is based (e.g. some components of the SGRQ-C are present but not all, so the total score cannot be created), then they will be considered a non-responder for that visit.

9.4.19. EuroQoL Data

This questionnaire is collected at baseline (visit 2) then at months 3, 6 and every 6 months thereafter, in a subset of countries. The EQ-5D-3L consists of 2 parts: the EQ-5D-3L descriptive system and the EuroQol Thermometer visual analogue scale (VAS).

The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels, where Level 1 (coded as '1') = 'No problems', Level 2 (coded as '2') = 'Some problems', and Level 3 (coded as '3') = 'Severe problems'. Subjects indicate their health state for each dimension by ticking (or placing a cross) in the box of the most appropriate level for that dimension. Ambiguous values (e.g. 2 boxes are ticked for a single dimension) will be considered missing. Missing values will be coded as '9'. The responses (1, 2 or 3) to the five questions will be converted into a single index score using the developer's instructions [EQ-5D user guide, 2013]

The EQ VAS records the subject's self-rated health state on a vertical, visual analogue scale where 0='worst imaginable health state' and 100='best imaginable health state'. Subjects indicate their own health state by drawing a line from the box on the left of the scale to whichever point on the scale indicates how good or bad their own health state is that day. Ambiguous values (e.g. the line crosses the VAS twice) will be considered missing. Missing values will be coded as '999'.

The baseline index score will be that recorded at the Randomisation visit (visit 2).

Only validated EurQoLs completed in the same language as that completed at Baseline (Visit 2) will be considered for analyses. Further, any questionnaires administered after a change in language will not be considered, even if the language used is the same as that used at baseline. Scores for questionnaires administered in a language different to that used at baseline or administered after such a change in language will be regarded as missing.

9.4.20. CAT

The CAT consists of eight items each formatted as a six-point differential scale: 0 (no impact) to 5 (high impact). A CAT score will be calculated by summing the non-missing scores on the eight items. If one or two items are missing, then the score for those items is set as the average of the non-missing items. If more than two items are missing, then the CAT score will be set to missing.

The baseline CAT score will be that recorded at the Randomisation visit (visit 2).

Only questionnaires administered in the same language as that used at baseline will be considered for analyses. Further, any questionnaires administered after a change in language will not be considered, even if the language used is the same as that used at baseline. Scores for questionnaires administered in a language different to that used at baseline or administered after such a change in language will be regarded as missing.

9.4.21. Healthcare Resource Utilisation

The number of days in intensive care and in general hospital wards due to a severe COPD exacerbation will be derived and summarised.

9.4.22. Intermountain Risk Score

The 30-day and 1-year Intermountain Risk Score (IMRS) will be calculated according to the scores set out in the reference [Horne, 2010]. The following laboratory parameters will be used within the calculation: Hematocrit (HCT_BLQ), white blood cell count (WBC_BLC), Platelet count (PLT_BLC), Mean Corpuscular Volume (MCV_BLV), Mean Corpuscular Hemoglobin concentration (calculated from Hemoglobin, HB_BLC divided by Hematocrit as a %), Red Cell Distribution (RDW_BLQ), Mean Platelet Volume (MPV_BLV), Sodium (NA_PLC), Potassium (K_PLC), Bicarbonate (CO2_PLC), Calcium (CA_PLC), Glucose (GLUC_PLC) and Creatinine (CRT_PLC). Age and gender are also used in the score calculation.

The scores will be calculated for the laboratory assessment visits at baseline and at month 3 (scheduled and unscheduled) in the United States subjects. If any components of the score calculation are missing then the overall IMRS score will be set to missing.

Baseline IMRS score will be the most recent recorded value before IP start date.

9.4.23. Body Mass Index (BMI) Calculation

Body Mass Index will be calculated using:

BMI = weight in kg / (height in metres)^2

9.4.24. Rate of Adverse Events per 100 Treatment Years

Rate of on-treatment adverse events per 100 treatment years will be calculated using:

Rate = number of events * 100 / total treatment exposure in years

where subjects can contribute more than one event. This is equivalent to

Rate = number of events * 100 / (number of subjects in treatment group * mean treatment exposure in years).

This is not to be confused with a subject incidence rate (which is not being calculated for this study) where

Subject Incidence Rate = number of subjects experiencing the event * 100 / total treatment exposure in years

where subjects only get counted once, regardless of the number of events they have.

9.4.25. Smoking Status

The smoking status variable will consist of values relating to whether the subject was a former smoker or is a current smoker. Subjects will be classified on the basis of information collected at the Screening Visit (Visit 1). Smoking status as recorded on the CRF will be overruled, if necessary, using the date of smoking cessation. A subject will only be defined as a former smoker if they have given up smoking at least 6 months prior to screening, otherwise they will be classified as a current smoker.

During the study, smoking status will be derived from smoking status at screening and records of change in smoking status at visits. A subject identified as a current smoker at screening who stopped smoking during the study will be assessed as a former smoker only at visits which are at least 6 months after the date the subject last smoked. Former smokers who started smoking will be considered current smokers at all visits after the date the subject started smoking.

Subjects whose smoking status changed during the course of the study will be summarised.

9.4.26. Concomitant Medications

Medications will be classified into Respiratory Medication Classes (RMC) as follows:

- Antibiotic
- Corticosteroid - Depot
- Corticosteroid - Inhaled
- Corticosteroid - Other
- Corticosteroid - Systemic, oral, parenteral and intra-articular
- Cytochrome P450 3A4 Strong Inhibitors
- Leukotriene Receptor Antagonist
- Long-acting anticholinergic
- Long-acting beta-2 agonist - Group 1

- Long-acting beta-2 agonist - Group 2 (Olodaterol or Indacaterol)
- Long-acting beta-2 agonist - Group 3 (Salmeterol and Formoterol)
- Mucolytics
- Nedocromil or Cromolyn Sodium
- Other COPD medication
- Other medication given for exacerbation
- Oxygen
- PDE4 Inhibitors
- Short-acting anticholinergic
- Short-acting beta-2 agonist
- Xanthine

RMC will be derived for each COPD concomitant medication as defined above.

The following medications reported on the concomitant medication page will not be presented in any tables or listings: COPD concomitant medication that were stopped more than 30 days prior to Screening and non COPD concomitant medications that were stopped prior to Screening.

Classification of a concomitant medication as being taken pre-treatment, on-treatment or post-treatment will be made with reference to the study treatment and medication start and stop dates. A medication will be classed in every period of the study in which it was taken. For medications with partial start and stop dates, the medication will be classed in every period of the study in which it could have been taken.

9.4.27. COPD Exacerbations

COPD exacerbations will be reported as being either pre-, on-, or post-treatment.

- An exacerbation will be considered as pre-treatment if the exacerbation onset date is prior to the IP start date.
- An exacerbation will be considered as on-treatment if the exacerbation onset date is between the IP start date and IP stop date + 1.
- An exacerbation will be considered as post-treatment if the exacerbation onset date is after the IP stop date + 1.

If the exacerbation onset date is missing or partial then the exacerbation will be considered on-treatment unless there is evidence to the contrary (e.g. the month of the onset date is present and is less than the month of the first dose of study treatment).

The duration of the exacerbation will be calculated as (exacerbation resolution date or date of death - exacerbation onset date + 1).

The time to the first on-treatment exacerbation will be calculated as (onset date of first on-treatment exacerbation – date of start of treatment + 1).

If a subject is recorded as having experienced two consecutive exacerbations with overlapping dates or a gap between them of 7 days or fewer, the exacerbations will be queried with the site. If by the time the database is locked they still overlap then these will be considered as only one exacerbation for the purposes of summary and analysis. If the severity of the exacerbations is different, the combined exacerbation will have the severity of the most severe.

For example if a site reports an exacerbation with exacerbation onset date of 1MAR and exacerbation resolution date 10MAR, and the next exacerbation starts on 7MAR, this will be considered as only one exacerbation

Another example: if a site reports a moderate exacerbation with exacerbation onset date 1MAY and exacerbation resolution date 10MAY, then reports a severe exacerbation with onset date up to and including 17MAY, it will then be deemed that the first exacerbation had not fully resolved by the time the second one started; this will be considered a continuation of the first one, and will be considered as only one severe exacerbation. If however the onset date of the second exacerbation was after 17MAY then it will be considered a new exacerbation.

9.4.28. Exposure to IP

See Section 9.4.4.

9.4.29. Study Exposure

The study exposure for a subject gives the "time in the study", not just when the subject was on IP. It can be calculated as:

(death date or last recorded alive date – treatment start date) + 1.

If a subject's overall treatment start date is missing then it will be assumed to be the date of their Randomisation visit (visit 2).

The study exposure for a subject up to the common end date can be calculated in a similar manner, only using exposure up to and including the common end date, such that if a subject had a last alive or death date after the common end date the exposure will be limited to the common end date.

9.4.30. Extent of Missing Follow-up

If full follow-up is not achieved, the extent of missing follow-up time will be calculated. This will be done by determining, for each subject without known survival status at the common end date, the difference in time between the subject's last known survival status date and the common end date, summing over all subjects, and dividing by the total follow-up time that should have been achieved. These exact steps are detailed below.

For every subject, the study exposure including all exposure up to and including the common end date will be calculated. This will be summed over all subjects to obtain the total exposure years in the study up to the common end date.

It has already been stated that the number of subjects whose survival status is unknown at the common end date is expected to be small, if not zero. However if any of these subjects exist, the "missing" exposure will be calculated using the difference between their actual study exposure and the exposure they would have had if they had been known to be alive at the common end date. This will be summed over all these subjects to obtain the total exposure years in the study up to the common end date which are "missing".

The theoretical study exposure for a subject (including those with unknown survival status) will be calculated using the earliest of the death date or common end date as the last exposure date, i.e. as:

(earliest of (death date or common end date) – treatment start date) + 1.

The "missing" exposure due to incomplete follow-up (i.e. subjects with survival status not known at the common end date) will be expressed as a percentage of the total theoretical exposure years in the study up to the common end date. This will be the percentage of missing subject follow-up time. This is the complement of the completeness index described by Clark et al, 2002.

9.4.31. Maximum Possible Follow-up

The maximum possible follow-up for a subject will be calculated as:

(common end date – treatment start date) + 1

If a subject's overall treatment start date is missing then it will be assumed to be the date of their Randomisation visit (visit 2).

By ignoring deaths, the maximum possible follow-up is an estimate of the potential survival follow-up. Schemper & Smith (1996) note that by ignoring loss to follow-up this can substantially overestimate follow-up, but for this study the extent of missing follow-up (for death) is expected to be small such that the maximum possible follow-up gives a simple estimate of potential survival follow-up unaffected by death hazards.

This will be summed over all subjects to obtain the total maximum possible follow-up.

9.4.32. Treatment Compliance

The number of doses of study treatment taken by each subject from each inhaler will be calculated from the dose counter start and stop counts for each inhaler used. If a dose counter start count is missing then it will be assumed to be 30. If all dose counter stop counts are non-missing then the percentage compliance will be calculated as:

$$\text{Compliance} = \frac{\text{sum of all (dose counter start – dose counter stop)} \times 100}{\text{(IP stop date – IP start date +1)}}$$

If any dose counter stop is missing then the treatment compliance will be set to missing for that subject.

Compliance with will be categorised as follows:

< 80 %
≥ 80 % to < 95 %
≥ 95 % to ≤105 %
>105 % to ≤120 %
>120 %.

If a subject received an incorrect treatment (i.e. other than treatment they were randomised to) during the study, the compliance will still be calculated using data from all containers received and overall IP exposure start and stop dates.

9.4.33. Adverse Events

Adverse events will be reported as being either pre-, on-, or post-treatment.

- An AE will be considered as pre-treatment if the onset date is prior to the IP start date.
- An AE will be considered as on-treatment if the onset date is between the IP start date and IP stop date + 1 (inclusive).
- An AE will be considered as post-treatment if the onset date is after the IP stop date + 1.

If the AE onset date is missing or partial then the AE will be considered on-treatment unless there is evidence to the contrary (e.g. the month of the onset date is present and is less than the month of the first dose of study treatment).

AEs reported by subjects who did not receive treatment will be classified as pre-treatment.

The most frequent on-treatment AEs will be defined as the on-treatment AEs experienced by 3% (before rounding) or more of subjects in any treatment group. A summary table of these will be produced. The most frequent on-treatment SAEs will be defined as the on-treatment SAEs experienced by 1% (before rounding) or more of subjects in any treatment group.

AE groups of special interest have been defined as AEs which have specified areas of interest for one or more of the treatment groups (FF/VI, FF and/or VI). The following table presents the AE groups and subgroups of special interest which are current for the FF/VI programme at the time of writing the RAP. However this list may be updated based on emerging data, and will be updated and documented prior to unblinding:

AE of special interest group	AE special interest subgroup
Cardiovascular effects	Cardiac arrhythmia
	Cardiac failure
	Cardiac ischaemia
	Hypertension
	Stroke
Effects on Potassium	
Tremor	
Hypersensitivity	
Effects on glucose	
Pneumonia and LRTI	Pneumonia
	LRTI excluding pneumonia
Decreased bone mineral density and associated fractures	
Adrenal Suppression	
Corticosteroid associated eye disorders	
Local Steroid Effects	

The time to the first on-treatment AE of any particular type will be calculated as (onset date of first on-treatment AE – date of start of treatment + 1). The duration of an AE will be calculated as (AE end date or date of death - AE onset date + 1).

9.4.34. Vital Signs

The baseline value for a vital sign endpoint will be the most recent recorded value for that endpoint on or prior to the start of treatment.

The 'maximum/minimum post-baseline' value will be the maximum value for pulse rate and systolic blood pressure, or the minimum value for diastolic blood pressure, recorded at any scheduled, unscheduled or Early Withdrawal visit made after the start of study treatment.

9.4.35. Previous CV History as Indicator of Ischemic Heart Disease

Subjects are asked at screening whether they have had a previous MI; and whether they have ever had a previous coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). An indicator variable for Ischemic Heart Disease will be made by combining the two factors of Previous MI and Previous CABG/PCI. If a patient has answered yes to either of these then the indicator for ischemic heart disease will be yes, otherwise (missing, unknown or no) it will be no. This variable will be used as a covariate in the analysis of the CV composite endpoint.

9.4.36. Previous CV History as Indicator of Vascular Disease

Subjects are asked at screening whether they have ever been treated with medication for carotid or aorto-femoral vascular disease; whether they have ever had surgery for carotid or aorto-femoral vascular disease; whether they have ever had carotid, abdominal or femoral bruits; whether they have ever been hospitalised for a cerebrovascular accident (CVA i.e. a stroke); and whether they have ever had a transient ischaemic attack (TIA) objectively confirmed by a healthcare professional. An indicator variable for Vascular Disease will be made by combining these five factors. If a patient has answered yes to any of these then the indicator for vascular disease will be yes, otherwise (missing, unknown or no) it will be no. This variable will be used as a covariate in the analysis of the CV composite endpoint.

9.4.37. Withdrawal Cohorts

Given the event-driven nature of this study, patients will have variable follow-up and not all subjects will have the opportunity to attend a standard number of visits. Therefore data could be missing for more than one reason - either the subject did not have the opportunity to participate or the subject did have the opportunity but did not attend.

However, it is anticipated that all subjects from the ITT Population will have been randomised early enough to have had data at year 1. These subjects should have had at least 1 year's measurements of endpoints such as FEV_1.

As part of the examination of the nature of missing data caused by early withdrawal, Withdrawal Cohorts of subjects will be defined based on the data available at the scheduled FEV_1 assessments during the first year of follow-up for the ITT population, as follows:

1. Subjects whose last FEV_1 measurement was at visit 2 (i.e. no assessments performed after randomisation)
2. Subjects whose last FEV_1 measurement was at month 3
3. Subjects whose last FEV_1 measurement was at month 6
4. Subjects whose last FEV_1 measurement was at month 9

5. Subjects whose last FEV_1 measurement was at month 12

9.5. Assessment Windows

All subjects will start the study at Visit 1 and if they meet all selection criteria, will enter a 4-10 day run-in period. Following this run-in period, subjects will be randomised at Visit 2 into the treatment period. At the end of the treatment period, subjects will enter a 7-day safety follow-up period.

Each study visit will be calculated from Visit 2, rather than from the previous study visit. The first on-treatment study visit is a medication resupply visit which occurs 1 month (28 days) after visit 2. The rest of the visits will be scheduled every 3 months (90 days) after Visit 2. The 7-day safety follow-up phone contact may vary from these timelines by ± 2 days, the 90-day visits may vary from these timelines by ± 14 days.

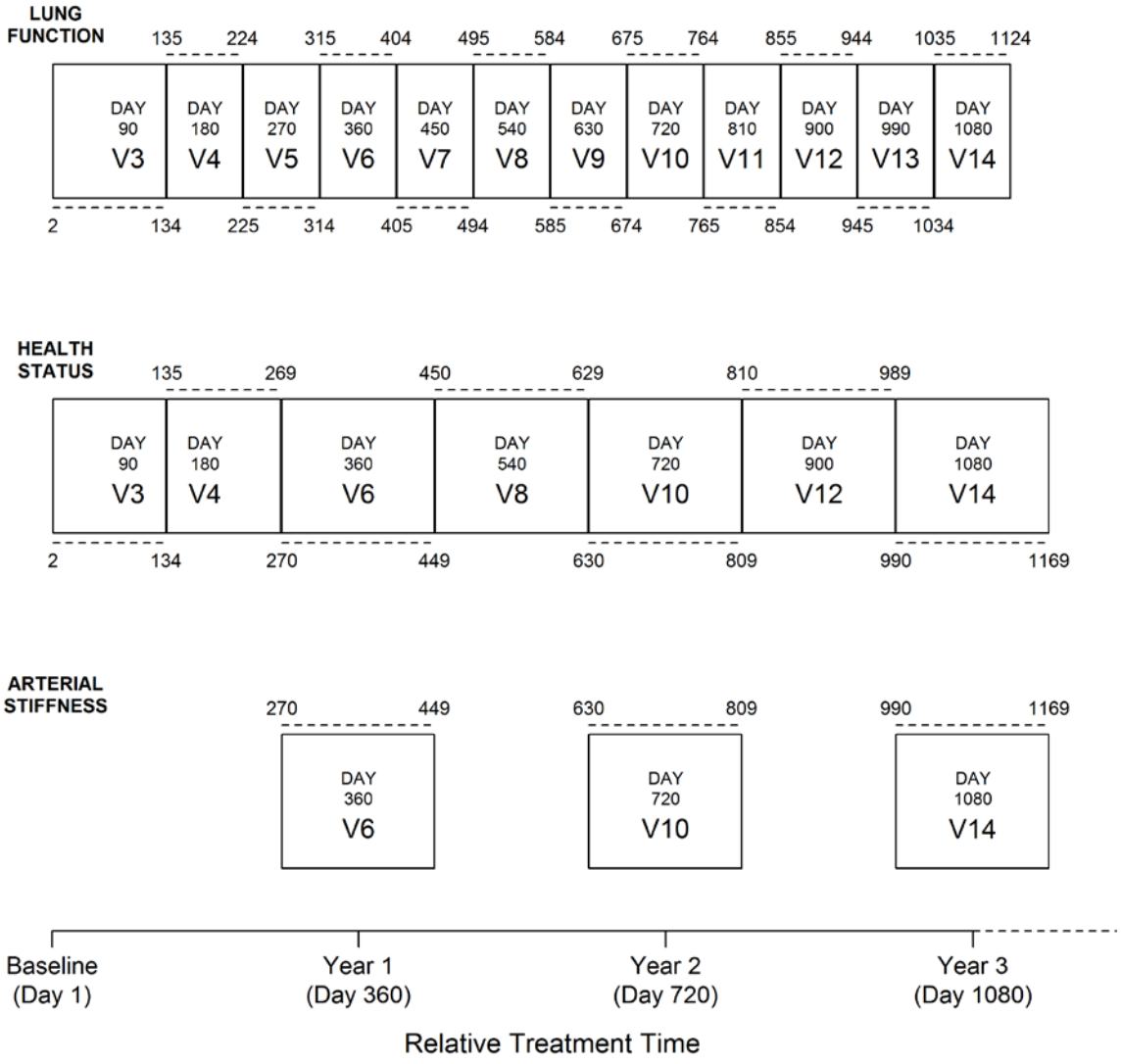
All lung function, health status and arterial stiffness efficacy data are collected at baseline (visit 2). Clinic Visit Lung Function data are collected every 90 days after Visit 2 and at the end of the study. Clinic Visit Lung Function data are also collected at Visit 1. SGRQ data, CAT data and EQ-5D-3L (health status data) are scheduled to be collected at 3 months (90 days), 6 months (180 days), then every 6 months (180 days). Arterial stiffness (AS) data are collected every 12 months. For these lung function, health status and arterial stiffness data, should a subject's visit fall closer to a later or earlier visit than to the scheduled visit then the clinic visit data collected at that visit will be reassigned to the appropriate visit for the purposes of summaries and analysis. Assessment windows will only be utilised when visit is considered as a categorical variable for the purposes of analyses.

For example: If the treatment start date for a subject is 05Jan2012 (visit 2, 1d), then the scheduled visit dates would be 1Feb12 (visit 2a, month 1, 28d), 3Apr12 (visit 3, month 3, 90d), 2Jul12 (visit 4, month 6, 180d), 30Sep12 (visit 5, month 9, 270d), 29Dec12 (visit 6, month 12, 360d). If the subject came in for their 180 day visit on 5May12, this falls closer to the 90 day visit than the 180 day visit. Therefore, such data would be reassigned to the 90 days visit for the summaries and analyses.

Lung function and health status will window to their closest scheduled visit. For AS, visits that fall within 90 days either side of a scheduled visit will be windowed to this visit, but data collected outside these windows will not be included in any summaries or analyses.

Assuming that treatment start date is assigned to Day 1, Figure 1 shows the windows applicable for the assignment of the lung function, health status and AS data to appropriate sessions:

Figure 1 **Windowing of visits outside schedule for Lung Function, Health Status and Arterial Stiffness visits. Windows are represented as boxes and dotted lines above and below windows indicate start and end relative days for inclusion in each windowed visit. The format is shown 3 years of visits - visits after that will follow the same pattern.**



The protocol does not mandate the collection of lung function or health status data after a subject withdraws from IP. Any lung function or health status data that has been recorded more than one day after the treatment stop date will not be included in any summaries or analyses of on-treatment data.

Any arterial stiffness data that has been recorded more than 7 days after the treatment stop date will not be included in the primary summaries or analysis.

When analysing continuous data, when a visit is considered as a categorical variable, should a visit subsequently have more than one measurement, then the average of the

measurements for that subject and visit will be taken and used within the summaries and analysis.

10. STUDY POPULATION

Unless stated otherwise all study population tables, figures and listings will be produced for the ITT population. All listings will be produced by centre and country.

10.1. Disposition of Subjects

The number of subjects in the ASE population, the number and percentage of subjects who attended the screening visit and of those the number and percentage of subjects who were screen failures with the reasons for failing will be presented overall. The number and percentage of subjects in the Screening and run-in failure population who failed each inclusion, exclusion or randomisation criterion or were re-screened will be presented.

Of those in the ASE population the number and percentage of subjects in the Safety, ITT, HO and AS populations will be presented by randomised treatment group and overall. The number and percentage of subjects in the ASE, Safety, ITT, HO and AS populations within each region will also be summarised by randomised treatment group and overall.

The number and percentage of countries and sites within the Safety, ITT, HO and AS populations will be presented by randomised treatment group and overall. This summary will be presented both by randomised treatment group and by region.

The number and percentage of subjects at each centre and within each country will be summarised by randomised treatment group and overall for the, Safety, ITT, HO and AS populations.

The number and percentage of subjects attending each clinic visit will be summarised by randomised treatment group and overall for the Safety, ITT, HO and AS populations.

The number and percentage of subjects who completed the study, who withdrew prematurely from IP and who reported each primary and sub-reason for withdrawal will be presented for each randomised treatment group and overall and also by region. IP discontinuation at the common end date will be summarised for the ITT, HO and AS populations. All IP discontinuations including those after the common end date will be summarised separately for the ITT and Safety populations.

Time to IP discontinuation up to common end date will be compared between treatment groups. Subjects dying while on treatment will be classified as having discontinued IP. A Kaplan-Meier plot and corresponding tables will be presented for the ITT, HO and AS populations and presented by region for the ITT and AS populations.

A Cox PH analysis of time IP discontinuation up to the common end date will be performed, including covariates of age and gender, for the ITT, HO and AS populations. The hazard ratios and p-values for each pairwise treatment comparison, along with 95% confidence limits, will be derived. This will be presented by region for the ITT and AS populations.

Additionally, to investigate the effects of on-treatment deaths on withdrawal, time to premature IP discontinuation up to common end date will be analysed, where subjects who have an on-treatment death will be censored at the date of IP discontinuation (rather than treated as an event). A Kaplan-Meier plot and corresponding tables will be presented for the ITT population.

A listing of reasons for withdrawal from IP will be produced for the Safety population

A listing of reasons for withdrawal for subjects in the ASE population who were randomised but not in the ITT Population will be produced.

A listing of randomised and actual treatments will be produced.

A listing of subjects randomised but not treated will be produced.

A listing of whether or not the subject was contacted for follow-up and the date of the contact will be produced.

10.2. Protocol Deviations

Subject data for randomised subjects will be examined for evidence of protocol deviations in order to assess how well the protocol was followed.

For the purposes of identifying protocol deviators, if the screening visit (Visit 1) spans multiple days it will be defined as the screening visit at which spirometry was measured.

Inclusion, Exclusion and Randomisation Deviations.

Inclusion, exclusion and randomisation criteria are detailed in Section 4.2, Section 4.3 and Section 4.4 of the protocol.

Sites enter the deviations from the inclusion and exclusion criteria into the Eligibility Form of the eCRF and this will be the primary source for reporting inclusion/exclusion deviations.

In addition to this, GSK will identify other inclusion/exclusion deviations using source data entered by sites into the eCRF. This will include identification of subjects:

- Outside the age range 40-80
- With a history of <10 pack-years of cigarette smoking
- With a score of less than 2 on the modified Medical Research Council Dyspnea scale
- With a recalculated FEV_1/FVC ratio >0.70 (i.e. recalculated from the actual FEV_1 and FVC values entered)
- With a recalculated percentage of predicted FEV_1 outside the allowed range of 50-70% (i.e. recalculated from the source data).

Note: The inclusion criteria for spirometry is after rounding, e.g. predicted FEV_1 of 49.5 rounds to 50 so is included.

- Who do not meet the requirements for risk or history of CV disease
- With an ejection fraction of <30%, or if they have an implantable cardioverter defibrillator (ICD) or New York Heart Class=4.
- A moderate/severe COPD exacerbation that has not resolved at least 14 days prior to Visit 1 and at least 30 days following the last dose of oral corticosteroids (if applicable).
- Additional medication: Use of the medications within the time intervals prior to Visit 1 or during the study (as defined in the protocol Section 4.3)

Section 4.4 of the protocol states "Any subject who experiences a moderate/severe COPD exacerbation (a COPD exacerbation requiring treatment with antibiotics and/or systemic corticosteroids or requiring hospitalisation) or pneumonia during the run-in period must not be randomised". The information sites enter on the Adverse Event Form will be used to identify deviations.

Withdrawal criterion

The withdrawal criterion is given in Section 4.5.1 of the protocol. This states that a subject will be withdrawn from IP if liver chemistry criteria are met. A subject will be identified as a protocol deviator if they experience a liver event, but the appropriate withdrawal procedure is not followed. The Liver Event form will be used to identify subjects where liver chemistry criteria are met, and the Investigational Product Compliance Form will be used to identify when IP was stopped, so that these deviations can be summarised.

Prohibited Medications

Section 5.6.2 of the protocol identifies the medications which are prohibited at baseline or during the study. These will be identified from the Concomitant Medication Form of the eCRF and summarised and listed.

Other Important Deviations

A listing of the date of and the reason for breaking the study blind will be produced for any subject for whom the blind was broken by the site.

A listing of any subjects that took the wrong pack will be produced for the Safety Population. A listing of any AEs that occurred while subjects were taking the wrong treatment will be produced. Note that subjects who have taken the wrong pack will be classified as Protocol Deviations. This will be listed and summarised.

Subjects who have been randomised at more than one site or those subjects that have been re-screened will be reported as a protocol deviation. The number and percentage of subjects in the ITT population who failed each inclusion, exclusion or randomisation criterion and other important deviations will be presented by randomised treatment group

and overall. They will not be excluded from the ITT Population. This table will also be produced for the randomised but not treated.

A listing of the protocol deviations specified above including inclusion/exclusion/randomisation criteria failures will be produced for the ITT and randomised but not treated population.

A listing of all subjects excluded from the ITT population will be produced.

10.3. Demographic and Baseline Characteristics

Unless otherwise specified, all displays in this section will be produced for the ITT Population and repeated by region.

A summary of demographic characteristics (age, gender, ethnicity, height, weight, body mass index, blood pressure and heart rate), by randomised treatment group and overall, will be produced. This summary will be repeated for the Safety, HO and AS populations.

Demographic characteristics will also be listed.

The number and percentage of subjects reporting each race and racial combination and each detailed race and racial combination will be presented by randomised treatment group and overall for all populations. Race will be listed.

The number and percentage of subjects reporting each current medical condition will be presented by randomised treatment group and overall for all populations. This summary will be repeated for past medical conditions. Current and past medical conditions will be listed.

A summary of baseline cardiovascular history and risk will be presented by randomised treatment group and overall for all populations. Cardiovascular history and risk will be listed.

COPD exacerbation history will be summarised by randomised treatment group and overall for the all populations. COPD exacerbation history will be listed.

Smoking history, smoking status at Screening and smoking status during the study will be summarised by randomised treatment group and overall for all populations. Smoking history and smoking status will be listed. A summary table of the smoking status changes during the study will also be produced.

Pre- and post-bronchodilator FEV_1 and FVC, pre- and post-bronchodilator FEV_1/FVC ratio, post- bronchodilator FEV1 as a percentage of predicted normal, FEV_1 reversibility to bronchodilator (expressed in mL and as a percentage) and FEV_1 reversibility to bronchodilator (expressed in mL and as a percentage) at Screening and Randomisation (Visit 2) will be summarised by randomised treatment group and overall for all populations.

Scores for the modified Medical Research Council dyspnoea scale will be summarised by randomised treatment and overall for all populations, and listed.

A baseline health status summary will also be produced for the HO populations.

A summary of baseline arterial stiffness parameters will be produced for the AS populations.

10.4. Concomitant Medications

Concomitant medications will be summarised by randomised treatment group and overall, and repeated by region for the following categories:

- COPD medications taken in the 12 months prior to the study, as recorded in the tick box on the CRF
- COPD medications taken on-treatment by respiratory medication class
- COPD medications taken pre-treatment by respiratory medication class
- COPD medications taken post-treatment use by respiratory medication class
- Non-COPD medications taken on-treatment
- Cardiovascular medications taken on-treatment

The number and percentage of subjects reporting any concomitant medication and each concomitant medication will be presented, for all populations. Non-COPD medications will be summarised by Anatomical-Therapeutic-Chemical (ATC) level 1 and ingredient. Multi-ingredient medications will be presented according to their combination ATC classification rather than the classifications of the ingredients.

10.5. Treatment Compliance

See Section 9.4.32 (Treatment Compliance) for how overall percentage compliance will be calculated.

Percentage of treatment compliance will be summarised overall for all populations.

Overall treatment compliance data will be listed (for the ITT population).

These displays will be repeated by region.

10.6. Study Exposure

Study exposure (defined in Section 9.4.29) will be summarised for the ITT population and repeated by region.

Extent of missing follow-up (as defined in Section 9.4.30 will be summarised for the ITT population.

Maximum possible follow-up (defined in Section 9.4.31) will be summarised for the ITT population.

11. EFFICACY ANALYSES

Any deviations from the original analysis planned in the protocol, which are agreed prior to finalisation of the RAP have been described in this document.

Hypothesis tests for main effects will use a 2-sided test at the 5% level of significance. Tests for interactions will be 2-sided at the 10% level of significance. If assumptions of the proposed method of analyses are not met, alternative methods of analyses will be used.

In all analyses described below, for all pairwise comparisons, the null hypothesis is that of no treatment difference. The alternative hypothesis asserts a difference between treatments. All treatment comparisons will be tested using a two-sided significance level of α=0.05, unless otherwise specified; p-values of ≤ 0.05 will be considered statistically significant.

For testing pairwise comparisons in these models the t statistic will be used (estimate divided by standard error). For parametric analyses, confidence intervals will be constructed in the normal manner (estimate $\pm$ t $\times$ standard error). Confidence intervals for the difference will use a confidence level of 95%.

Normality assumptions will be checked using residual plotting. Proportional hazards assumptions will be assessed by plotting the logarithm of the negative logarithm of the estimated survivor functions against the logarithm of time, for each treatment group. If the hazards are proportional, the lines should be approximately parallel.

Unless otherwise stated, efficacy analyses will be conducted only for the ITT Population; analyses of health status data will be conducted only for the Health Outcomes Population; analyses of arterial stiffness data will be conducted only for the Arterial Stiffness Population.

Whenever Kaplan Meier plots of cumulative incidence are presented, supporting tables will also be produced which show the incidences at regular time points during the study. For the purposes of graphical representation, Kaplan Meier plots will be "cut off" on the right hand side when the number of patients per arm becomes unduly small e.g. <5%. However this only applies to the plots – all appropriate data will be used in analyses, i.e. the data to be used in analyses will not be cut off at this point. The SAS PROC PHREG procedure will be used to fit the Cox proportional hazards regression models. The SAS PROC MIXED procedure will be used to fit the MMRM and random coefficients models.

The following treatment comparisons will be made:

- FF/VI vs placebo
- FF/VI vs VI
- FF/VI vs FF
- FF vs placebo
- VI vs placebo

Multiple treatment comparisons for the secondary endpoints are discussed in Section 8.4.

The protocol specified that baseline % predicted FEV_1, BMI, geographical region and smoking status may be included as covariates in parametric models as these would be important prognostic variables - however these will not be included in the primary models. This is to reduce the number of covariates in the primary models, as recommended by the European Medicines Agency Guideline on adjustment for baseline covariates [European Medicines Agency, 2013].

11.1. Primary Efficacy Analysis

The primary efficacy analysis of the primary efficacy endpoint of time to death from any cause will be compared between the FF/VI and placebo treatment groups within the ITT population, using a Cox Proportional Hazards (PH) Model, using the deaths which occur up to or on the common end date.

The hazard ratio for the FF/VI vs. placebo comparison, along with 95% and 99% confidence limits, will be derived, using time to death as the outcome variable, and covariates of treatment group, age and gender. Age in years will be a continuous covariate. The model will be:

Log (hazard ratio) = Treatment group + age + gender

The model will be fitted using the following SAS code

Proc PHReg; Model time*censor(1) = age gender treatment / ties = efron;

The p-value to be used will be the one associated with the chi-square p-value from the analysis on maximum likelihood estimates for the parameter estimate for treatment. This model will contain all four treatment arms.

Time to death will be calculated in days using the (date of death minus the treatment start date) + 1. Only deaths which occurred on or before the pre-determined common end date will be used in this primary analysis. Subjects who have not died by then, but who are known to be alive on or after the common end date, will be censored at the common end date.

Survival status at the common end date will be summarised. The number of subjects whose survival status is unknown at the common end date is expected to be small, if not zero. If however there are any, these subjects will be censored at the date at which they were last known to be alive.

The method for determining last alive date is specified in Section 9.4.2 (Death used in Primary Analysis) but, in summary, uses the last visit date or the last date on the Survival Assessment CRF page.

A Kaplan-Meier plot will be presented, showing the cumulative incidence curves of the two treatment groups.

A stopping guideline for efficacy of FF/VI vs placebo will be applied at the interim analysis, using the Haybittle-Peto method using a one sided p-value of 0.00005, (equivalent to a two-sided p<0.0001). A one-sided 0.01 p-value will be applied as a non-binding stopping guideline for harm. This approach would essentially preserve the alpha level at 5% in the final analysis and therefore there are no plans to adjust the alpha level in the final analysis.

The interim analysis will be carried out by the independent statistician in the Statistical Data Analysis Centre, who reports to the IDMC. These results will remain unknown to GSK until after final unblinding of the study. The final analysis will be performed by the GSK statistician.

11.1.1. Supportive Analyses of the Primary Endpoint

11.1.1.1. Cox PH Test without covariates

In order to understand whether the results for the primary analysis are robust a Cox PH score test will be performed, with no covariates, just treatment in the model. This is equivalent to a Log Rank test, which is a nonparametric test. This will use the deaths that occur up to or on the common end date, and will be a supportive analysis to the primary.

The model will be fitted using the following SAS code

Proc PHReg; Model time*censor(1) = treatment / ties = efron;

The hazard ratio for the FF/VI vs. placebo comparison, along with associated 95% confidence interval (CI) and p-value from the score test will be presented.

This should give identical results to the Log Rank p-value obtained from the Lifetest procedure using the syntax

Proc Lifetest; time*censor(1) ; strata treatment ;

11.1.1.2. Cox PH Test Including Covariates for Region and Participation in the Arterial Stiffness Substudy

Because of the stratified nature of the randomisation, a supportive analysis will be performed using a Cox PH test, including covariates of region and participation in the Arterial Stiffness Substudy, as described in Section 8.2 (Other Strata and Covariates). Again, this will use the deaths which occur up to or on the common end date, and will be a supportive analysis to the primary.

The model will be fitted using the following SAS code

Proc PHReg; Model time*censor(1) = age gender treatment substudy_region / ties = efron;

The p-value to be used will be the one associated with the score test.

11.1.1.3. Summary Including Deaths After the Common End Date

A summary of survival status at study closeout will be produced. This will include deaths that were reported prior to database lock which occurred after the common end date.

11.1.2. Other Treatment Comparisons for the Primary Endpoint

There will be interest in the comparisons of the combination arm to the components and the components to placebo, in order to help understand whether each component contributes to the overall treatment effect. It is acknowledged that the study is not powered for comparisons of the components with placebo or for the combination with components; however there will be interest in these from a scientific viewpoint. As the study will utilise an equal randomisation scheme it will provide as precise an estimate of the magnitude of the mortality effect as is practically achievable for these comparisons.

Each of the analyses produced for the FF/VI comparison will also be produced for the comparisons of the combination arm with the components and the components with placebo. These will include presenting the Cox PH models and the Kaplan-Meier plots showing the cumulative incidence curves of the four treatment groups. The Kaplan Meier plot will be produced using all four treatment groups in the proc lifetest procedure and the Cox PH Model will be produced using all four treatment groups in the proc PHReg procedure.

11.1.3. Additional Summaries of the Primary Endpoint using Safety Population

In order to give a more complete picture of the results a summary of the deaths occurring up to the common end date will be produced for the Safety Population - this includes data from excluded sites. However it should be borne in mind that these sites have been excluded because of doubts about the integrity of their data and so no statistical analysis will be performed.

Due to small numbers, summaries of deaths will not be produced for any of the substudy populations.

11.1.4. Interactions with Subgroups for the Primary Endpoint

The following subgroups will be investigated: smoking status, age, gender, ethnic origin, race, region, and Cardiovascular disease or risk by age. The levels of these categorical subgroups are specified in Section 8.3 (Examination of subgroups).

The statistical significance of interactions between each of these subgroups and treatment will be investigated within the ITT population, using a Cox proportional hazards model. All 4 treatment groups will be used when fitting these models. A separate model will be used for each interaction to determine its significance. Age (fitted as a continuous term) and gender will be included in all models. The model will be:

Log (hazard ratio) = treatment group + age + gender + subgroup + subgroup*treatment

The subgroup could be one of the other explanatory variables in the model (in which case, that variable would be replaced by subgroup) or it could an additional variable. For example, if investigating the interaction of gender and treatment, the model would be

Log (hazard ratio) = treatment group + age + gender + gender*treatment

whereas if investigating the interaction of region and treatment, the model would be

Log (hazard ratio) = treatment group + age + gender + region + region*treatment

A table showing interaction p-values for each subgroup will be produced.

Summary tables of deaths will be produced for each of the subgroups, containing information on the number of subjects in the subgroup, the number of deaths, the number of subjects censored and the Kaplan Meier probability of death with associated 95% Confidence Interval (CI) for each treatment group. Kaplan Meier estimates will be produced at a range of time points. Statistical testing of treatment comparisons will not be performed within subgroups and p-values for these will not be produced. However for each comparison of active with placebo and combination vs component, hazard ratios and 95% CIs will be produced and plotted for all subgroups on one overall plot. These will be generated using a model that only contains the data for each subgroup in turn, i.e. not from the model including the interaction term for the subgroup by treatment interaction.

Graphs will be produced, using a point for the hazard ratio estimate and bars for the confidence interval, for a visual comparison of the hazard ratios for different subgroups.

11.2. Secondary Efficacy Analyses

11.2.1. Rate of Decline in Post-Bronchodilator FEV_1

Descriptive statistics of actual clinic post-bronchodilator FEV_1 and change from baseline FEV_1 will be reported for baseline and all subsequent visits. The raw mean change from baseline at each visit will be presented graphically. All four treatment arms will be presented. To investigate the effect of any differential withdrawal, the baseline values of the patients remaining in the study over time, in each treatment arm will also be summarised and presented graphically.

For the analyses of rate of decline, each subject's actual time on treatment will be used, rather than assigning visit as a categorical variable. Only values which are measured between the start of IP and IP stop date + 1 (inclusive) will be used in these efficacy analyses. The residuals will be examined to check that the models fit adequately.

All the methods used to calculate a difference in slopes will not include the contribution of any initial increase in FEV_1, (i.e. increase between baseline and the first post-baseline measurement, which per protocol is at 3 months) as they test the difference in slopes from the first post-baseline measurement onwards. All methods in the following sections specify an unstructured covariance matrix. If the model fails to converge, then alternative covariance structures may be investigated.

11.2.1.1. Primary Model for Analysis of Rate of Decline – Random Coefficients

The primary analysis will use a particular form of a mixed effects model – a random coefficients model.

FEV_1 will be fitted as the response variable with treatment group, age, gender, baseline FEV_1 and time on treatment as fixed effects. In this analysis, time on treatment is treated as a continuous variable, and defined as the number of days which have elapsed since the start of treatment. Subject effects are assumed to be random. The random coefficients model allows random variation between slopes of individual subjects, as well as intercepts of individual subjects.

The treatment by time interaction is used to test whether the treatments have a different effect on the decline of FEV_1 over time, i.e. the slope. Contrasts will be formed for the difference in treatment by time interaction for any two treatments, and these contrasts will give an estimate of the difference in slopes between those treatments.

For the random coefficients model, the null hypothesis is that the treatment by time interaction term is zero, i.e. that the slope of FEV_1 over time is the same for all treatments. The alternative hypothesis is that the treatment by time interaction term is not zero, i.e. the slopes are not equal.

An artificial example of how the dataset might be structured is below:

Subject	Age	Gender	Treatment	Baseline FEV1	Post baseline FEV_1	Time in days from treatment start
300101	42	M	1	1.23	1.39	92
300101	42	M	1	1.23	1.30	183
300101	42	M	1	1.23	1.38	276
300102	65	F	2	1.56	1.76	88
300102	65	F	2	1.56	1.70	178
300102	65	F	2	1.56	1.62	273

The model will be:-

FEV_1 = Treatment group + age + gender + baseline FEV_1+ time + treatment*time

The estimate of the slope is the parameter estimate associated with the treatment by time interaction in the model. The adjusted means, pairwise treatment differences, p-values and 95% confidence limits for the treatment differences will be summarised overall and also estimated for 6 monthly timepoints. The results will also be presented graphically.

Only FEV_1 values measured after baseline are used as the response. So in this model a subject needs to have at least one post-baseline value to be included in the analysis. This model allows for an initial increase in FEV_1, but then tests the difference in slopes from the first post-baseline measurement onwards (which per protocol is at 3 months). The SAS code will be

```
proc mixed;
  class subject treatment gender;
  model fev = baseline gender age treatment timeyr treatment*timeyr /
ddfm=kr;
  random intercept timeyr / sub = subject type = un g ;

  estimate 'Slope for Trt1' timeyr 1 treatment*timeyr 1 0 0 0  /CL;
  estimate 'Slope for Trt2' timeyr 1 treatment*timeyr 0 1 0 0  /CL;

  estimate 'Trt2 vs Trt1'  timeyr 0 treatment*timeyr -1 1 0 0  /CL;
   estimate 'Trt1 time=1yr'
    intercept 1 basefev &mnbase age &mnage gender &propgender
    treatment 1 0 0 0 timeyr 1 treatment*timeyr 1 0 0 0    /CL ;
   estimate 'Trt2 time=1yr'
    intercept 1 basefev &mnbase age &mnage gender &propgender
    treatment 0 1 0 0 timeyr 1 treatment*timeyr 0 1 0 0    /CL ;

  estimate 'Trt2 vs Trt1 at 1yr'  treatment -1 1 0 0 timeyr 0
treatment*timeyr -1 1 0 0  /CL;
```

Where timeyr is the time in years, &mnage is the mean age of the subjects in the study and &propgender is the proportion of males in the study, which are used for calculating the adjusted means.

11.2.1.2. Additional Models for Analysis of Rate of Decline

Random Coefficients Model Using Baseline as First Time Point for Response

For the primary model a subject needs to have at least one post-baseline measurement to be included. In this sensitivity analysis this will not be the case. A random coefficients model will be fitted where baseline is treated as the first time point for the response variable. So in this model all subjects are included, even those who have only a baseline value.

FEV_1 will be fitted as the response variable with treatment group, age, gender, and time on treatment as fixed effects. In this analysis, time on treatment is treated as a continuous variable, and defined as the number of days that have elapsed since the start of treatment. Subject effects are assumed to be random. The random coefficients model allows random variation between slopes of individual subjects, as well as intercepts of individual subjects.

The treatment by time interaction is used to test whether the treatments have a different effect on the decline of FEV_1 over time, i.e. the slope. Contrasts will be formed for the difference in treatment by time interaction for any two treatments, and these contrasts will give an estimate of the difference in slopes between those treatments.

For the random coefficients model, the null hypothesis is that the treatment by time interaction term is zero, i.e. that the slope of FEV_1 over time is the same for all treatments. The alternative hypothesis is that the treatment by time interaction term is not zero, i.e. the slopes are not equal.

In this model rather than using baseline FEV_1 as a covariate, it is used as the first measurement of the response variable. The four treatment groups are set up as normal for each post-baseline measurement of FEV_1. However, for each observation of baseline FEV_1 a fifth treatment group is set up. This fifth treatment group takes the same level for each subject, regardless to which treatment group the subject is randomised, because at the point of baseline, the measurement is prior to assignment of treatment.

An artificial example of how the dataset might be structured is below (note that for baseline measurements the time from treatment start will be defined as zero):

Subject	Age	Gender	Treatment	FEV1	Time in days from treatment start
300101	42	M	0	1.23	0
300101	42	M	1	1.39	92
300101	42	M	1	1.30	183
300101	42	M	1	1.38	276
300102	65	F	0	1.56	0
300102	65	F	2	1.76	88
300102	65	F	2	1.70	178
300102	65	F	2	1.62	273

Fixed effects will be treatment, time (as a continuous variable) and the covariates of age and gender (but not baseline FEV_1). Subject effects are assumed to be random. The values of baseline FEV_1 are incorporated as part of the response variable, rather than as a covariate. The treatment by time interaction is used to test whether the treatments has a different effect on the decline of FEV_1 over time, i.e. the slope.

The model will be:-

FEV_1 = Treatment group + age + gender + time + treatment*time

This parameterisation means that subjects who have only a baseline FEV_1 value but no post-baseline values still have an effect on the estimate of the slope because of the correlation between the intercept and the slope terms. This model allows for an initial

increase in FEV1, but then tests the difference in slopes from the first post-baseline measurement onwards (which per protocol is at 3 months).

The adjusted means, pairwise treatment differences, p-values and 95% CI for the treatment differences will be summarised overall and also estimated for 6 monthly timepoints.

The SAS code will be

```
proc mixed data=datasetname noclprint;
  class subject treatment gender ;
  model fev1 = age gender treatment timeyr treatment*timeyr
               / solution ddfm=kr;
  random intercept timeyr / sub=subject type=un g;* solution;

  *- Estimates of slopes -*;
  estimate 'Trt1 Slope (1 yr)' timeyr 1 tmtgr*timeyr 0 1 0 0 0 / cl;
  estimate 'Trt2 Slope (1 yr)' timeyr 1 tmtgr*timeyr 0 0 1 0 0 / cl;


  *- Estimates of differences in slopes -*;

  estimate 'Trt2 vs Trt1 Slope' timeyr 0 tmtgr*timeyr 0 -1  1  0 0 /
cl;


  *- Estimates of adjusted mean at each time point -*;

  estimate "Trt1 at Year1" intercept 1 treatment 0 1 0 0 0
   age &mnage gender &propgender timeyr 1 treatment*timeyr 0 1 0 0 0
/cl;
  estimate "Trt2 at Year1" intercept 1 treatment 0 0 1 0 0
   age &mnage gender &propgender timeyr 1 treatment*timeyr  0 0 1 0
0 /cl;

  *- Estimates of differences at each time point -*;
  estimate "Trt1 vs Trt2 at Year1" treatment0 -1 1 0 0
         timeyr 0 tmtgr*timeyr 0 -1 1 0 0  / cl;
```

Where timeyr is the time in years, &mnage is the mean age of the subjects in the study and &propgender is the proportion of males in the study, which are used for calculating the adjusted means.

Individual Regression Slopes

For the random coefficients models subjects with more data are given more weight. A further sensitivity analysis will be performed where each subject is given the same weight.

For each individual subject in the ITT Population, FEV_1 will be regressed on time (as a continuous variable), to estimate a slope for each subject. The first on-treatment value of FEV_1 will be the first value used in the regression.

Subjects who entered the study towards the end or recruitment and who do not have at least 2 post-baseline measurements of FEV_1 will not be used in the analysis, as they will not have had a chance to accrue enough data, and can be safely considered Missing Completely at Random. The only reason they do not have enough data is that they did not enter the study soon enough.

However subjects who entered the study earlier, and who should have had at least 2 post-baseline measurements but who are missing one or both of these cannot be used in the analysis. So this analysis will ignore those patients without these and assumes these missing patients have been selected under a missing completely at random (MCAR) process.

Summary statistics for the individual regression slopes will be presented.

The slopes will then be analysed using an unweighted analysis of covariance, including terms for treatment and the covariates age, gender and baseline FEV_1.

The model will be:-

Slope = Treatment group + age + gender + baseline FEV_1

The slopes will be expressed in millilitres per year, and the adjusted means, treatment differences and associated 95% confidence limits and p-values will be produced.

Again, this method of calculating a difference in slopes will not include the contribution of any initial effect, as it is calculated after this initial effect has already occurred.

Individual Regression Slopes, Incorporating Imputation.

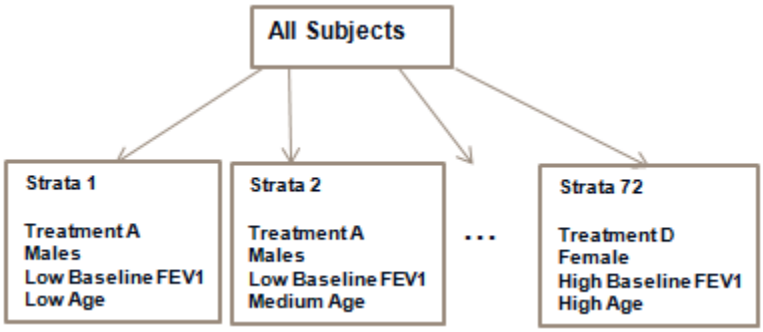
The individual regression slopes approach discussed previously cannot use those subjects who do not have at least 2 post-baseline observations, as a regression slope cannot be estimated for them. That analysis assumes these missing subjects have been selected under a missing completely at random (MCAR) process.

In order to estimate the difference in slopes between the treatments under a less severe missing at random assumption (MAR), slopes for those excluded from the previous analysis will be imputed under MAR using a nonparametric or "hot deck" method related to an approximate Bayesian bootstrap [Carpenter et al, 2013]. This analysis will conform to ITT in terms of including all subjects but will estimate a de jure estimand as those who withdraw are imputed using data for those who remain. This is the same estimand as the primary analysis of random coefficients.

For each individual subject in the ITT Population, FEV_1 will be regressed on time (as a continuous variable), with no covariates, to estimate a slope for each subject. The first post-baseline value of FEV_1 will be the first value used in the regression. Precision associated with these individual regression coefficients will be ignored, (i,e, it will not be a weighted ANCOVA.). Those subjects who do not have at least 2 post-baseline observations will have their slope imputed using two-step sampling.

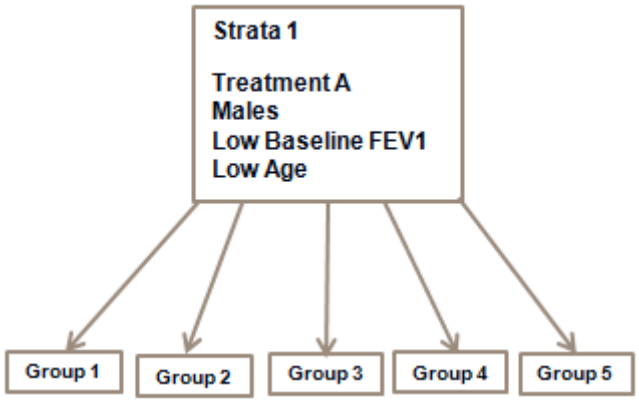
The imputation procedure will be stratified by treatment (4 levels) and also by sex (2 levels), age category (3 levels) and baseline FEV_1 (3 levels). This will provide 72 different strata (approximately 230 patients per stratum). We expect the average slopes to vary between these strata.

Figure 2 Process flow of placement of subjects into strata.



An approximate Bayesian bootstrap will be carried out in the following way based on a propensity score using a range of variables which we expect to be related to withdrawal. The propensity score equation will be shared across strata. A logistic regression will be fitted to all the data with presence or absence of an estimable slope as response, and with covariates in the model including BMI and previous exacerbation history. This equation will be used to score every subject and then subjects will be grouped into 5 groups within each stratum based on which 20% percentile they lie in within the stratum. . For example if Strata 1 had 230 subjects, this would give 5 groups of size 46 (Figure 3). This will give 360 groups once this process is repeated for the other 71 strata.

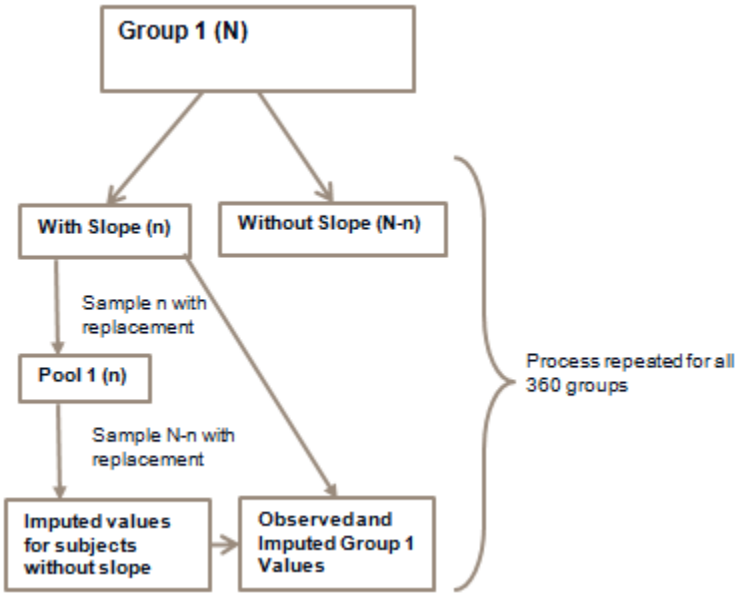
Figure 3 Process flow of Strata 1.



Within each group-stratum combination (approximately 50 subjects) subjects will be split into a set of n(with) patients with slopes and N-n(without) patients without slopes who require imputed values. First a donor pool, Pool(1), of size N(with) will be drawn at random with replacement from the n(with) patients in this group-stratum with slopes.

Then the imputed values for each of the N-n(without) patients in this group-stratum will be selected at random from this Pool(1) set of slopes with replacement. See Figure 4 for an example using Group 1 from Figure 2, this process is then repeated for the remaining 359 groups.

Figure 4 Process flow for imputation method.

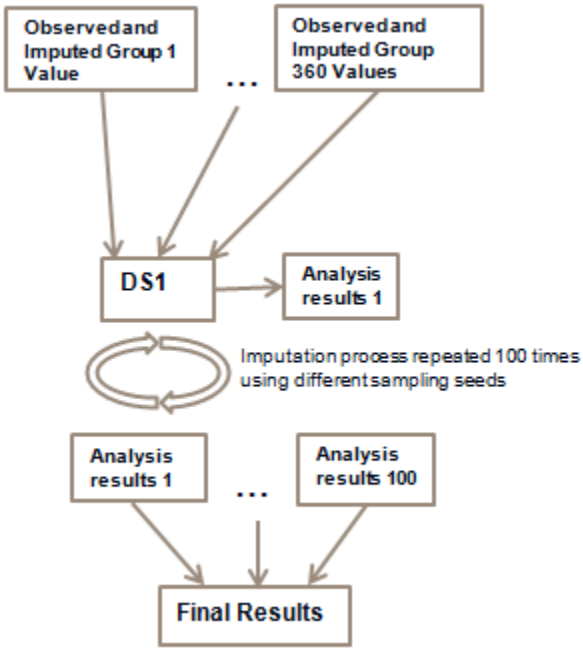


Once we have imputed the data for all 360 groups, these groups of observed and imputed data will be combined to form an imputed data set DS(1). Values are only imputed for those subjects for whom an individual regression slope cannot be estimated (i.e. those who do not have at least 2 post-baseline observations) (Figure 4).

The procedure described above is then repeated using different sampling seeds to produce a series of 100 imputed data sets DS(1), DS(2), ..., DS(100) (Figure 4).

Each of these data sets will be analysed using an unweighted analysis of covariance (ANCOVA) with terms for treatment, age, gender and baseline FEV_1. From each data set the treatment difference for each specified treatment comparison will be estimated and its associated standard error recorded. These will be combined into a single estimate of treatment difference and standard error (for each specified treatment comparison) using Rubin's rules as implemented in the SAS MIANALYZE procedure, and the 95% confidence intervals and p-values derived (Figure 5).

Figure 5 Process flow for Analysis of data.



Sensitivity Analysis – Examination of Missing Data Patterns

The following tables and figures examining missing data patterns will be presented.

To examine the nature of missing data, the number and percentage of subjects on each treatment in each Withdrawal Cohort (see Section 9.4.37) will be presented.

FEV_1 values will be summarised by visit and Withdrawal Cohort for each treatment. FEV_1 over time will be plotted by Withdrawal Cohort, for each treatment separately. Similar plots will be produced for change from baseline.

The number and percentage of subjects on each treatment at each visit who had any subsequent assessment non-missing or had all subsequent assessments missing will be reported.

11.2.1.3. Other Treatment Comparisons

The analyses produced for the FF/VI vs placebo comparison will also be produced for the comparisons of the combination arm with the components and the components with placebo.

11.2.1.4. Interactions with Subgroups

The following subgroups will be investigated for interactions with treatment: smoking status, age, gender, ethnic origin, race, region, and Cardiovascular disease or risk by age.

Statistical significance of interactions between treatment and these subgroups will be tested within the ITT population, using a Random Coefficients model. A separate model

will be used for each interaction to determine its significance. Age (fitted as a continuous term), gender and baseline FEV_1 will be included in all models. The model will be:

FEV_1 = Treatment group + age + gender + baseline FEV_1 + time + treatment*time + subgroup + subgroup*time + subgroup*time*treatment

The subgroup could be one of the other explanatory variables in the model (in which case, that variable would be replaced by subgroup) or it could an additional variable. All 4 treatment groups will be used when fitting these models. A table showing interaction p-values for each subgroup will be produced.

Summary tables for the subgroups will also be produced. A Random Coefficients model will also be fitted separately within each subgroup. For each model a table will be produced containing for each treatment group the number of subjects in the subgroup, the baseline mean FEV_1 and the adjusted rate of decline with 95% CI. In addition the adjusted means with 95% CI for a range of time points will be produced. Statistical testing of treatment comparisons will not be performed within subgroups and p-values for these will not be produced.

An example of the model giving treatment effects for males and females separately would be

```
proc mixed;
  class subject treatment;
  model fev = baseline age treatment timeyr treatment*timeyr / ddfm=kr;
  random intercept timeyr / sub = subject type = un g ;
```

where the model would be run for each gender in turn.

For each comparison of active with placebo and combination vs component, treatment differences and 95% CIs will be produced and plotted for all subgroups (smoking status, age, gender, ethnic origin, race, region and Cardiovascular disease or risk by age) on one overall plot. As noted above, these will be generated using a Random Coefficients model that only contains the data for each subgroup in turn, i.e. not from the model including the interaction term for the subgroup by treatment interaction.

Graphs will be produced, using a point for the treatment difference estimate and bars for the confidence interval, for a visual comparison of the treatment differences for different subgroups.

11.2.2. Time to First On-Treatment Composite Cardiovascular Event

A subject's first on-treatment cardiovascular composite endpoint event is comprised of the first event that is adjudicated as on-treatment CV death, on-treatment MI, on-treatment stroke, on-treatment unstable angina or on-treatment TIA. This endpoint will use events occurring up to and including the common end date.

The definitions of on-treatment CV death, on-treatment MI, on-treatment stroke, on-treatment unstable angina or on-treatment TIA are given in Section 9.4.5 and Section 9.4.7 (i.e. on-treatment events occur no more than 7 days after the subject's last dose of study medication).

The secondary efficacy endpoint of time to first on-treatment CV composite event will be compared between treatment groups within the ITT population, using a Cox Proportional Hazards Model. Time to first event will be calculated in days using [date of (CV event or CV death) minus the treatment start date] + 1.

Where the event is an adjudicated on-treatment stroke, MIA, UA or TIA, the event date for the analysis will be the start date of the corresponding adverse event. Where the event is an adjudicated on-treatment CV death which has not been adjudicated as an on-treatment stroke, MIA, UA or TIA, the event date for the analysis will be the date of death.

Subjects who have not had an event at least 7 days after they stop IP will be treated as censored observations and their censoring date will be IP stop date + 7.

The hazard ratio of the FF/VI treatment comparison, along with 95% confidence limits, will be derived, using time to first event as the outcome variable, and covariates of treatment group, age (as a continuous variable), gender, an indicator for ischemic heart disease and an indicator for vascular disease. The model will be:

Log (hazard ratio) = Treatment group + age + gender + ischemic heart disease indicator + vascular disease indicator

The model will be fitted using the following SAS code

Proc PHReg; Model time*censor(1) = age gender heartdisease vasculardisease treatment / ties =efron;

The p-value to be used will be the one associated with the score test.

A Kaplan-Meier plot will be presented, showing the cumulative incidence curves of the two treatment groups.

The number of subjects who experienced each of the components that are used in the time to first event analysis will be summarised, showing the type of CV event experienced, as well as the number of subjects experiencing any of the specified CV events, along with the number of events. The summaries will show adjudicated on-treatment strokes, MIA, UA or TIA, separately as fatal or non-fatal, and adjudicated on-treatment CV deaths. There are no plans to analyse these as separate endpoints.

11.2.2.1. Supportive Analysis

Cox PH Test without covariates. In order to understand whether the results are robust a Cox PH score test will be performed, with no covariates, just treatment in the model. This will be a supportive analysis. This is equivalent to a Log Rank test, which is a nonparametric test.

The model will be fitted using the same procedure as described in Section 11.1.1.1.

The hazard ratio for the FF/VI vs. placebo comparison, along with associated 95% confidence interval (CI) and p-value from the score test will be presented.

11.2.2.2. Other Treatment Comparisons

The analyses produced for the FF/VI vs placebo comparison will also be produced for the comparisons of the combination arm with the components and the components with placebo. These will include presenting the Cox PH model with covariates, the Cox PH model with no covariates, and the Kaplan-Meier plot showing the cumulative incidence curves of the four treatment groups.

11.2.2.3. Interactions with Subgroups

The following subgroups will be investigated for interactions with treatment: smoking status, age, gender, ethnic origin, race, region, Cardiovascular disease or risk by age, ischemic heart disease status and vascular disease status. The interactions with subgroups will be investigated in a similar manner as for the primary endpoint.

That is, statistical significance of interactions between treatment and these subgroups will be investigated within the ITT population, using a Cox PH model. A separate model will be used for each interaction to determine its significance. Age (fitted as a continuous term), gender, an indicator for ischemic heart disease and an indicator for vascular disease will be included in all models. The model will be:

Log (hazard ratio) = treatment group + age + gender + ischemic heart disease + vascular disease + subgroup + subgroup*treatment

The subgroup could be one of the other explanatory variables in the model (in which case, that variable would be replaced by subgroup) or it could an additional variable. All 4 treatment groups will be used when fitting these models. A table showing interaction p-values for each subgroup will be produced.

In addition, summary tables of events will be produced, with the same format as those specified for the primary endpoint.

Statistical testing of treatment comparisons will not be performed within subgroups and p-values for these will not be produced. However for each comparison of active with placebo and combination vs component, hazard ratios and 95% CIs will be produced and plotted for all subgroups on one overall plot (i.e. smoking status, age, gender, region, ischemic heart disease status and vascular disease status all on one plot). These will be

generated using a model that only contains the data for each subgroup in turn, i.e. not from the model including the interaction term for the subgroup by treatment interaction.

Graphs will be produced, using a point for the hazard ratio estimate and bars for the confidence interval, for a visual comparison of the hazard ratios for different subgroups.

11.3. Other Efficacy Analyses

11.3.1. All-Cause Mortality

The analyses of all-cause mortality performed for FF/VI vs placebo as described in Section 11.1 will also be performed for the following treatment comparisons.

- FF/VI vs VI
- FF/VI vs FF
- VI vs placebo
- FF vs placebo

11.3.2. Adjudicated Cause of Death

Assignment of primary cause of death is by Clinical Endpoint Committee (CEC) review of blinded CRFs, case narratives and any additional documents available (including death certificates and hospital discharge summaries).

The cause of death is adjudicated as CV, Pulmonary, Cancer, Other and Unknown (with subcategories under most of these). If the cause of death has been adjudicated on more than one occasion, then the latest adjudication will be summarised and analysed, since this would be based on the most up to date documentation. Summaries of the adjudicated primary cause of death (including subcategories) will be produced for the ITT and Safety populations, for deaths up to and including the common end date and separate summaries will be produced using deaths occurring after the common end date.

For cancer deaths, the type of cancer under 'other' is free text, so will be collapsed and categorised wherever possible. E.g. if the verbatim from the CEC is "bladder cancer" for one subject and "cancer of the bladder" for another subject, a category of "bladder" will be made and they will both be reported under this.

A listing of the primary cause of death assigned by the CEC and fatal adverse events will be provided for each deceased subject.

11.3.3. COPD-Related Mortality

In addition to assigning primary cause of death, the CEC assign whether the death was COPD-related using the following categories: No or Unlikely; Yes or Probable; or Unknown. Deaths assigned 'Yes or Probable' by the CEC will be classed as COPD-related deaths.

COPD-related death will be summarised for all four treatment groups, using deaths occurring up to and including the common end date.

11.3.4. On-Treatment Mortality

Mortality on treatment (as defined in Section 9.4.5) will be compared between treatment groups within the ITT population. The events in this analysis will be the deaths that occur up to and including 7 days after the subject stops IP, and the date of death will be used as the event date. Subjects who are still alive more than 7 days after they stop IP will be treated as censored observations and their censoring date will be IP stop date + 7.

A Kaplan-Meier plot will be presented, showing the survival curves of all the treatment groups.

The hazard ratio for each treatment comparison, along with 95% confidence limits and p-values, will be derived using a Cox proportional hazards model, using time to on-treatment death as the outcome variable, treatment group as the explanatory variable, and covariates of age and gender.

11.3.5. Time to First Moderate/Severe COPD Exacerbation

Moderate exacerbations are defined as exacerbations that require treatment with systemic corticosteroids and/or antibiotics; and severe exacerbations are defined as exacerbations that require hospitalisation. Moderate/severe exacerbations are those exacerbations that are moderate and/or severe.

The time to first on-treatment moderate or severe exacerbations will be compared between treatment groups within the ITT population, using a Cox's Proportional Hazards Model. The definitions of "on-treatment" events are given in Section 9.4.27.
Subjects who have not had an event at least 1 day after they stop IP will be treated as censored observations and their censoring date will be IP stop date + 1.

The analysis will use events occurring up to and including the common end date. Time to first event will be calculated in days using [date of COPD exacerbation minus the treatment start date] + 1.

The hazard ratios for all pairwise treatment comparisons, along with 95% confidence limits, will be derived, using time to first event as the outcome variable, and covariates of treatment group, age (as a continuous variable), gender and previous exacerbations (the number of exacerbations reported in the 12 months prior to Screening (0, 1, $\geq$2).

A Kaplan-Meier plot will be presented, showing the cumulative incidence curves of the four treatment groups.

11.3.6. Time to First COPD Exacerbation Requiring Hospitalisation

Severe exacerbations are defined as those that require hospitalization. Time to First COPD exacerbation requiring hospitalisation will be compared between treatment groups using the same methods as described in Section 11.3.5.

11.3.7. Time to First COPD Exacerbation Requiring Systemic Corticosteroids

Time to First COPD Exacerbation requiring treatment with systemic corticosteroids will be compared between treatment groups using the same methods as described in Section 11.3.5.

11.3.8. Rate of Moderate/Severe COPD Exacerbations

As a supporting analysis, the number of moderate and severe exacerbations occurring during the treatment period for the ITT Population will be analysed using a generalised linear model, assuming the Negative Binomial distribution, with time on treatment as an offset variable. The model will include a covariate of the number of exacerbations reported in the 12 months prior to Screening (0, 1, $\geq$2).

The adjusted mean rates per year, pairwise treatment rate ratios and associated p-values and confidence limits will be presented.

The fit of the Negative Binomial model will be examined using "Q-Q" plots of standarised residuals with simulated envelopes [Atkinson, 1985]. Provided the majority of the points lie within the envelope then the model will be deemed to be well-fitting.

For the purposes of summarising these data, the number of exacerbations for subjects who withdraw prior to the end of treatment will be calculated. Exacerbation rate per year will be calculated for each subject as the number of exacerbations / time on IP (in years). This imputation will only be required for the summary of the data, as the above model takes into account the time on treatment for a subject.

11.3.9. Rate of COPD Exacerbations Requiring Hospitalisation

The rate of severe exacerbations will be compared between treatment groups using the same methods as described in Section 11.3.8

11.3.10. Rate of Exacerbations Requiring Systemic Corticosteroids

The rate of exacerbations requiring treatment with systemic corticosteroids will be compared between treatment groups using the same methods as described in Section 11.3.8.

11.3.11. Rate of Exacerbations by Withdrawal Period

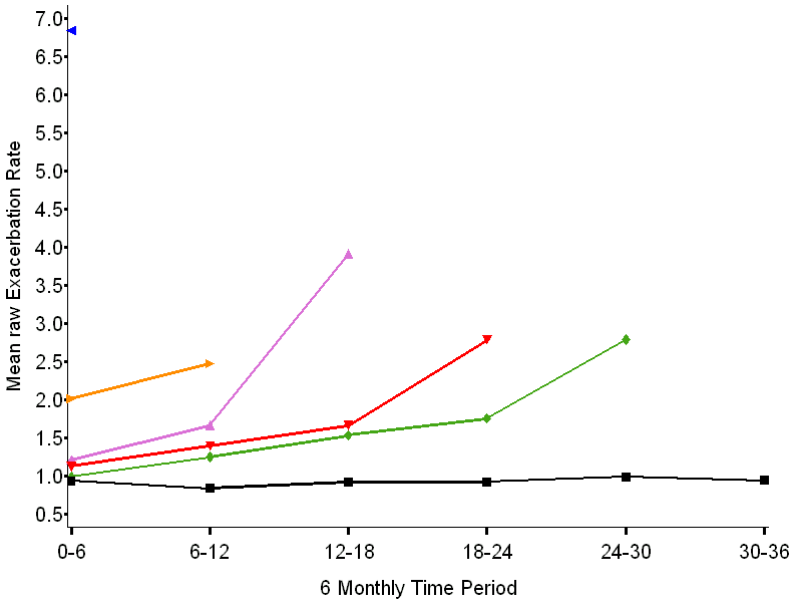
Withdrawal cohorts have already been defined for FEV_1, and in a similar process, these will be defined to investigate exacerbations. Withdrawal Cohorts of subjects who withdrew from IP prior to the common end date will be defined based on as follows:

1. Subjects who withdrew from IP within the first 3months
2. Subjects who withdrew from IP between 3 and 6months
3. Subjects who withdrew from IP between 6 and 9 months
4. Subjects who withdrew from IP between 9 and 12months

Mean raw exacerbation rates will be calculated for each group at each 3 monthly period 0-3 months, 3-6 months, 6-9 months and 9-12months) and plotted. This will be done separately for each arm. For example for a subject from group 4, their mean exacerbation rate will be calculated over the period 0-3 months and then calculated over the period 3-6 months and then over the period 6-9 months and finally for the period 9-12 months. The mean exacerbation rates will be connected with a line over time.

Note that the only group that will have all 4 periods will be group 4 (the others will have fewer periods depending on when their last potential exacerbation measurement could have taken place.). An example from another study using 6 month periods rather than 3 is below (Figure 6).

Figure 6 Example plot of withdrawal cohorts for exacerbation rates.



11.3.12. Change in Post-Bronchodilator FEV_1

Change in FEV_1 will be compared between treatment groups, using a mixed model repeated measures Analysis of Covariance (MMRM) analysis (Siddiqui, 2009). Treatment group will be fitted as the explanatory variable, and age (as a continuous variable), gender and baseline FEV_1 will be fitted as covariates. The primary treatment comparison will be at the 1 year timepoint. The variance-covariance matrix will be assumed to be unstructured. If the model fails to converge, then alternative covariance structures may be investigated. Visit will be fitted as a categorical variable.

Two models will be fitted; one with a response variable of FEV_1, and one with a response variable of change from baseline in FEV_1. For the analyses specified below, the adjusted means and adjusted mean change from baseline values will be presented with their associated standard errors. Estimated pairwise treatment differences along with their corresponding p-values and 95% confidence limits for each visit will be presented for the treatment comparisons in Section 7 (Treatment Comparisons). The adjusted means from the model for change from baseline, along with the corresponding 95% CIs will be plotted for each visit.

Due to the event driven nature of the trial there will be a much smaller amount of data at later time-points, hindering model fit. Therefore we anticipate having to exclude later visits, cutting off when the number of observations dips below 100-200 in any arm which we expect will be at 3 years. This is not anticipated to impact the primary comparison which will be made at 1year.The model will use all available FEV_1 recorded at scheduled visits up to the cut-off. Missing data are not directly imputed in this analysis; however, all non-missing data for a subject will be used within the analysis to estimate the treatment effect.

The model for change from baseline will be:-

Change in FEV_1 from baseline = Treatment group + age + gender + baseline FEV_1+ visit + treatment*visit+ baseline FEV_1*visit

The following SAS code will be used:

```
proc mixed data=datasetname;

  class visit treatment gender subject;

   model change = treatment age gender baseline visit visit*baseline visit*treatment / ddfm=kr;

   lsmeans visit*treatment / cl diff e om=OMdset at (baseline)=(&blm.);

   repeated visit /subject=subject   type=un;
```

The Kenward Roger (kr) method will be used for calculating degrees of freedom. If the analysis does not run using the Kenward Roger method for the ddfm option, then the residual method will be used instead.

The OMdset is a dataset with a row for every visit by-subject combination that contains all of the covariates and blm is a macro variable containing the mean baseline for the subjects used in the analysis. This is used to derive the least squares (LS) means using coefficients which are based on the subjects used in the analysis.

Since the study is event-driven, although subjects are recruited over a period of several years they all conclude the study at the same time. This means some subjects will have several years of FEV_1 measurements, while others will have a much shorter period when FEV_1 could be measured. If a subject is in the study for example 4 years, he/she could

have up to 16 visits. However if a subject has only been recruited 1 year prior to the study stopping then by design the subject can only have a maximum of four visits, at which on-treatment FEV_1 is measured. Data missing for this reason can be assumed missing at random (MAR). Data missing due to withdrawal will also be treated as missing at random in these analyses (see Section 9.3 for discussion).

The primary comparison for this endpoint will be the treatment differences in change from baseline at 1 year.

11.3.13. Change in Post-Bronchodilator FVC

Change in FVC will be compared between treatment groups, using MMRM, in the same way as described for change in FEV_1 (Section 11.3.12). Instead of baseline FEV1, baseline FVC will be used. The primary treatment comparison will be at the 1 year timepoint. Summaries will also be produced in the same way as previously described for change in FEV_1.

11.3.14. Summary Including On-treatment Cardiovascular Composite Events After the Common End Date

A summary will be produced including on-treatment cardiovascular composite events that were reported prior to database lock which occurred after the common end date.

11.3.15. Time to First On- or Post-treatment Cardiovascular Composite Event

A subject's first on- or post-treatment cardiovascular composite endpoint event is comprised of the first event that is adjudicated as CV death, MI, stroke, unstable angina or TIA. This analysis will use events occurring at any time during the study (whether the subject is taking IP or after the subject withdraws from IP) up to and including the common end date. The time to first CV composite event will be compared between the four treatment groups within the ITT population, using a Cox PH Model. Time to first event will be calculated in days using [date of (CV event or CV death) minus the treatment start date] + 1.

Where the event is an adjudicated stroke, MIA, UA or TIA, the event date for the analysis will be the start date of the corresponding adverse event. Where the event is an adjudicated CV death that has not been adjudicated as a stroke, MIA, UA or TIA, the event date for the analysis will be the date of death.

Subjects who have not had an event by the common end date will be treated as censored observations and their censoring date will be the common end date.

The hazard ratios for all pairwise treatment comparisons, along with 95% confidence limits, will be derived, using time to first event as the outcome variable, and covariates of treatment group, age (as a continuous variable), gender, an indicator for ischemic heart disease and an indicator for vascular disease.

A Kaplan-Meier plot will be presented, showing the cumulative incidence curves of the four treatment groups.

The number of subjects who experienced each of the components that are used in the time to first event analysis will be summarised, showing the type of CV event experienced, as well as the number of subjects experiencing any of the specified CV events, along with the number of events. There are no plans to analyse these as separate endpoints.

11.3.16. Time to First On-Treatment Revascularisation or Cardiovascular Composite Event

A subject's first on-treatment revascularisation or cardiovascular composite endpoint event is comprised of the first event that is an on-treatment revascularisation or adjudicated as on-treatment CV death, on-treatment MI, on-treatment stroke, on-treatment unstable angina or on-treatment TIA. The definitions of "on-treatment" events are given in Section 9.4.5 and Section 9.4.7. The analysis will use events occurring up to and including the common end date.

The time to first revascularisation or CV composite event will be compared between treatment groups within the ITT population, using a Cox Proportional Hazards Model. Time to first event will be calculated in days using [date of (CV event or CV death) minus the treatment start date] + 1.

Where the event is an on-treatment revascularisation the event date for the analysis will be the start date of the corresponding procedure. Where the event is an adjudicated on-treatment stroke, MIA, UA or TIA, the event date for the analysis will be the start date of the corresponding adverse event. Where the event is an adjudicated on-treatment CV death that has not been adjudicated as an on-treatment stroke, MIA, UA or TIA, the event date for the analysis will be the date of death.

Subjects who have not had an event at least 7 days after they stop IP will be treated as censored observations and their censoring date will be IP stop date + 7.

The hazard ratios for all pairwise treatment comparisons, along with 95% confidence limits, will be derived, using time to first event as the outcome variable, and covariates of treatment group, age (as a continuous variable), gender, an indicator for ischemic heart disease and an indicator for vascular disease.

A Kaplan-Meier plot will be presented, showing the cumulative incidence curves of the four treatment groups.

The number of subjects who experienced each of the components that are used in the time to first event analysis will be summarised, showing the type of CV event experienced, as well as the number of subjects experiencing any of the specified CV events, along with the number of events.

11.3.17. Revascularisation

The number of subjects who experienced any on-treatment revascularisation will be summarised, showing the type of revascularisation (coronary or peripheral), as well as the number of subjects experiencing any revascularisation, along with the number of events. The number of subjects who experienced a coronary revascularisation will be summarised along with the number of vessels, whether PCI or CABG and whether bare metal or drug eluting stents were used. The number of subjects who experienced a peripheral revascularisation will be summarised, along with the type of procedure (Carotid Endarterectomy or Peripheral angioplasty/stent).

11.3.18. Pulse Wave Velocity

Arterial Stiffness will be assessed by carotid-femoral Pulse Wave Velocity (PWV in m/sec) in a sub-study. Summary statistics for raw and change from baseline in PWV at every clinic visit will be tabulated for each treatment and presented graphically. These summaries will be presented for the AS population.

Change in PWV will be compared between treatment groups, using a mixed model repeated measures Analysis of Covariance (MMRM) in a similar manner to that performed for change in FEV_1 (Section 11.3.12) except that baseline PWV will be fitted instead of baseline FEV_1 and the cut-off (as defined Section 11.3.12) applied is expected to be somewhere between 1 and 2 years. The primary treatment comparison will be at the 1 year timepoint.

11.3.18.1. Interaction with Subgroups

To investigate whether the treatment effect is similar for the two subgroups of subjects with Baseline PWV <11m/sec and ≥11m/sec, the analyses will be produced separately for the two subgroups.

From each model a table will be produced containing for each treatment group the number of subjects in the subgroup, the baseline mean PWV and the adjusted mean PWV and change in PWV. Formal treatment comparisons will not be made within subgroups and p-values for these will not be produced.

11.3.19. Risk Scores

The 30-day and 1-year IMRS will be summarised at Baseline and 3 months. Summary statistics will also include Q1 and Q3 values in addition to n, mean, standard deviation, median, minimum and maximum. A scatter plot of time to death by IMRS by treatment group.

12. SAFETY ANALYSES

All safety tables, figures and listings will be produced for the Safety population, unless stated otherwise.

All listings will be produced by centre and country.

In case of treatment misallocation, additional outputs to those specified below will be provided, showing the subjects impacted by misallocation and the treatments they actually received.

12.1. Extent of Exposure

A histogram and cumulative distribution plot of the extent of exposure (defined in Section 9.4.28) to IP will be presented by treatment group for the Safety Population.

The extent of exposure to IP (in days) will be summarised in a tabular form by treatment group. This summary will be repeated for the ITT, HO and AS populations. Exposure data will be listed.

12.2. Adverse Events

Adverse events will be classified pre-, on- or post-treatment (as defined in Section 9.4.33).

An overview of AE incidence by treatment group will be produced. This will include the following categories: any on-treatment AE, any on-treatment drug related AE, any on-treatment AE leading to permanent discontinuation of study treatment, any on-treatment SAE, any on-treatment drug related SAE and any on-treatment fatal AE. The number and percentage of subjects will be displayed.

The number and percentage of subjects reporting at least one adverse event will be summarised by treatment group using the primary System Organ Class (SOC) and preferred term (PT). For on-treatment AE displays, a summary of the number of events and associated rate per 100 treatment years (Section 9.4.24) will also be produced.

The following AE summary tables will be produced:

- On-treatment AEs.
- Most frequent on-treatment AEs (defined in Section 9.4.33) (SOC will not be presented for this display).
- Most frequent non-serious on-treatment AEs (defined in Section 9.4.33) (SOC will not be presented for this display).
- On-treatment AEs by SOC, High level term (HLT) and PT.
- On-treatment AEs in the Respiratory, Thoracic and Mediastinal Disorders SOC (Primary or Secondary).
- On-treatment drug related AEs.
- Post-treatment AEs.
- On-treatment AEs by subgroup factors .

The subgroup factors used will be age, race, ethnic origin, region and gender .

In addition, displays will be produced by age categories <65, 65-74, 75-84, ≥85 for the following AEs: Fatal, Serious, Withdrawal, Central Nervous System (confusion/extrapyramidal), AE related to falling, Cardiovascular events, Cerebrovascular events and Infections. All listings unless specified otherwise will include an identification of whether each AE occurred pre-, on- or post-treatment.

The following AE listings will be produced:

- Subject numbers for each AE (ASE population).
- All AEs (ASE population).
- Relationship of primary SOC, preferred term and verbatim adverse event text.

12.3. Deaths and Serious Adverse Events

The following SAE summary tables will be produced:

- SAEs that occurred prior to randomisation (ASE population; this display will not be split by treatment).
- Most frequent On-treatment SAEs (defined Section 9.4.33.) (SOC will not be presented for this display).
- On-treatment SAEs.
- On-treatment non-fatal SAEs
- On-treatment SAEs by SOC, HLT and PT.
- On-treatment SAEs in the Respiratory, Thoracic and Mediastinal Disorders SOC (Primary or Secondary).
- On-treatment drug related SAEs.
- Post-treatment SAEs.
- On-treatment SAEs by subgroup factors.

All listings unless specified otherwise will include an identification of whether each SAE occurred pre-, on- or post-treatment.

The following SAE listings will be produced:

- Non-fatal SAEs (ASE population).
- On-treatment drug related SAEs.
- Subject Numbers for each SAE.

A summary of number and percentage of subjects with fatal AEs by the classification of the AE (pre- on- or post-treatment) will be produced by treatment group. Note that these additional summaries may be different from the summary of deaths as it is possible for a subject to have more than 1 SAE recorded with a fatal outcome.

The following Fatal AE summary tables will be produced:

- On-treatment Fatal AEs.
- On-treatment drug related Fatal AEs.
- Post-treatment Fatal AEs.

The following Fatal AE listings will be produced:

- Fatal AEs that occurred prior to randomisation (ASE population).
- On-treatment Fatal AEs.
- Post-treatment Fatal AEs.
- On-treatment drug related Fatal AEs.
- Subject Numbers for each Fatal AE.

12.4. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

On-treatment AEs leading to permanent discontinuation of IP and/or withdrawal from the study will be summarised by treatment group. This will also be done for SAEs.

AEs leading to permanent discontinuation of study treatment will be listed (this listing will include AE classification).

In addition separate tables of AEs and SAEs of Special Interest will be produced. All on-treatment AEs in the special interest groups/subgroups (as defined in Section 9.4.33) will be summarised by treatment for the Safety population. This will include incidence and event rate. SOC will not be used for this summary.

In addition to the standard displays, for each separate AESI group a Kaplan-Meier plot showing the percentage of subjects with an AESI will be produced, provided the number of subjects with an event is at least 200 overall. These Kaplan-Meier figures will be repeated for SAEs in the SI Groups, again provided the number of subjects with an event is at least 200 overall.

Double dot plots will be produced for each AESI and SAESI grouping.

12.5. Pregnancies (as applicable)

Any pregnancies reported during the study will be summarised in case narratives. Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE and included in summaries and listings of AEs/SAEs as described above in Section 12.2 and Section 12.3.

12.6. Potential Novel Dry Powder Inhaler Malfunctions Reported by Subjects

The reasons for potential NDPI malfunctions will be listed.

12.7. Clinical Laboratory Evaluations

There are no central clinical laboratory evaluations performed.

12.8. Other Safety Measures

12.8.1. Vital Signs

Summary statistics for vital signs (pulse rate, systolic and diastolic blood pressure) at Screening, Baseline and raw and change from baseline in vital signs at each visit will be produced. All vital signs data will be listed.

12.8.2. Liver Events

Liver event information will be summarised and listed.

A summary of time on treatment before stopping due to liver criteria will be presented by treatment.

A summary of liver biopsy results by treatment will be produced. A summary of liver imaging results by treatment will be produced.

Liver event information will be listed for all subjects who report a liver event, to include:

- The time from the start of randomised study treatment to the liver event.
- The information captured on the Liver Event Assessment Form which is used to calculate the Roussel Uclaf Causality Assessment Method score.
- If liver biopsy was performed, the size of the biopsy and the recorded outcomes.
- If liver imaging was performed, the recorded outcomes for the liver imaging assessment.

Information on alcohol use for subjects who report a liver event will be listed.

Medical conditions reported at the time of the liver event will be listed.

13. HEALTH OUTCOMES ANALYSES

13.1. Humanistic Measures

Health outcomes summaries and analyses will be performed for the HO population.

Further analyses of cost-effectiveness will also be performed using these data, and will be the subject of a separate RAP.

13.1.1. Quality of Life Determined using the St. George's Respiratory Questionnaire (SGRQ)

The SGRQ-C questionnaire is collected at baseline (visit 2) then at months 3, 6 and every 6 months thereafter, in a subset of countries.

The scores from the SGRQ-C will be multiplied to make them comparable to the SGRQ (as described in Section 9.4.18), and all summaries and analysis performed on these values. All summaries will be presented for the HO population

A transformed score will be calculated for each of the three domains of the St George's Respiratory Questionnaire (symptoms, impacts and activity) and the overall total score, in accordance with the developers' scoring guidelines. Descriptive statistics will be reported for the domain and total scores for baseline and all subsequent visits and at withdrawal. The change from baseline will also be summarised at all visits after baseline. The raw change from baseline at each visit will be presented graphically for the total score and for each of the domains. To investigate the effect of any differential withdrawal, the baseline values of the patients remaining in the study over time, in each treatment arm will be summarised and presented graphically for the total score and each of the domains.

To examine the nature of missing data, the number and percentage of subjects on each treatment in each Withdrawal Cohort (see Section 9.4.37) will be presented.

SGRQ values will be summarised by visit and Withdrawal Cohort for each treatment. SGRQ over time will be plotted by Withdrawal Cohort, for each treatment separately. Similar plots will be produced for change from baseline.

The number and percentage of subjects on each treatment at each visit who had any subsequent assessment non-missing or had all subsequent assessments missing will be reported.

13.1.1.1. Main Analysis of SGRQ

Change in Total SGRQ will be compared between treatment groups, using a mixed model repeated measures Analysis of Covariance (MMRM) in a similar manner to that performed for change in FEV_1 (Section 11.3.12) except that baseline SGRQ score will be fitted instead of baseline FEV_1. The primary treatment comparison will be at the 1 year timepoint.

This analysis will also be performed for each of the domains, with baseline SGRQ Total score replaced by the baseline value of the appropriate domain.

13.1.1.2. Responder Analysis of SGRQ

The proportion of subjects classified as responders according to SGRQ total score as defined in Section 9.4.18 (St. George's Respiratory Questionnaire) will be summarised by treatment and visit. The proportion of subjects with each category of response will also be summarised by treatment and visit. At each visit, the proportion of responders according to SGRQ will be analysed using a separate logistic regression model with treatment as an explanatory variable and baseline SGRQ total score, age and sex included as covariates. The main analysis will be performed on the HO population. . Due to the event driven nature of the trial there will be a much smaller amount of data at later time-points, hindering model fit. Therefore we anticipate having to exclude later visits, cutting off when the number of observations dips below 100-200 in any arm which we expect

will be between 1-2 years. For each treatment comparison defined in Section 7 (Treatment Comparisons), the odds ratio, 95 % CI and p-value will be presented.

The following SAS code will be used:

```
proc logistic data=datasetname descending;
    class treatment (ref='1') / param=ref;
    model respond=treatment base age gender / clodds=wald expb;
   ods output logistic.oddsratios=odds1
               (where=(index(effect,'TREATMENT')>0
                or index(effect,'treatment')>0));
   ods output logistic.parameterestimates=pval1
              (keep=probchisq variable classval0
              where=(variable in ('TREATMENT','treatment')));
run;
```

13.1.2. Quality of Life Determined using the COPD Assessment Tool (CAT)

This questionnaire is collected at baseline (visit 2) then at months 3, 6 and every 6 months thereafter, in a subset of countries.

Descriptive statistics will be reported for the CAT scores for baseline and all subsequent visits and at withdrawal. The change from baseline will also be summarised at all visits after baseline. The raw change from baseline at each visit will be presented graphically.

Change in CAT will be compared between treatment groups, using a mixed model repeated measures Analysis of Covariance (MMRM) in a similar manner to that performed for change in SGRQ (Section 13.1.1.1), except that baseline CAT score will be fitted instead of baseline FEV_1. The main analyses will be performed on the HO population. The primary treatment comparison will be at the 1 year timepoint.

13.1.3. Quality of Life Determined using the EuroQol 5-D-3L (EQ-5D-3L)

This questionnaire is collected at baseline (visit 2) then at months 3, 6 and every 6 months thereafter, in a subset of countries. The EQ-5D-3L consists of two parts: the EQ-5D-3L descriptive system and the EuroQol VAS (see Section 9.4.19).

For the EQ-5D-3L descriptive system, the number and percentage of subjects with each level within a dimension will be summarised by visit.

Descriptive statistics will be reported for the VAS scores for baseline and all subsequent visits and at withdrawal. The change from baseline will also be summarised at all visits after baseline. The raw change from baseline at each visit will be presented graphically.

The main summaries will be performed on the HO population.

13.2. Resource Utilisation Measures

For severe COPD exacerbations, the total number days in intensive care and in general ward will be summarised and an associated rate per100 treatment exposure years. . The rate is intended to provide a more accurate representation of direct healthcare resource use should there be an imbalance in the exposure to study medication between the treatment groups.

Any other analyses of health outcomes measures for this study will be documented in a separate RAP.

14. BIOMARKER DATA ANALYSIS

Serum and plasma samples were collected at the US sites at visit 2 (pre-dose at randomization visit) and visit 3 (pre-dose at the 3 month visit). It is anticipated that these will be used to measure known inflammatory markers (e.g., hsCRP and fibrinogen) and also for measuring a CBC and Chem 7 panel for use in predictive modelling. Any exploratory analysis of these data will be the subject of a separate analysis plan. A summary table of baseline, visit 3 and change from baseline will be presented. The distributional properties will be assessed and the parameter will be log-transformed if the data suggest sufficient skewness. In this case, the geometric means and coefficient of variation will be presented.

15. PHARMACOGENETIC DATA ANALYSES

Any genetic analyses will be the subject of a separate analysis plan.

16. REFERENCES

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17. ATTACHMENTS

17.1. Table of Contents for Data Displays

The table of contents for data displays are available upon request.

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Poland	ANDRZEJEWSKI, WIESLAW; ARTEMIUK, EDYTA; ASANKOWICZ-BARGIEL, BEATA; BIELOUS-WILK, ANNA; BLACH, ELZBIETA; BLASZCZAK, ROBERT; BOGUSZ, ANNA; BOKIEJ, JULIUSZ; BOZEK, ANDRZEJ; BROMIRSKA, JOANNA; BUKOWCZAN, ZENON; CELINSKI, ALEKSANDER; CHAMERA, JOANNA; CHYLAK, MACIEJ; CIEKALSKA, KORNELIA; CIESLAK, MALGORZATA; CIESLICKI, JAN; CZERWINSKA, ANNA; DOBRYNIEWSKA, MALGORZATA; DWORNICZAK, SZYMON; FIREK, BOHDAN; FOLCIK, KRYSTYNA; GALUSZKA-BILINSKA, ALICJA; GARBICZ, SLAWOMIR; GESINSKA, HANNA; GRZELEWSKA-RZYMOWSKA, IWONA; HAJOL, ELZBIETA; HARAT, RAFAL; HOFMAN, TERESA; JANKOWSKA, RENATA; JANOWICZ, ANNA; JEDRZEJCZAK, MARIOLA; JUREK-URBANOWSKA, AGNIESZKA; KACHEL, TOMASZ; KANIA, GRZEGORZ; KARCZ, DANUTA; KASZTELOWICZ, PIOTR; KAZIROD, TOMASZ; KELM-WARCHOL, AGATA; KORZENIAK, ROMUALD; KRUPA-BOREK, IZABELLA; KUCHARSKI, LECH; KUKLINSKA, BEATA; LABACKA-BARAN, JADWIGA; LIS, KRZYSZTOF; MADRA - ROGACKA, DANUTA; MAGNER, ALINA; MAJOREK-OLECHOWSKA, BERNADETTA; MALOSEK, DOROTA; MARCINIAK, PIOTR; MICHALSKA, EWA; MIEKUS, PAWEL; MINC, PIOTR; MINCEWICZ, GRZEGORZ; MROZ, ROBERT; NIEZGODA, KRZYSZTOF; OLECH-CUDZIK, ANNA; OLECHNOWICZ, DARIUSZ; PARADOWSKA-NOWAKOWSKA, ELZBIETA; PASTERNAK, DARIUSZ; PIETRAK, JUSTYNA; PIOTROWSKI, WOJCIECH; PISARCZYK-BOGACKA, EWA; PORAWSKA, WIESLAWA; PRZEKWAS-JARUCHOWSKA, MAGDALENA; PRZYSIECKI, TOMASZ; PULKA, GRAZYNA; RAJTAR, IRENA; RENTFLEJSZ, MARZENA; ROSLAN, ANDRZEJ; ROZYCKA-GRUDNIEWICZ, MALGORZATA; RYBACKA - CHABROS, BARBARA; RYBACKI, CEZARY; SAWICKI, ANDRZEJ; SCIBORSKI, RYSZARD; SIDOROWICZ-BIALYNICKA, ANNA; SKRZYPCZYNSKA - MANIKOWSKA, ALINA; SLIWINSKI, PAWEL; SMIALOWSKI, ADAM; SZELERSKA-TWARDOSZ, HANNA; SZUMLANSKA, ZYTA; TARNOWSKA - MATUSIAK, MARZENNA; TRAWINSKA, EWA; WIERZCHOWSKA, DOROTA; WOJNOWSKI, PIOTR; WOLF, HANNA; ZUROWSKA-GEBALA, MALGORZATA
Romania	ALEXA, IOANA DANA; ALEXANDRESCU, DANA; ALEXANDRU, TOM-MIHAI; ANDRAS, GABRIELA; ANDREI, LAURENTIA; ARGHIR, OANA CRISTINA; BARBU, CORNELIA; BARTOS, DANIELA; BOGDAN, MIRON; BUMBACEA, DRAGOS; CAMPIAN TATAR, VIOLETA AURORA; COJOCARU, CRISTIAN; DRAMBAREANU, ILEANA; JIMBOREAN, GABRIELA; MAN, MILENA-ADINA; MIHAICUTA, STEFAN; MIHALACHE, LUMINITA VASILICA; MIHALTAN, FLORIN; MINCU, VIORICA; MOCANESCU, DANIELA; MONTIA, TATIANA; NEGREAN, VASILE; OLAR, DANA; PALL, ENIKO-VERA; PETRUI, IOAN DORIN; POPESCU, ELENA; SAVU, ANGELICA; STANCIU, ALEXANDRU; TANASEANU, CRISTINA MIHAELA; TANASESCU, COMAN; TODEA, DOINA; TRAILESCU, ANA-MARIA; TUDORAN, MARIANA; TUTESCU, ADRIANA-CARMEN; ULMEANU, RUXANDRA; UNGUREANU, DRAGOS; VOICULESCU, MIHAI
Russian Federation	ABROSIMOV, VLADIMIR; AGAFINA, ALINA; AKATOVA, EUGENIA; ALEKSEEVA, ELENA; ANTONOV, ALEXANDER; ARKHIPOVSKIY, VADIM; ARUTYUNOV, GRIGORIY; AVERYANOV, ALEXANDER; BALLUZEK, MARINA; BARBARASH, OLGA; BELENKOV, YURY; BELOUSOV, YURY; BERKOVICH, OLGA; BERNS, SVETLANA; BEZLEPKO, ALEXANDER; BUGROVA, OLGA; BUKREEVA, EKATERINA; CHERMENSKIY, ALEXEY; CHIZHOV, PETR; CHIZHOVA, OLGA; DEMKO, IRINA; ESIP, VALERIA; EVDOKIMOVA, ANNA; FEDOROVA, OLGA; GALVAS, NATALIA; GIORGADZE, MARINA; GIVIROVSKIY, STANISLAV; GONCHAROVA, SVETLANA; GRIGORYEV, SERGEY; IGNATOVA, GALINA; ILKOVICH, MIKHAIL; ILKOVICH, YULIYA; IRKHINA, IRINA; ISHINA, TATIANA; IZMOZHEROVA, NADEZHDA; KHOKHLOV, ALEXANDER; KHRUSTALEV, OLEG; KOBALAVA, ZHANNA; KOSTIN, VLADIMIR; KOSTINA, NATALIA; KOZIOLOVA, NATALYA; KRIVOSHEEV, ALEXANDER; KUKOL, LIDIA; KUZIN, ANATOLY; KUZMENKO, ALEXANDER; KUZUBOVA, NATALIA; LARINA, OLGA; LEBEDEVA, ANASTASIA; LENSKAYA, LIUDMILA; LESHCHENKO, IGOR; LIBIS, ROMAN; LOGVINENKO, NADEZHDA; LYAMINA, NADEZHDA; MARTYNENKO, VLADIMIR; MARTYNOV, ALEXEY; MOLOTKOV, ARTEM; MYASOEDOVA, SVETLANA; NEMTSOV, BORIS; NOVIKOVA, TATIANA; OBREZAN, ANDREY; OLEYNICHENKO, EKATERINA; OSIPOVA, IRINA; PALYUTIN, SHAMIL; PESKOV, ANDREY; PLATONOV, DMITRY; POLEVTSOVA, GALINA; POLKANOVA, ELENA; POLUBOYAROVA, NINA; POPOVA, VERONIKA; POSTNIKOVA, LARISA; POTERYAEVA, ELENA; PRONINA, SVETLANA; RAGOZINA, NADEZHDA; RASPOPINA, NATALIA; REBROV, ANDREY; REPIN, ALEXEY; REPIN, MIKHAIL; RESHEDKO, GALINA; RESHETKO, OLGA; SAIFUTDINOV, RAFIK; SEMENOVA, IRINA; SHALNEV, VLADIMIR; SHAPOROVA, NATALIA; SHAPOVALOVA, YULIA; SHAYDYUK, OXANA; SHCHEKOTOV, VLADIMIR; SHERENKOV, ALEXANDER; SHILKINA, NATALIA; SHMELEV, EVGENY; SHOSTAK, NADEZHDA; SHPAGINA, LUBOV; SHUTKIN, ALEXANDER; SHVARTS, YURY; SMIRNOVA, YANA; STEPANENKO, TATYANA; STITSENKO, IRINA; TERESCHENKO, SERGEY; TKACHEV, ALEXANDER; TROFIMOV, VASILIY; URYASEV, OLEG; VERTKIN, ARKADY; VIZEL, ALEXANDER; VOROBEVA, ELENA; YAKUSHIN, SERGEY; ZADIONCHENKO, VLADIMIR; ZAGIDULLIN, SHAMIL; ZATEYSHCHIKOV, DMITRY; ZATEYSHCHIKOVA, ANNA; ZHILYAEV, EUGENY; ZRAZHEVSKIY, KONSTANTIN
Serbia	DOPUDJA PANTIC, VESNA; GRUJIC, MILAN; KOPITOVIC, IVAN; LAZIC, ZORICA; LAZOVIC, BILJANA; LAZOVIC, NADA; MILENKOVIC, BRANISLAVA; OGRIZOVIC PONJEVIC, ALEKSANDRA; RAKOVIC, SLAVICA; SOVLJANSKI, GORANA; STANKOVIC, IVANA; STOJANOVIC, ANA
Slovakia	ARPASOVA, KATARINA; BABCAKOVA, EMILIA; DRUGDOVA, MARIA; FRAJTOVA, LUBOSLAVA; HORVATHOVA, HELENA; HREBENAR, SLAVOMIR; JURCO, PETER; KARAKO SR, PAVOL; KURTHOVA, SVETLANA; MICHALICKOVA, MIRIAM; MIHALECOVA, YVONNA; POBEHOVA, MARIA; PRIBULOVA, ERIKA; SALATOVA KOZLOVSKA, IVETA; SZARAZOVA, MONIKA

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Spain	ANDREO GARCIA, FELIPE; BOADA VALMASEDA, ALBERT; BUSTAMANTE RUIZ, ANA; ECHAVE-SUSTAETA, JOSE; ESPINOSA DE LOS MONTEROS, MARIA; HERREJON SILVESTRE, ALBERTO; LORES OBRADORS, LUIS; LUENGO PLANAS, MARIA TERESA; MONSO MOLAS, EDUARD; RAMOS BARBON, DAVID; RODRIGUEZ ALVAREZ, MARIA; SALA LLINAS, ERNEST; SANTOS PEREZ, SALUD; SAURA VINUESA, ALBERTO; SERRA BATLLES, JOAN; SOLER PORCAL, NESTOR; SOTO CAMPOS, JOSE; TORAN MONTSERRAT, PERE; VALDES CUADRADO, LUIS; VILLASANTE FERNANDEZ-MONTES, CARLOS; VIOZQUEZ MEYA, MARIA
Taiwan, Province of China	CHENG, KUO-CHEN; CHERN, JIA-HAUR; HUANG, MING-SHYAN; KUO, PING-HUNG; LEE, CHUN-NIN; LIN, CHING-HSIUNG; LIU, YU-CHIH; PAI, PEI-YING; PAN, HSIN-HUNG; TSAO, SHIH-MING; WANG, CHIN-CHOU; YANG, CHAO-HUEI
Thailand	CHANTAROTHORN, SOMCHAI; CHUAYCHOO, BENJAMAS; KEERATICHANANONT, WARANGKANA; NIYOMPATTAMA, ANICHIT; PIPATVECH, KANOK; POTHIRAT, CHAICHARN; SANGSAYUNH, PIAMLARP; SITTIPUNT, CHANCHAI; SUNTRAPIWAT, KAJORN; WATTANATHUM, ANAN
Turkey	BULBUL, YILMAZ; KARADAG, MEHMET; ORTAKOYLU, GONENC; SARYAL, SEVGI; UNSAL, MEFTUN
Ukraine	ABRAHAMOVYCH, OREST; AMER, LARYSA; BERENFUS, VADYM; BILOGLAZOV, VOLODYMYR; BILOKONNA, NATALIIA; BLAZHKO, VIKTOR; BOROVYK, VALENTYNA; BOYKO, MYKOLA; BUTVYN, SERGIY; CHOPEY, IVAN; DUDCHENKO, LEYLA; DZIUBLYK, OLEKSANDR; FESHCHENKO, YURIY; FUSHTEY, IVAN; GAVRYSYUK, VOLODYMYR; GODLEVSKA, OLGA; GOLOVCHENKO, NATALIIA; GOLOVCHENKO, OLEKSANDR; GRISHYNA, OLENA; GYRINA, OLGA; HOSPODARSKYY, IHOR; IABLUCHANSKYI, MYKOLA; IASHYNA, LIUDMYLA; KAIDASHEV, IGOR; KAZYMYRKO, VITALIY; KHOMAZYUK, TETYANA; KHVELOS, SERGIY; KNOPYK, LIUBOV; KOPYTSYA, MYKOLA; KORZHEVNYK, IRYNA; KOSHUKOVA, GALYNA; KOVALCHUK, TAMARA; KRAKHMALOVA, OLENA; KRASNOKUTSKIY, SERGIY; KRASYUK, SERGII; KULYK, ANNA; KULYNYCH, OLEKSII; KURYATA, OLEXANDR; LEVCHENKO, OLENA; MONOGAROVA, NADIYA; MOSTOVOY, YURIY; NALOTOV, SERGIY; OSPANOVA, TETYANA; OSTROVSKYY, MYKOLA; PANINA, SVITLANA; PASIYESHVILI, LYUDMYLA; PAVLYK, STEPAN; PERTSEVA, TETYANA; PLESH, IGOR; PRYSTUPA, LYUDMYLA; RODIONOVA, VIKTORIYA; ROMANIUK, LILIIA; SHVETS, NINA; SKRYPNYK, IGOR; STANISLAVCHUK, MYKOLA; STETS, ROMAN; SYNENKO, VOLODYMYR; SYVOLAP, VITALIY; TELIATNIKOVA, ZINAIDA; TOVT- KORSHYNSKA, MARIANNA; VATUTIN, MYKOLA; VAYDA, MYROSLAVA; VISHNIVETSKY, IVAN; VIZIR, VADYM; VOLOSHYNA, OLENA; VYNNYCHENKO, LYUDMYLA; YAGENSKY, ANDRIY; YATSYSHYN, ROMAN; ZHARINOVA, VIKTORIIA; ZHEBEL, VADYM
United Kingdom	BLAGDEN, MARK; CALVERLEY, PETER; CHHOKAR, BALGIT; DESHPANDE, MAYURA; EYRE, SUSANNAH; FIORE, GIUSEPPE; GEORGE, ALUN; HORVATHOVA, VERONIKA; KONDAGUNTA, VENKATA; MACNEE, WILIAM; MATHEW, AMIT; SAXENA, MANISH; SHARMA, RAJIV RAJ; TAKHAR, AMRIT; TURNER, ALICE

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LISBERG, EDWARD; LIU, JING; LIU, MARK; LOCKEY, RICHARD; LOYNAZ, ALEJANDRO; LUMICAO, BENJAMIN; LYNCH, MICHAEL; MAAS, ANDREA; MACGILLIVRAY, BRIAN; MADISON, JAN; MADOR, JEFFERY; MAHMOOD, KHALID; MAKE, BARRY; MAKSOUD, ALFRED; MAPEL, DOUGLAS; MARASCO, CHRIS; MARCHETTI, NATHANIEL; MARTINEZ, RAFAEL; MASCOLO, MARIA; MASON, RAYMOND; MASRI, BASSEM; MATARIA, HAMED; MATTAR, PETER; MAUGHAN, GEORGE; MAZDISNIAN, FARHAD; MBOGUA, CAROLINE; MCEVOY, CHARLENE; MCGUIRE, MICHAEL; MCNEIL, DONALD; MEHTA, KIRAN; MELI, JAMES; MELLO, CURTIS; MENDEZ, ELVIN; MINTON, STEPHEN; MIRANDA, FRANCISCO; MOBIN, SYED; MONTANARO, ANTHONY; MORAN, JOSEPH; MORIN, SCOTT; MOSES, LEONARD; MOY, JAMES; MUNOZ, FRANCISO; MURPHY, FRANK; MURRAY, ALEXANDER; NACCARI, BRIAN; NASSERY, MANOOCHER; NATHANSON, MICHAEL; NEVINS, BROOKE; NUALART, MARIA; NYANJOM, DAVID; OBEID, DANY; OBEROI, MANDEEP; OBRIEN, THOMAS; OCAMPO, ALVARO; OCONNOR, THOMAS; ODIO, ALBERTO; ODONNELL, PHILLIP; ONG, STEPHEN; PACE, MICHAEL; PAINE, WARD; PALATNIK, MIKHAIL; PANOS, RALPH; PATEL, AMIT; PATEL, BHADRESH; PERRY, CHRISTOPHER; PHAM, DAVID; PLAUTZ, MARK; PLUTO, TIFFANY; POLLOCK, MARK; POPEIL, LARRY; POPOVICH, KEITH; PRISCO, DOUGLAS; QAQUNDAH, PAUL; RAIKHEL, MARINA; RAMASWAMY, MURALI; RAMSDELL, JOE; RANDALL, WILLIAM; RANGEL, ORLANDO; RASTOGI, PADMASHRI; REHMAN, SYED; RENNARD, STEPHEN; REYES, HUBERT; RHUDY, JACKSON; RICE, KATHRYN; RICE, LUCIAN; RILEY, EUSTACE; RISKE, TERRANCE; RISSER, JOSEPH; RIVERO, ORLANDO; ROBINETTE, EMORY; RODRIGUEZ, HECTOR; ROMEU, HUGO; ROSSRUCKER, JILL; RUOFF, GARY; RUZI, JONATHAN; RYAN, EUGENE; SAGALOVICH, BORIS; SALIAN, NAGESH; SALMON, JAMES; SALTZMAN, MARC; SAMUDRALA, STEVE; SAMUELSON, ROBERT; SANCHEZ-CAZAU, DOLORES; SANDBERG, JAY; SANTIAGO, JOSE; SARGEANT, WILLIAM; SAWYER, HOWARD; SCANLON, PAUL; SCHARF, STEVEN; SCHIFFMAN, GEORGE; SCHWARTZ, MITCHELL; SEHGAL, SUDHIR; SEIBERT, ALLAN; SELLMAN, RICHARD; SEVERA, LARRY; SHAH, AMIT; SHAPERO, PAUL; SHARAFKHANEH, AMIR; SHAUKAT, MUHAMMAD; SHEA, JEFFREY; SHEARER, STEPHANIE; SHEIKH, SALMAN; SHEPHERD, TIM; SHERER, KEVIN; SHU, WARREN; SIDDIQUI, AKHTAR; SIMON, STUART; SOUTHARD, JOHN; SRIRAM, PERUVEMBA; STEELE, RALPH; STEGEMOLLER, RONALD; STERN, THOMAS; STEVENS, JOHNNIE; STILLERMAN, ALLAN; STOCKS, JAMES; STORMS, WILLIAM; SUAREZ, JOSE; SUEN, JOHN; SYED, FAIZULLAH; TANUS, TONNY; TARLETON, GREGORY; TATU, HORIA; TERRELONGE, ANTONIO; TIDMAN, RAYMOND; TOPKIS, ROBERT; TORRES, MARIO; TREJO, RODOLFO; TREVINO, MIGUEL; TRIKHA, GIRISH; TROYAN, BARRY; TWIDDY, SHANNON; UPDEGROVE, JOHN; VAN GINKEL, ERIK; VOYCE, STEPHEN; WACHTEL, ANDREW; WAINZ, RONALD; WALIA, JASJIT; WALKER, ROBERT; WEBSTER, DAVE; WEINBERG, PAUL; WEISS, ROBERT; WELLS, TERRY; WENOCUR, HOWARD; WIESKOPF, BRAM; WILLIAMS, ADAM; WILSON, SCOTT; WRIGHT, PATRICK; WRIGHT, SCOTT; YAMADA, HUGO; YAU, PETER; YERGIN, BRUCE; YIM, ROGER; YOUNG, DOUGLAS; YUNGER, THOMAS; ZEIDLER, MICHELLE; ZENO, BRIAN; ZUWALLACK, RICHARD
Viet Nam	DAO, THI DUA; DINH, NGOC SY; DO, QUYET; LE, THI THU HUONG; LE, THI TUYET LAN; NGO, QUY CHAU; NGUYEN, HUY DUNG; NGUYEN, VAN THANH; TRAN, MANH HONG; TRAN, VAN NGOC