

TITLE PAGE

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Title:	A phase IIIB, 24-week randomised, double-blind study to compare 'closed' triple therapy (FF/UMEC/VI) with 'open' triple therapy (FF/VI + UMEC), in subjects with chronic obstructive pulmonary disease (COPD)
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2015N261999_01	2016-JAN-25	Amendment No. 1- Global
<p>1. Synopsis, Section 1 and Overall Design, Section 4.1: Text updated to include the requirement for an early withdrawal study for subjects who stop study treatment early.</p> <p>2. Time and Events Table, Section 7.1: Scheduling of pulse oximetry corrected and scheduling of genetics sample collection revised.</p> <p>3. Appendix 3 - Genetics Research: Text corrected to include combinations of study medications used in the protocol and the scheduled visit for sample collection revised.</p> <p>Appendix 8 – Hair Sample, Scalp & Finger Secretion PK Sub-Study: Discrepancy regarding the timing of sample collection corrected.</p>		
2015N261999_02	2016-FEB-11	Amendment No. 2- South Korea ONLY
<p>Appendix 6 updated, for South Korea, with study medication labeling and information regarding study equipment.</p>		
2015N261999_03	2016-JUN-29	Amendment No. 3- Global (excluding South Korea)
<p>1. Minor discrepancies corrected and clarifications made to some of the footnotes in the Time and Events Table.</p> <p>2. The requirement of two views (posteroanterior and lateral) for Screening chest x-rays and chest x-rays for suspected pneumonias and moderate/severe exacerbations specified.</p> <p>3. Reference section updated.</p> <p>4. A minor update to the wording for when the genetics sample can be collected made in the Time and Events Table and Appendix 3.</p>		

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 200812

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 Signature

Date

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1. PROTOCOL SYNOPSIS FOR STUDY 200812

Rationale

GlaxoSmithKline (GSK) is currently developing a once-daily ‘closed’ triple therapy of a ICS/LAMA/LABA combination [fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) (100mcg/62.5mcg/25mcg)] in a single inhaler, with the aim of providing a new treatment option for the management of advanced (GOLD Group D) COPD which will reduce the exacerbation frequency, allow for a reduced burden of polypharmacy, convenience, and improve lung function, health related quality of life (HRQoL) and symptom control over established dual/monotherapies.

The primary purpose of this study is to demonstrate the non-inferiority of closed triple therapy (FF/UMEC/VI) to open triple therapy (FF/VI + UMEC) on lung function.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To compare the effect of FF/UMEC/VI with FF/VI + UMEC on lung function after 24 weeks of treatment 	<ul style="list-style-type: none"> Change from baseline in trough FEV₁ at 24 weeks
Secondary	
<ul style="list-style-type: none"> To compare the effects of FF/UMEC/VI with FF/VI + UMEC on health related quality of life and dyspnoea after 24 weeks of treatment 	<ul style="list-style-type: none"> Proportion of Responders based on the St George Respiratory Questionnaire (SGRQ) Total Score at Week 24 Change from baseline in SGRQ Total Score at Week 24 Proportion of Responders based on Transitional Dyspnoea Index (TDI) focal score at Week 24 TDI focal score at Week 24
<ul style="list-style-type: none"> To compare the effect of FF/UMEC/VI with FF/VI + UMEC on time to first moderate or severe exacerbation during 24 weeks of treatment 	<ul style="list-style-type: none"> Time to first moderate or severe exacerbation

Objectives	Endpoints
Pharmacokinetics (PK)	
<ul style="list-style-type: none"> To compare the PK of FF, UMEC and VI when given as FF/UMEC/VI or FF/VI+UMEC in a subset of subjects 	<ul style="list-style-type: none"> Population PK (in a subset of approximately 180 subjects)
Safety	
<ul style="list-style-type: none"> To compare the safety profile of FF/UMEC/VI with FF/VI + UMEC over 24 weeks of treatment 	<ul style="list-style-type: none"> Incidence of adverse events Incidence of adverse events of special interest¹ ECG measurements Vital signs Haematological and clinical chemistry parameters

Overall Design

This is a phase IIIB, 24-week, randomised, double-blind, parallel group multicenter study evaluating FF/UMEC/VI (100mcg/62.5mcg/25mcg) via a single ELLIPTA™ (‘closed triple’) plus matching placebo versus FF/VI + UMEC delivered via two ELLIPTA’s (‘open triple’), all taken once daily. The target enrollment is 1020 randomised subjects at approximately 150 study centres globally. Subjects will run-in on their existing COPD medications for 2 weeks and in addition will be provided with short acting albuterol/salbutamol to be used on an as-needed basis (rescue medication) throughout the study. Subjects will discontinue all existing COPD medications at the start of the randomised treatment period but may continue their study-supplied rescue albuterol/salbutamol.

Clinic Visits will occur at Pre-Screening (V0), Screening (V1), Randomisation (Week 0, V2), Week 4 (V3), Week 12 (V4) and Week 24 (V5). A safety follow-up telephone contact or clinic visit will be conducted 1 week after completing either randomised treatment or an Early Withdrawal Visit. Subjects will sign an informed consent form (ICF) at a Pre-Screen or Screening Visit (V1) and will be assigned a subject identifier.

At Screening (V1), responses to the COPD Assessment Tool (CAT) questionnaire will be collected using an electronic device, prior to completing other Screening assessments. Subjects will self-administer their first doses of study treatment in the clinic during Randomisation (V2). On the morning of each study clinic visit, subjects will refrain from

¹ See Section 7.4.3. for further information on AESI’s

taking their morning doses of study treatment until instructed to do so by clinic personnel. At clinic visits, responses to questionnaires, SGRQ-C and Baseline Dyspnoea Index (BDI) and TDI, will be collected using an electronic device, in that order and prior to dosing or completing other assessments. Subjects will take their last dose of study treatment in the clinic during V5 and a safety follow-up will be conducted either by phone call or clinic visit approximately one week later.

Approximately 180 subjects, in selected sites, will be asked to participate in PK research. There will be two PK groups (subset A and subset B). Approximately 120 subjects will be assigned to subset A and approximately 60 subjects will be assigned to subset B.

Subjects in subset A will provide a blood sample at two time-points at Week 12 (V4) and at Week 24 (V5). Subjects in subset B will provide blood samples at seven time points at Week 12 (V4).

Subjects providing PK samples for subset A may also be asked to take part in a hair sample, scalp & finger secretion PK Sub-Study. See [Appendix 8](#) (Section 12.8).

A subject will be considered to have completed the study when they have completed all phases of the study including screening, run-in, the randomised treatment phase, and safety follow-up. Subjects who stop study treatment early will complete an Early Withdrawal Visit, followed by a Safety Follow-Up a week later and finally be withdrawn from the study.

Treatment Arms and Duration

Subjects who meet all the inclusion/exclusion criteria and who have successfully completed all protocol procedures at Screening (V1) will enter the two-week run-in period. Following the run-in period, eligible subjects will be randomised (1:1) to one of the following double-blind treatment groups for 24 weeks.

- FF/UMEC/VI 100mcg/62.5mcg/25mcg and placebo, both via the ELLIPTA once daily in the morning.

or,

- FF/VI 100mcg/25mcg and UMEC 62.5mcg, both via the ELLIPTA once daily in the morning.

The ELLIPTA contains 30 doses (FF/UMEC/VI, FF/VI, UMEC or placebo) and subjects will be instructed to administer one dose from each ELLIPTA once daily in the morning.

The randomisation will be stratified based on **long-acting bronchodilator** usage during the run-in (none, one or two **long-acting bronchodilators** per day).

The total duration of subject participation will be approximately 27 weeks, consisting of a 2-week run-in period, 24-week treatment period and a 1-week follow-up period.

Type and Number of Subjects

Approximately 1275 subjects with advanced COPD (GOLD Group D) will be screened in order to randomise approximately 1020 subjects in order to achieve an estimated 816 subjects who are included in the Adherent Population and complete V5.

Approximately 150 centres globally will be required to recruit the study.

Analysis

The null hypothesis is that the difference in trough FEV₁ between treatment groups is less than or equal to a pre-specified non-inferiority margin $-\Delta$:

$$H_0: T_1 - T_2 \leq -\Delta$$

The alternative hypothesis is that the difference between treatment groups is greater than the margin.

$$H_1: T_1 - T_2 > -\Delta$$

where T_1 and T_2 are the treatment means for FF/UMEC/VI and FF/VI+UMEC, respectively.

The non-inferiority margin has been set at 50mL, which is half the generally accepted minimal clinically important difference (MCID) for trough FEV₁.

If the lower bound of the two-sided 95% confidence interval around the (FF/UMEC/VI vs. FF/VI+UMEC) treatment difference is above -50mL then FF/UMEC/VI will be considered non-inferior to FF/VI+UMEC.

The primary analysis population will be the Adherent Population, comprising all subjects randomized to treatment except those randomized in error, who do not have a full protocol deviation or other event considered to impact efficacy.

The primary treatment comparison is the comparison of FF/UMEC/VI with FF/VI+UMEC for the primary endpoint of trough FEV₁ at Week 24. This comparison will be performed for the Adherent population, using data collected prior to withdrawal/completion of study treatment.

The primary treatment comparison will evaluate the “de jure” estimand for the primary endpoint of trough FEV₁ at Week 24, in the Adherent population, using a mixed model repeated measures (MMRM) analysis, including trough FEV₁ recorded at each of Weeks 4, 12 and 24. The model will include covariates of stratum (number of long-acting bronchodilators taken per day during the run-in), baseline FEV₁, Week, centre group, treatment and Week by baseline interaction. A Week by treatment interaction term will also be included to allow treatment effects to be estimated at each visit separately. The variance-covariance matrix will be assumed unstructured.

A “tipping point” sensitivity analysis of trough FEV1 will be conducted for the Adherent Population. This will explore the impact of missing data by using differing assumptions regarding the mean treatment effect in subjects who discontinue study treatment or have data excluded from Adherent Population analyses. Assumptions will include scenarios where subjects who discontinue FF/UMEC/VI have a lower treatment effect than those who discontinue FF/VI+UMEC. The analysis results will be used to explore the conditions under which the conclusion of non-inferiority no longer holds.

2. INTRODUCTION

COPD guidelines advocate the use of one or more long-acting bronchodilators (long-acting muscarinic receptor antagonists [LAMA]) or long-acting β_2 -adrenergic receptor agonists [LABA]) in addition to inhaled corticosteroids (ICS) as second line therapy for the most advanced patients with significant symptoms and a high risk of exacerbations. Regular treatment with ICS has been reported to improve respiratory symptoms, lung function, health related quality of life (HRQoL) and reduce the frequency COPD exacerbation in patients with a FEV1<60% predicted. Additionally, withdrawal of ICS treatment has also lead to exacerbations in some patients [[GOLD](#), 2013].

Population based studies of COPD treatment patterns demonstrate that ‘open’ triple therapy (use of ICS/LAMA/LABA delivered via multiple inhalers) is already widely used in the real-life management of COPD. In 2011, 26% of patients in the USA who were taking controller medicines for the treatment of COPD were taking an ‘open’ triple therapy, typically by adding fluticasone propionate/salmeterol (ICS/LABA) to tiotropium (LAMA) or vice versa [[Wolters](#), 2012]. A study in the UK Clinical Practice Research Database (CPRD) revealed that over a two year period of time, 35% of COPD patients initially prescribed a LAMA and 39% initially prescribed an ICS/LABA stepped up to an ‘open’ triple therapy regimen [[Wurst](#), 2013]. In the four year long term safety study conducted with tiotropium (LAMA), 46% of patients were receiving a concurrent fixed combination of ICS/LABA in addition to tiotropium [[Tashkin](#), 2008].

2.1. Study Rationale

GlaxoSmithKline (GSK) is currently developing a once-daily ‘closed’ triple therapy of an ICS/LAMA/LABA [Fluticasone furoate (FF)/Umeclidinium (UMEC)/Vilanterol (VI) (100mcg/62.5mcg/25mcg)] in a single inhaler, with the aim of providing a new treatment option for the management of advanced (GOLD Group D) COPD. It is expected that this therapy will reduce the exacerbation frequency, allow for a reduced burden of polypharmacy, convenience, and improve lung function, HRQoL and symptom control compared to established dual/monotherapies.

The primary purpose of this study is to demonstrate the non-inferiority of closed triple therapy (FF/UMEC/VI) to open triple therapy (FF/VI + UMEC) on lung function.

2.2. Brief Background

Adult patients with a clinical diagnosis of COPD have previously been exposed to the open triple combination FF/VI + UMEC, in two 12-week, placebo controlled studies (200109 and 200110). In these studies, the addition of UMEC (62.5) to FF/VI (100/25) once daily, resulted in statistically significant and clinically meaningful improvements in the primary endpoint of trough FEV₁ at Day 85 compared to placebo plus FF/VI (124 mL (95% CI 93, 154, p<0.001) and 122 mL (95% CI 91, 152, p<0.001)). The safety profile for UMEC in combination with FF/VI was similar across treatment arms, and no additive effects or new safety concerns were identified.

Two healthy volunteer clinical pharmacology studies have also been conducted (CTT116415 and 200587) which supports the conclusion that there are no clinically relevant systemic pharmacokinetic or systemic pharmacodynamic interactions between the components of the closed triple combination product (FF, UMEC and VI) when administered through a single inhaler.

A number of studies have assessed the use of an ‘open’ triple therapy of fluticasone propionate/salmeterol or budesonide/formoterol (ICS/LABA) with tiotropium (LAMA) in moderate-severe COPD patients. These studies have reported greater improvements in lung function, HRQoL, hospitalization rates and rescue medication use, compared to dual (ICS/LABA) or LAMA alone, thus supporting the use of triple therapy in COPD [Aaron, 2007; Cazzola, 2007; Hanania, 2012; Jung, 2012; Welte, 2009]. These studies have also shown that the number and type of reported adverse events (AE) were generally similar with administration of dual or monotherapy doses for periods of up to one year, and were mostly related to their pharmacological mode of action.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To compare the effect of FF/UMEC/VI with FF/VI + UMEC on lung function after 24 weeks of treatment 	<ul style="list-style-type: none"> Change from baseline in trough FEV₁ at 24 weeks
Secondary	
<ul style="list-style-type: none"> To compare the effects of FF/UMEC/VI with FF/VI + UMEC on health related quality of life and dyspnoea after 24 weeks of treatment 	<ul style="list-style-type: none"> Proportion of Responders based on the St George Respiratory Questionnaire (SGRQ) Total Score at Week 24 Change from baseline in SGRQ Total Score at Week 24 Proportion of Responders based on Transitional Dyspnoea Index (TDI) focal score at Week 24 TDI focal score at Week 24

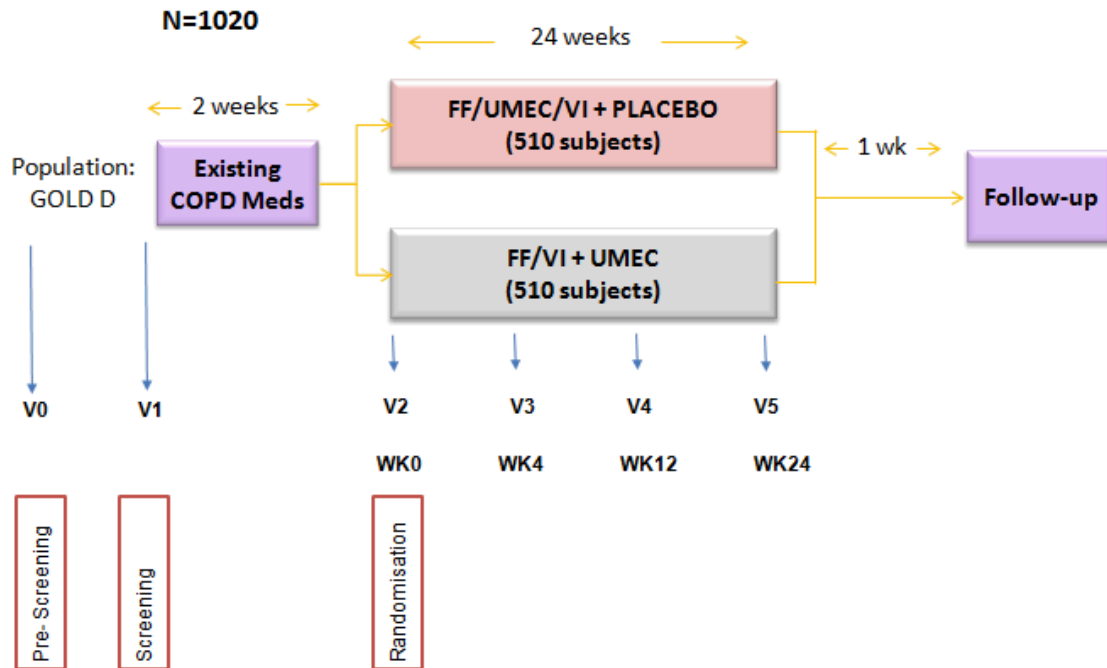
Objectives	Endpoints
<ul style="list-style-type: none"> To compare the effect of FF/UMEC/VI with FF/VI + UMEC on time to first moderate or severe exacerbation during 24 weeks of treatment 	<ul style="list-style-type: none"> Time to first moderate or severe exacerbation
Pharmacokinetics (PK)	
<ul style="list-style-type: none"> To compare the PK of FF, UMEC and VI when given as FF/UMEC/VI or FF/VI+UMEC in a subset of subjects 	<ul style="list-style-type: none"> Population PK (in a subset of approximately 180 subjects)
Safety	
<ul style="list-style-type: none"> To compare the safety profile of FF/UMEC/VI with FF/VI + UMEC over 24 weeks of treatment 	<ul style="list-style-type: none"> Incidence of adverse events Incidence of adverse events of special interest² ECG measurements Vital signs Haematological and clinical chemistry parameters

² See section 7.4.3. for further information on AESI's

4. STUDY DESIGN

4.1. Overall Design

Figure 1 Study Schema



This is a phase IIIB, 24-week, randomised, double-blind, parallel group multicenter study evaluating FF/UMEC/VI (100mcg/62.5mcg/25mcg) via a single ELLIPTA ('closed triple') plus matching placebo versus FF/VI + UMEC delivered via two ELLIPTA's ('open triple'), all taken once daily. The target enrollment is 1020 randomised subjects at approximately 150 study centres globally. Subjects will run-in on their existing COPD medications for 2 weeks and in addition will be provided with short acting albuterol/salbutamol to be used on an as-needed basis (rescue medication) throughout the study. Subjects will discontinue all existing COPD medications at the start of the randomised treatment period but may continue their study-supplied rescue albuterol/salbutamol.

Clinic Visits will occur at Pre-Screening (V0), Screening (V1), Randomisation (Week 0, V2), Week 4 (V3), Week 12 (V4) and Week 24 (V5). A safety follow-up telephone contact or clinic visit will be conducted 1 week after completing either randomised treatment or an Early Withdrawal Visit. Subjects will sign an informed consent form (ICF) at a Pre-Screen or Screening Visit (V1) and will be assigned a subject identifier.

At Screening (V1), responses to the COPD Assessment Tool (CAT) questionnaire will be collected using an electronic device, prior to completing other Screening (V1) assessments. Subjects will self-administer their first doses of study treatment in the clinic

during Randomisation (V2). On the morning of each study clinic visit, subjects will refrain from taking their morning doses of study treatment until instructed to do so by clinic personnel. At clinic visits, responses to questionnaires, SGRQ-C and Baseline Dyspnoea Index (BDI) and TDI, will be collected using an electronic device, in that order and prior to dosing or collecting other assessments. Subjects will take their last dose of study treatment in the clinic during V5 and a safety follow-up will be conducted either by phone call or clinic visit approximately one week later.

Approximately 180 subjects, in selected sites, will be asked to participate in pharmacokinetic (PK) research. There will be two PK groups (subset A and subset B). Approximately 120 subjects will be assigned to subset A and approximately 60 subjects will be assigned to subset B.

Subjects in subset A will provide a blood sample at two time-points at Week 12 (V4) and at Week 24 (V5). Subjects in subset B will provide blood samples at seven time points at Week 12 (V4).

Subjects providing PK samples for subset A may also be asked to take part in a hair sample, scalp & finger secretion PK Sub-Study. See [Appendix 8](#) (Section 12.8).

A subject will be considered to have completed the study when they have completed all phases of the study including screening, run-in, the randomised treatment phase, and safety follow-up. Subjects who stop study treatment early will complete an Early Withdrawal Visit, followed by a Safety Follow-Up a week later and finally be withdrawn from the study.

4.2. Treatment Arms and Duration

Subjects who meet all the inclusion/exclusion criteria and who have successfully completed all protocol procedures at Screening (V1) will enter the two-week run-in period. Following the run-in period, eligible subjects will be randomised (1:1) to one of the following double-blind treatment groups for 24-weeks.

- FF/UMEC/VI 100mcg/62.5mcg/25mcg and placebo, both via the ELLIPTA once daily in the morning.
- or,*
- FF/VI 100mcg/25mcg and UMEC 62.5mcg, both via the ELLIPTA once daily in the morning.

The ELLIPTA contains 30 doses (FF/UMEC/VI, FF/VI, UMEC or placebo) and subjects will be instructed to administer one dose from each ELLIPTA once daily in the morning.

The randomisation will be stratified based on **long-acting bronchodilator** usage during the run-in (none, one or two **long-acting bronchodilators** per day).

The total duration of subject participation will be approximately 27 weeks, consisting of a 2-week run-in period, 24-week treatment period and a 1-week follow-up period.

4.3. Type and Number of Subjects

Approximately 1275 subjects with advanced COPD (GOLD Group D) will be screened in order to randomise approximately 1020 subjects in order to achieve an estimated 816 subjects who are included in the Adherent Population and complete V5.

Approximately 150 centres globally will be required to recruit the study.

4.4. Design Justification

This study will use a multicenter, randomised, double-blind, matching placebo, parallel-group design. Eligible subjects will be included in a 24-week treatment period; a duration which is compatible with the guidelines and previous recommendations of national health technology assessment agencies in countries including France ([Haute Autorité de Santé, 2009](#)), Germany ([Institute for Quality and Efficiency in Health Care, 2015](#)) and Australia ([Pharmaceutical Benefits Advisory Committee, 2013](#)). A placebo arm is not included because the primary comparison of interest is FF/UMEC/VI (closed triple) vs. FF/VI + UMEC (open triple) and it is not considered appropriate to include a placebo arm in a study in patients with advanced COPD. A placebo ELLIPTA is included in the closed triple arm to maintain the double-blind by requiring each dose to be administered using two ELLIPTA's.

Eligible subjects must have been on continuous daily maintenance COPD medication for at least 3 months prior to Screening (V1). During the 2-week run-in period they must not change their COPD medication (dosage or regimen). The 2-week run-in period is necessary in order to allow sufficient time for the results of screening assessments to be returned to the site in order to establish eligibility.

4.5. Dose Justification

The FF/UMEC/VI (100/62.5/25mcg) dose was selected based on the doses that have been licensed for COPD for the FF/VI (100/25mcg) and UMEC/VI (62.5/25mcg) dual combinations through extensive studies in the mono and dual therapy programmes. They are the doses which are currently being studied in the ongoing Phase IIIA closed triple registration programme.

4.6. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2834425 can be found in the Investigator's Brochure (IB). The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Treatment [GSK2834425]		
Pneumonia in patients with COPD	<p>Pneumonia is a class concern for any ICS containing product for the treatment of COPD. In two replicate 12 month studies with FF/VI (HZC102871 & HZC102970) in a total of 3,255 patients with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia (6%- 7%) reported in patients receiving the FF (at strengths of 50, 100, and 200 mcg)/VI 25 mcg combination than in those receiving VI 25 mcg alone (3%). Pneumonia which required hospitalisation occurred in 3% of patients receiving FF/VI (all strengths) and in <1% of patients receiving VI. In these studies, nine fatal cases of pneumonia were reported. Of these, seven were reported during treatment with FF/VI 200/25 mcg, one during treatment with FF/VI 100/25 mcg and one post-treatment with VI monotherapy. Risk factors for pneumonia on FF/VI compared with VI in these studies included current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m² and patients with an FEV₁<50% predicted. These factors should be taken into consideration when using an ICS in patients with COPD.</p> <p>Initial results from the recently completed Study to Understand Mortality and Morbidity (SUMMIT) with Relvar/Breo ELLIPTA provide further data for the risk of pneumonia in patients with COPD. This study included 16,485 patients (from 43 countries) with COPD who had moderate airflow limitation (FEV₁ 50-70% predicted) and either a history or increased risk of cardiovascular disease. The preliminary results from this study indicate that the incidence of</p>	<ul style="list-style-type: none"> - Exclusion criteria as specified in Section 5.2 of the protocol - Collection of information on previous history of pneumonia in past 12 months, including hospitalisation at baseline - Use of pneumonia electronic Case Report Form (eCRF) - All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable), as specified in Section 7.4.9 - Chest x-ray (CXR) required at baseline and whenever a patient has suspected pneumonia or mod/severe exacerbations during the study. The chest x-rays will be reviewed by the investigator and appropriate action taken (if required) based on the investigator's clinical

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>pneumonia was 5.7% on FF/VI 100/25mcg and 5.2% on placebo and the incidence of serious pneumonia was 3.4% on FF/VI 100/25mcg and 3.1% on placebo (data on file).</p> <p>Pneumonia risk will be important in the benefit-risk assessment for both open triple and closed triple in COPD patients, hence a robust risk mitigation strategy is being proposed.</p>	<p>discretion</p> <ul style="list-style-type: none"> - Instream review of blinded data
<p>Systemic effects of corticosteroids: bone disorders, bone mineral density decrease and associated fractures</p>	<p>A decrease in bone mineral density and risk of fractures is a class concern for any ICS-containing product for treatment of COPD.</p> <p>The incidence of bone fractures in patients with COPD (n=3,255) administered FF/VI in two replicate 12 month studies (HZC102871 and HZC102970) was higher in all FF/VI groups (2%) compared with the VI 25 mcg group (<1%). Overall, the incidence of fractures was low. Although there were more fractures in the FF/VI groups compared to the VI 25 mcg group, fractures typically associated with corticosteroid use (e.g. spinal compression/thoracolumbar vertebral fractures) occurred in <1% of the FF/VI and VI treatment arms.</p> <p>As part of the FF/VI development program, a bone mineral density study with FF/VI is being conducted, and this will provide data relevant to both closed and open triple.</p>	<ul style="list-style-type: none"> - Evaluation of the potential for bone systemic corticosteroid effects will be conducted through instream assessment of reported bone adverse events - Use of bone fracture eCRF
<p>Systemic effects of corticosteroids: cortisol</p>	<p>Although all steroids are likely to have some impact on the hypothalamic pituitary axis (HPA axis), the proposed dose of inhaled FF in this study is unlikely to lead to any clinically significant changes. No studies have shown a clinically relevant effect of FF/VI on HPA axis. This includes a formal HPA</p>	<ul style="list-style-type: none"> - Instream review of AE/SAE reports

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
suppression	study in asthma subjects, which assessed the effects of FF/VI 100/25 and 200/25 doses on serum cortisol and 24 hour urinary cortisol excretion, and multiple studies with COPD subjects which monitored 24 hour urinary cortisol. During clinical development of FF & FF/VI, no events of Adrenal Suppression were reported.	
Systemic ocular effects of corticosteroids: glaucoma, cataract, raised intra-ocular pressure	<p>Systemic ocular effects (e.g. cataract and glaucoma) may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. However, these effects are much less likely to occur with inhaled corticosteroids compared with oral corticosteroids.</p> <p>In study HZA106839 (FF/VI, FF and FP in subjects with asthma), formal ophthalmic assessments were conducted (including LOCS III evaluations for ocular opacities) throughout the study. The study showed no apparent effects on lens opacification compared to baseline.</p> <p>During studies with FF/VI in subjects with asthma and COPD, no associated effect on ocular disorders was observed.</p>	<ul style="list-style-type: none"> - As per Section 5.2 of the protocol, patients with known narrow-angle glaucoma that, in the opinion of the investigator contraindicates study participation or use of an inhaled anticholinergic, will be excluded from participating in this study. - Instream review of AE/SAE reports
Cardiovascular effects of UMEC and VI	<p>Cardiovascular effects are a potential class effect associated with LAMA and LABA class of drugs.</p> <p>Clinical data from VI and FF/VI</p> <p>In clinical studies, changes in heart rate >6bpm compared with placebo were uncommon except at supra-therapeutic doses of 400mcg VI (formulated in lactose alone) or at a VI dose of 100mcg or greater. No clinically relevant effect on heart rate was observed from Phase IIb studies (up to 50mcg VI).</p>	<ul style="list-style-type: none"> - Exclusion criteria as specified in Section 5.2 of the protocol - Collection of cardiovascular risk factors and medical history at baseline - ECGs as per protocol - Vital sign assessments (heart rate and

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>Pooled QT analysis for VI Phase I and II studies did not suggest any effect on QT at recommended therapeutic doses. There were no statistically or clinically significant differences compared to placebo observed in weighted mean or maximum change from baseline (0 to 4 hour) in QTc(F) in Phase IIb studies</p> <p>In subjects with asthma and COPD, there were no significant effects on systolic blood pressure at VI doses up to 200mcg. Small (less than or equal to 4mmHg) but statistically significant mean decreases in diastolic blood pressure seen with VI (25 - 100mcg) versus placebo were not considered clinically significant. No clinically relevant effect on blood pressure was observed from Phase IIb studies (up to 50mcg VI).</p> <p>Analysis from NHANES III data from COPD and asthma participants suggests an independent association between asthma and QTcB prolongation. In COPD, the risk of QTc prolongation did not appear related to severity. Due to having multiple co-morbidities, COPD patients are likely to be more at risk than asthma patients for adverse cardiovascular adverse events.</p> <p>A significant proportion of subjects (>60%) in the Phase III FF/VI COPD program had cardiovascular comorbidities described. In the placebo controlled studies (HZC112206/ HZC112207), the incidence of serious adverse events from the cardiac disorder system organ class was similar across treatment arms</p> <p>The overall incidence of cardiac disorder events was higher in the one year exacerbation studies than in the 6 month studies, but this is likely to be due to the longer duration of treatment, and may also be as a consequence of more</p>	<p>blood pressure) as per protocol</p> <ul style="list-style-type: none"> - Cardiovascular eCRF for collection of AEs and SAEs (see Section 7.4.2.4) - Instream review of blinded data <p>Based on non-clinical, clinical pharmacology, clinical trial data and labelling background with FF/VI and UMEC/VI, there are no pre-specified protocol defined QTc based exclusion or study treatment stopping criteria. However, as mentioned in Section 5.2 and Section 5.5, investigators should use their clinical judgment to assess the suitability of patients to enrol and continue study treatment in the study</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>severe COPD disease, in relation to their exacerbation risk.</p> <p>An analysis performed on the FF/VI pivotal studies (HZC112206, HZC112207, HZC102871, HZC102970, HZC110946, HZC111348, and B2C111045) to summarise events that could be considered cardiac in nature found that the percentages of subjects with fatal events that were cardiovascular in nature were similar across all treatment groups (0 to <1%).</p> <p>Clinical data from UMEC/VI</p> <p>Overall, the UMEC/VI clinical studies revealed a similar incidence of AEs in the Cardiac Disorders SOC and CNS haemorrhages and cerebrovascular conditions (SMQ) for UMEC/VI, the individual components and placebo. A low number of AEs relating to atrial arrhythmias (e.g. supraventricular extrasystoles, atrial fibrillation) were reported, of which some occurred with a higher incidence in active treatment groups compared to placebo, in the Primary Efficacy Studies and the Long-term Safety Study. There were no additive effects on AE incidence with the combination over individual components. A slightly higher proportion of subjects with ECG abnormalities (e.g. ectopic supraventricular beats/rhythm) relating to atrial arrhythmias reported at any time post-baseline in the Primary Efficacy Studies and Long-term Safety Study were reported compared with placebo. These arrhythmias appeared to be clinically silent and were not associated with relevant symptoms or sequelae.</p> <p>Pooled QT analysis for VI Phase I and II studies did not suggest any effect on QT at recommended therapeutic doses. There were no statistically or clinically significant differences compared to placebo observed in weighted mean or maximum change from baseline (0 to 4 hour) in QTc(F) in Phase IIb studies</p>	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<p>Anticholinergic effects (including Narrow angle glaucoma, bladder outflow obstruction and urinary retention)</p>	<p>There was one report of angle closure glaucoma (UMEC/VI 62.5/25 mcg) in the UMEC/VI development program in COPD.</p> <p>The incidence of urinary retention AESIs was low (<1%) in all treatment groups including placebo. Three PTs were reported for this AESI group: urinary hesitation, urinary retention, and urine flow decreased. No subjects had urinary retention AESIs in the placebo, UMEC 62.5 mcg group or UMEC 125/25 mcg group. The PT of 'urinary retention' was reported by one subject each (<1%) in the UMEC/VI 62.5/25 mcg, VI 25 mcg and tiotropium treatment groups, with 2 subjects (<1%) reporting the event in the UMEC 125 mcg treatment group. One event of 'urinary hesitation' was reported in the UMEC 125 mcg treatment group. No subjects in the Long-term Safety Study had an event in the urinary retention AESI group. None of the urinary retention AESIs reported were considered serious.</p> <p>ICS has a similar class risk of glaucoma and elevated IOP; however these effects occur by a different mechanism that is not expected to be synergistic or additive when FF is used in combination with UMEC.</p>	<ul style="list-style-type: none"> - Patients with known narrow-angle glaucoma, prostatic hyperplasia or bladder outflow obstruction that in the opinion of the investigator contraindicates study participation or use of an inhaled anticholinergic, will be excluded from participating in the study. - Instream review of AE/SAE reports
<p>Hypersensitivity</p>	<p>Clinical data from FF/VI</p> <p>In the COPD placebo controlled studies (HZC102206/HZC102207), events related to hypersensitivity, such as pruritis and rash occurred at similar incidences in the active treatment groups (<1% to 2%) and placebo (<1%) and there appeared to be no increased risk of drug- associated hypersensitivity.</p>	<ul style="list-style-type: none"> - As specified in Section 5.2 of the protocol, subjects with a history of allergy or hypersensitivity to lactose/milk protein or magnesium stearate, any corticosteroid, anticholinergic/muscarinic receptor antagonist, and/or beta₂-

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>Adverse events in the Anaphylactic reactions SMQ occurred at similar incidences in all active treatment groups (3% to 4%) and placebo (4%) except for a lower incidence in the FF/VI 200/25 mcg treatment group (<1%). Angioedema occurred at a slightly higher incidence in the FF/VI 200/25 mcg group (2%) and at lower incidences within each of the remaining treatment groups (<1% to 1%).</p> <p>In the COPD one year exacerbation studies (HZC102871/HZC102970), events related to hypersensitivity such as pruritis and rash occurred at similar incidences in the FF/VI groups (4% to 5%) and the VI 25 mcg group (3%) and analysis indicated no increased risk of drug-associated hypersensitivity in any treatment group. Adverse events in the anaphylactic reaction SMQ occurred at similar incidences in all FF/VI treatment groups (10% to 13%) and at similar incidence to that in the VI 25 mcg treatment group (11%). Angioedema occurred at similar incidences in the FF/VI groups (3% to 5%) to the VI 25 mcg group (5%). In these studies as all patients were on VI, either as monotherapy or in combination with FF assessment of hypersensitivity to an individual component is not possible.</p> <p>Spontaneous data from FF/VI</p> <p>Spontaneous reports consistent with hypersensitivity reactions to inhaled FF/VI were identified on the GSK safety database. Seventeen post-marketing spontaneous reports were considered typical of hypersensitivity reactions and a further seven cases documenting atypical reactions that may possibly have indicated a hypersensitivity reaction were identified. There were four serious cases, of which two were considered life-threatening. A fatal case of</p>	<p>agonist, that in the opinion of the investigator contraindicates study participation, would not be included in the study</p> <ul style="list-style-type: none"> - Instream review of AE/SAE reports

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>angioedema and swollen tongue was reported by a health care professional; however the case was poorly documented and insufficient for evaluation.</p> <p>FF/VI formulation contains lactose. There have been reports of serious allergic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose.</p> <p>Clinical data from UMEC/VI</p> <p>Following a safety evaluation which included serious spontaneous case reports of hypersensitivity reactions it was concluded that there is sufficient evidence for an association between UMEC/VI and these events.</p>	
Paradoxical bronchospasm	There have been no reports of paradoxical bronchospasm with UMEC/VI in the clinical development program in COPD. Rare reports of paradoxical bronchospasm (which may be life threatening) with other bronchodilators have been reported.	- Instream review of AE/SAEs

4.6.2. Benefit Assessment

COPD guidelines advocate the use of one or more long-acting bronchodilators (long-acting muscarinic receptor antagonists [LAMA]) or long-acting β 2-adrenergic receptor agonists [LABA]) in addition to inhaled corticosteroids (ICS) as second line therapy for the most advanced patients with significant symptoms and a high risk of exacerbations.

Patients enrolled in this study will receive triple combination as FF/UMEC/VI or FF/VI + UMEC. Based on available data with the components FF, UMEC and VI, it is expected that patients will potentially derive clinical benefit from studytreatment:

- Benefits of dual combination FF/VI have already been demonstrated. In clinical studies in COPD patients, FF/VI demonstrated clinically meaningful and sustained improvement in lung function and there were clinically meaningful reductions in rate of moderate or severe COPD exacerbations. FF/VI is licensed for COPD indication in a number of countries around the world.
- The UMEC/VI development program demonstrated that UMEC/VI provided clinically relevant efficacy, as defined by measures of lung function over 24 weeks of treatment, as compared with placebo, the individual monotherapies and tiotropium in a broad range of subjects with COPD. UMEC/VI is licensed for COPD indication in number of countries.
- Benefits of open triple therapy with an ICS, LAMA and LABA have been shown in published studies which assessed the use of an ‘open’ triple therapy in moderate-severe COPD patients, These studies reported improvements in lung function, HRQoL, hospitalisation rates and rescue medication use, compared to dual therapy (ICS/LABA) or LAMA alone [[Aaron, 2007](#); [Cazzola, 2007](#); [Hanania, 2012](#); [Jung, 2012](#); [Welte, 2009](#)]. These studies also showed that the number and type of reported AEs were generally similar with administration of dual or monotherapy doses for periods of up to one year, and were mostly related to their pharmacological mode of action.
- Patients with COPD have been exposed to the open triple combination FF/VI + UMEC in GSK sponsored studies. In two 12-week, placebo controlled studies (200109 and 200110), the addition of UMEC to FF/VI (100/25) once daily in adult patients with a clinical diagnosis of COPD, resulted in statistically significant and clinically meaningful improvements in the primary endpoint of trough FEV₁ at Day 85 compared to placebo plus FF/VI (124 mL (95% CI 93, 154, p<0.001) and 122 mL (95%CI 91, 152, p<0.001)). The safety profile for UMEC in combination with FF/VI was similar across treatment arms, and no additive effects or new safety concerns were identified.
- No efficacy data is available for the closed triple combination FF/UMEC/VI as the two Phase III efficacy and safety studies are currently ongoing (CTT116855, CTT116853). However, as the delivery of the components of the triple combination product (FF, UMEC and VI) are comparable when delivered as the

closed triple or the open triple, the efficacy of closed triple is expected to be as good as open triple.

The current study will provide data to demonstrate non-inferiority of closed triple and open triple on lung function. In a disease where polypharmacy is common, the 'closed' triple, once-daily combination has the potential to optimise bronchodilator therapy, improve patient adherence to therapy and, as a result, improve overall disease management in COPD patients.

4.6.3. Overall Benefit: Risk Conclusion

Current risks that have been identified for closed triple and open triple are based on the known pharmacology of the individual components FF, UMEC and VI. These include key risks of pneumonia and bone disorders/fractures from ICS-containing combinations, and the risk of adverse cardiovascular effects from LAMA/LABA-containing combinations.

The clinical development programs for dual combinations FF/VI and UMEC/VI demonstrated a favourable benefit/risk for these therapies in patients with COPD. This led to their approval and both dual combinations are now marketed for COPD indication in a number of countries around the world.

The safety profile for UMEC in combination with FF/VI was similar across treatment arms, and no additive effects or new safety concerns were identified in replicate studies in COPD patients exposed to the open triple combination FF/VI + UMEC for 12 weeks. Patients with COPD have been exposed to the closed triple combination FF/UMEC/VI as part of ongoing clinical studies (CTT116853 and CTT116855). There are currently no new safety signals based on review of blinded data from these studies. Additionally an Independent Data Monitoring Committee (IDMC) is in place for CTT116855 study, which meets periodically to review unblinded safety data.

For the current study, a safety monitoring strategy is being proposed for all the risks, including key risks (Section 4.6).

Given the clinical experience with FF, UMEC and VI, and that the associated risks with these compounds are anticipated from their known pharmacology, the potential benefit of a new therapy option in patients with moderate to severe COPD supports the conduct of this study as part of the clinical development program for closed triple combination.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

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

5.1. Inclusion Criteria

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

1. **Informed Consent:** A signed and dated written informed consent prior to study participation.
2. **Type of subject:** Outpatient.
3. **Age:** Subjects 40 years of age or older at Screening (V1).
4. **Gender:** Male or female subjects.

Females:

A female subject is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin (hCG) test), not lactating, and at least one of the following conditions applies:

- a. Non-reproductive potential defined as:
 - Pre-menopausal females with one of the following:
 - Documented tubal ligation
 - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
 - Hysterectomy
 - Documented Bilateral Oophorectomy
 - Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

- b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see [Appendix 5](#)) from 30 days prior to the first dose of study treatment and until after the last dose of study treatment and completion of the follow-up visit.

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

5. **COPD Diagnosis:** An established clinical history of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society [[Celli, 2004](#)].
6. **Smoking History:** Current or former cigarette smokers with a history of cigarette smoking of ≥ 10 pack-years at Screening (V1) [number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)]. Previous smokers are defined as those who have stopped smoking for at least 6 months prior to Screening (V1).

NOTES:

- Pipe and/or cigar use cannot be used to calculate pack-year history.
7. **Severity of COPD symptoms:** A score of ≥ 10 on the COPD Assessment Test (CAT) at Screening (V1).
8. **Severity of COPD Disease:** A post-albuterol/salbutamol FEV₁/FVC ratio of < 0.70 at Screening (V1).
9. **Existing COPD maintenance treatment:** Subject must be receiving daily maintenance treatment for their COPD for at least 3 months prior to Screening (V1).

NOTES:

- Subjects receiving only PRN COPD medications are not eligible.
10. **History of Exacerbations:** Subjects must demonstrate:
- a **post-bronchodilator FEV₁ $< 50\%$** predicted normal at Screening (V1) and a documented history of ≥ 1 moderate or severe COPD exacerbation in the 12 months prior to Screening

OR

a **post-bronchodilator $50\% \leq \text{FEV}_1 < 80\%$** predicted normal at Screening (V1) and a documented history of ≥ 2 moderate exacerbations or a documented history of ≥ 1 severe COPD exacerbation (hospitalised) in the 12 months prior to Screening (V1).

NOTES:

- Percent predicted will be calculated using the European Respiratory Society Global Lung Function Initiative reference equations [[Quanjer, 2012](#)].

- A documented history of a COPD exacerbation (e.g., medical record verification) is a medical record of worsening COPD symptoms that required systemic/oral corticosteroids and/or antibiotics (for a moderate exacerbation) or hospitalisation (for a severe exacerbation). Prior use of antibiotics alone does not qualify as an exacerbation history unless the use was associated with treatment of worsening symptoms of COPD, such as increased dyspnoea, sputum volume, or sputum purulence (colour). Subject verbal reports are not acceptable.
11. **French subjects:** In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. **Pregnancy:** Women who are pregnant or lactating or are planning on becoming pregnant during the study.
2. **Asthma:** Subjects with a current diagnosis of asthma. (Subjects with a prior history of asthma are eligible if they have a current diagnosis of COPD, which is the primary cause of their respiratory symptoms).
3. **α 1-antitrypsin deficiency:** Subjects with α 1-antitrypsin deficiency as the underlying cause of COPD.
4. **Other respiratory disorders:** Subjects with active tuberculosis are excluded. Subjects with other respiratory disorders (e.g. **clinically significant:** bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases) are excluded if these conditions are the primary cause of their respiratory symptoms.
5. **Lung resection:** Subjects with lung volume reduction surgery (including procedures such as endobronchial valves) within the 12 months prior to Screening (V1).
6. **Risk Factors for Pneumonia:** immune suppression (e.g. advanced HIV with high viral load and low CD4 count, Lupus on immunosuppressants that would increase risk of pneumonia) or other risk factors for pneumonia (e.g. neurological disorders affecting control of the upper airway, such as Parkinson's Disease, Myasthenia Gravis).

NOTES:

- Patients at a high risk for pneumonia (e.g. very low BMI, severely malnourished or very low FEV1) will only be included at the discretion of the investigator.
7. **Pneumonia and/or moderate or severe COPD exacerbation** that has not resolved at least 14 days prior to Screening (V1) and at least 30 days following the last dose of oral/systemic corticosteroids (if applicable).
 8. **Other Respiratory tract infections** that have not resolved at least 7 days prior to Screening (V1).

9. **Abnormal Chest x-ray:** Chest x-ray (posteroanterior and later) reveals evidence of pneumonia or a clinically significant abnormality not believed to be due to the presence of COPD, or another condition that would hinder the ability to detect an infiltrate on chest x-ray (e.g. significant cardiomegaly, pleural effusion or scarring). All subjects will have a chest x-ray at Screening (V1) [or historical radiograph or CT scan obtained within 3 months prior to Screening (V1).

NOTES:

- Subjects who have experienced pneumonia and/or moderate or severe COPD exacerbation within 3 months of Screening (V1) must provide a post pneumonia/exacerbation chest x-ray or have a chest x-ray conducted at Screening (V1).
 - For sites in Germany: If a chest x-ray (or CT scan) within 3 months prior to Screening (V1) is not available, approval to conduct a diagnostic chest x-ray will need to be obtained from the Federal Office for Radiation Protection (BfS).
10. **Other diseases/abnormalities:** Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, gastrointestinal, urogenital, nervous system, musculoskeletal, skin, sensory, endocrine (including uncontrolled diabetes or thyroid disease) or haematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.
11. **Unstable liver disease:** ALT >2xULN; and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment).

NOTES:

- Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.
 - Chronic stable hepatitis B and C (e.g., presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment) are acceptable if subject otherwise meets entry criteria.
12. **Unstable or life threatening cardiac disease:** subjects with any of the following at Screening (V1) would be excluded:
- Myocardial infarction or unstable angina in the last 6 months
 - Unstable or life threatening cardiac arrhythmia requiring intervention in the last 3 months
 - NYHA Class IV Heart failure

13. **Abnormal and clinically significant 12-Lead ECG finding:** Investigators will be provided with ECG reviews conducted by a centralized independent cardiologist to assist in evaluation of subject eligibility. The investigator will determine the clinical significance of each abnormal ECG finding in relation to the subject's medical history and exclude subjects who would be at undue risk by participating in the trial. An abnormal and clinically significant finding that would preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:
 - AF with rapid ventricular rate >120 BPM;
 - sustained or nonsustained VT;
 - Second degree heart block Mobitz type II and third degree heart block (unless pacemaker or defibrillator had been inserted)
14. **Contraindications:** A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, beta₂-agonist, lactose/milk protein or magnesium stearate or a medical condition such as narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the investigator contraindicates study participation.
15. **Cancer:** Subjects with carcinoma that has not been in complete remission for at least 3 years. Subjects who have had carcinoma *in situ* of the cervix, squamous cell carcinoma and basal cell carcinoma of the skin would not be excluded based on the 3 year waiting period if the subject has been considered cured by treatment.
16. **Oxygen therapy:** Use of long-term oxygen therapy (LTOT) described as resting oxygen therapy >3L/min (Oxygen use ≤3L/min flow is not exclusionary.)
17. **Medication prior to spirometry:** Subjects who are medically unable to withhold their albuterol/salbutamol for the 4-hour period required prior to spirometry testing at each study visit.
18. **Drug/alcohol abuse:** Subjects with a known or suspected history of alcohol or drug abuse within the last 2 years.
19. **Non-compliance:** Subjects at risk of non-compliance, or unable to comply with the study procedures. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits.
20. **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.
21. **Affiliation with investigator site:** Study investigators, sub-investigators, study coordinators, employees of a participating investigator or study site, or immediate family members of the aforementioned that is involved with this study.
22. **Inability to read:** In the opinion of the investigator, any subject who is unable to read and/or would not be able to complete study related materials.

23. **Medication prior to Screening:** Use of the following medications within the following time intervals prior to Screening (V1) or requirement for their use during the study:

Table 1 Prohibited medications prior to Screening (V1)

Medication	No use within the following time intervals prior to Screening
Long term continuous antibiotic therapy for ≥ 30 days	30 days
Systemic, Oral, parenteral corticosteroids	30 days (Intra-spinal and intra-articular injections are allowed)
Any other investigational drug	30 days or 5 half lives whichever is longer.

5.3. Randomisation Criteria

Those subjects who meet the randomisation criteria will be randomised into the study until the target of approximately 1020 randomised subjects is reached. At the end of the run-in period, study subjects must not meet any of the following criteria in order to be randomised to study treatment:

1. Pneumonia or moderate/severe COPD exacerbation during run-in
2. Any change to COPD maintenance medications (including dosage and regimen) during the run-in
3. Antibiotics for respiratory tract infections during the run-in

5.4. Screening/Baseline/Run-in Failures

A subject will be assigned a subject number at the time the informed consent is signed. A subject who is assigned a subject number but does not have Screening (V1) will be considered a pre-screen failure.

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.4.2.5).

Subjects who are Pre-Screen (V0) or Screen (V1) failures cannot be re-screened.

5.5. Withdrawal/Stopping Criteria

5.5.1. Protocol defined withdrawal criteria

A subject must be permanently withdrawn if any of the following stopping criteria are met:

- **Liver Chemistry:** Meets any of the protocol-defined liver chemistry stopping criteria³ as defined in Section 5.5.2.
- **Pregnancy:** Positive urine pregnancy test.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. Subjects who are withdrawn from the study will not be replaced.

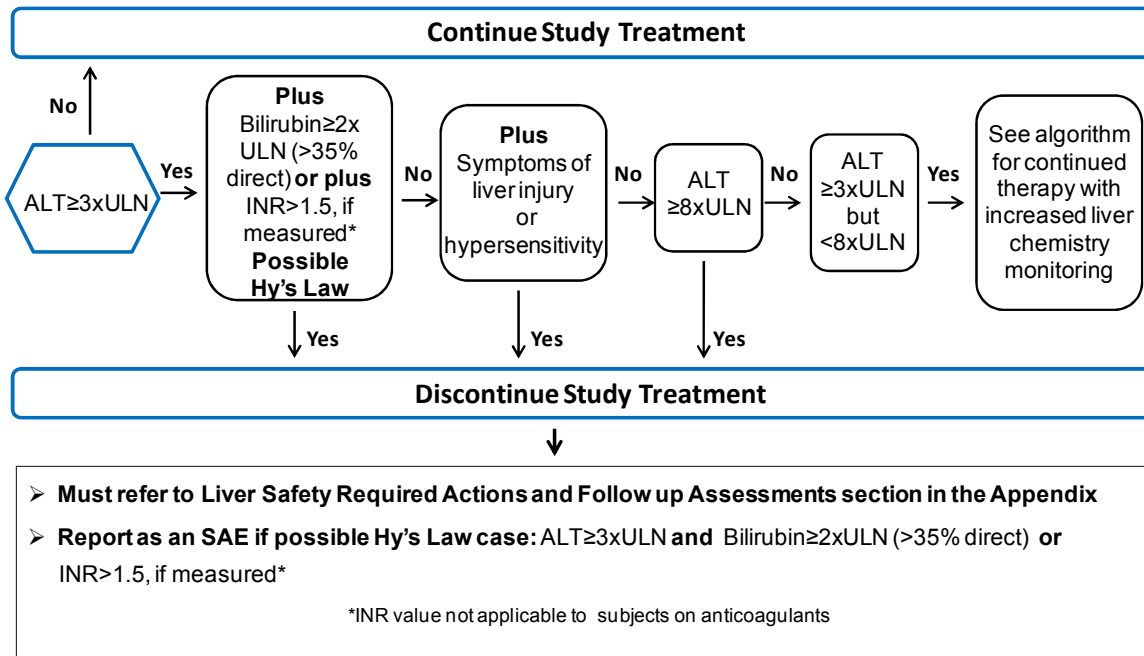
5.5.2. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

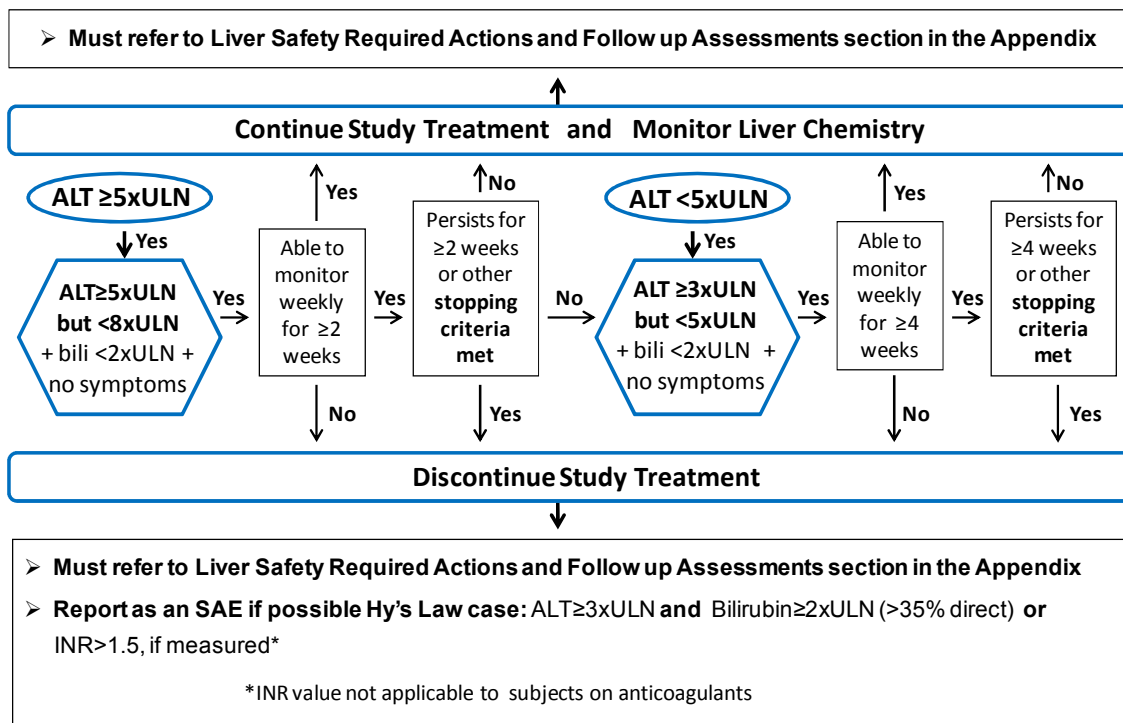
³ Based on findings from any routine labs done at site

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 2, Section 12.2](#)

Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥ 3xULN but < 8xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 2](#), Section 12.2.

5.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up phone-call or visit.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

All treatments will be delivered by ELLIPTA containing 30 doses.

Following the run-in period, eligible subjects will be randomized (1:1) to one of the following double-blind treatment groups:

- FF/UMEC/VI 100mcg/62.5mcg/25mcg and placebo, both via the ELLIPTA once daily in the morning
or,
- FF/VI 100mcg/25mcg and UMEC 62.5mcg, both via the ELLIPTA once daily in the morning.

The randomisation will be stratified based on long-acting bronchodilator usage during the run-in (none, one or two long-acting bronchodilators per day).

The ELLIPTA contains 30 doses (FF/UMEC/VI, FF/VI, UMEC or placebo). Each subject will be instructed on the proper use of the ELLIPTA and will inhale once from each of their ELLIPTAs each morning for the duration of the 24-week treatment period. Subjects will self-administer their first dose of blinded study treatment in the clinic during Randomisation (V2). On the morning of the other study clinic visits, subjects will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel. Subjects will take their last dose of study treatment at the clinic at Visit 5 and a safety follow-up will be conducted either by phone call or clinic visit approximately one week later. Subjects will discontinue their existing COPD medication on the day before Randomisation (V2) but may continue their study-supplied rescue albuterol/salbutamol.

There are no plans to provide the study drug for compassionate use following study completion.

Descriptions of the study treatments administered via the ELLIPTA are provided in [Table 2](#).

Table 2 Description of study treatment inhalation powder via ELLIPTA

FF/UMEC/VI	First strip	Second strip
		FF blended with lactose
Dosage Form	ELLIPTA with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	100mcg per blister	62.5 mcg per blister UMEC, 25 mcg per blister VI
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	
FF/VI	First strip	Second strip
	FF blended with lactose	VI blended with lactose and magnesium stearate
Dosage Form	ELLIPTA with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	100mcg per blister	25 mcg per blister
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	
UMEC	First strip	Second strip
	UMEC blended with lactose and magnesium stearate	NA – one strip only
Dosage Form	ELLIPTA with 30 doses (1 strip with 30 blisters)	
Unit Dose Strengths	62.5 mcg per blister	NA
Physical description	Dry white powder	NA
Route of Administration	Inhaled	
Placebo to match	First strip	Second strip
	Lactose	NA – one strip only
Dosage Form	ELLIPTA with 30 doses (1 strip with 30 blisters)	
Unit Dose Strengths	NA	NA
Physical description	Dry white powder	NA
Route of Administration	Inhaled	

Albuterol/salbutamol via metered-dose inhaler (MDI) with a spacer will be issued for reversibility testing at Screening (V1). Albuterol/salbutamol MDI or NEBULES™ for as needed (prn) use throughout the study will be provided starting at Screening (V1). Albuterol/salbutamol and spacers will be sourced from local commercial stock. If not available locally, GSK will source centrally.

6.1.1. Storage

All study treatment should be stored up to 25°C (77°F). Each ELLIPTA contains 30 doses and is packaged in a foil pouch with a desiccant sachet and stored in a carton. The inhaler should not be used for more than 30 days after opening the foil. The sites must maintain a daily temperature log for the storage of investigational product.

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. Details of study treatment administration oversight are provided in the Study Procedures Manual (SPM). Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

6.1.2. Investigational Product and albuterol/salbutamol Return

All used and unused study treatment and albuterol/salbutamol will be returned to GSK at the end of the study to be available for disposal. In some instances for sites outside the US, study supplies will be disposed of locally either by the site, the country medical department or third-party vendor. Detailed instructions for the return of the study drug can be found in the SPM.

If any ELLIPTA fails to function properly, the subject should return to the clinic as soon as possible to obtain a new inhaler. The site will use the interactive response technology (IRT) system to obtain a new treatment pack number for the subject and dispense a new study treatment kit from the site's investigational product supply as instructed by the IRT system.

In addition, any ELLIPTA or metered-dose-inhaler (MDI) that fails to function properly must be identified and returned to GSK for testing. Details of the failure will be documented in the eCRF.

6.2. Medical Devices

Medical devices (not manufactured by or for GSK) provided for use in this study are spacers/holding chambers.

Instructions for medical device use are provided in the SPM.

6.3. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomisation schedule. The randomisation code will be generated by GSK using a validated computerized system. Subjects will be randomized using an IRT System, RAMOS NG. The study will use country based randomisation to allocate treatments. Once a randomisation number is assigned to a subject it cannot be reassigned to any other subject in the study.

Subjects who meet the eligibility criteria and successfully complete the 2-week run-in period will be randomized (1:1) to one of the following study treatment regimens:

- FF/UMEC/VI 100mcg/62.5mcg/25mcg and placebo, both via the ELLIPTA once daily in the morning
- or,
- FF/VI 100mcg/25mcg and UMEC 62.5mcg, both via the ELLIPTA once daily in the morning.

The randomization will be stratified based on **long-acting bronchodilator** usage during the run-in (none, one or two **long-acting bronchodilators** per day).

Subjects will be instructed to take one dose each morning from each ELLIPTA.

The duration of treatment for each subject is 24 weeks. On the morning of each clinic study visit, subjects will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel. Study treatment will be given at the clinic at approximately the same time of day as Randomisation (V2). On the other days during the treatment period (*i.e.* “non-clinic days”), subjects will be instructed to take their study treatment each morning at approximately the same time of day. The IRT system will provide a means for site-based allocation of drug. Each investigator will be supplied with sufficient supplies to conduct the trial. Additional treatment packs will be supplied as needed to the sites. Details of how to use the IRT system to randomize subjects is provided in the SPM.

6.4. Blinding

This will be double-blind study (with a placebo ELLIPTA used to maintain the blind) and the following will apply.

- The investigator or treating physician may unblind a subject’s treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject’s individual study treatment.

- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, 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 fully documented in the eCRF

A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.

- 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 investigators in accordance with local regulations and/or GSK policy. Subjects will not be withdrawn from the study.

6.5. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.6. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SPM.
- Under normal conditions of handling and administration, study treatment 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. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.7. Compliance with Study Treatment Administration

When subjects are dosed at the site, they will receive study treatment under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff. When subjects self-administer study treatment at home, compliance with study treatment will be assessed through querying the subject during the site visits and recording the number of doses remaining in the ELLIPTA in the eCRF. A record of the number of ELLIPTAs dispensed to each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates will also be recorded in the eCRF. Study treatment non-compliance is defined as <80% or >120% over the 24-week treatment period.

6.8. Treatment of Study Treatment Overdose

An overdose is defined as a dose greater than the total doses described above which results in clinical signs and symptoms. These should be recorded by the investigator on the AE/SAE pages. In the event of an overdose of study treatment, the investigator should use clinical judgment in treating the overdose and contact the GSK medical monitor.

GSK is not recommending specific treatment guidelines for overdose and toxicity management. The investigator is advised to refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug being used in this study. Such documents may include, but not be limited to, the IB or equivalent document provided by GSK.

6.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because other treatment options are available.

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

6.10. Concomitant Medications and Non-Drug Therapies

All COPD medications used within approximately 3 months prior to Screening (V1) and during the study (including the post-treatment period) should be recorded in the eCRF.

All non-COPD medications taken during the study (after randomisation including post-treatment) and any changes to concomitant medications will be recorded in the eCRF. [Note: Study provided albuterol/salbutamol should not be recorded in the eCRF however non-study supplied albuterol/salbutamol will be recorded in the eCRF]. The minimum requirement is that drug name, dose, route and the dates of administration are to be recorded.

Medications initiated after completion of the randomized treatment phase of the study (V5) or started after withdrawal from the study must be recorded in the eCRF, along with any changes up to the Safety Follow-Up Visit/Phone-call.

6.10.1. Permitted Medications and Non-Drug Therapies

- The following COPD medications are permitted during the study treatment period:
- Study supplied albuterol/salbutamol MDI or Nebules (must be withheld for at least 4 hours prior to spirometry testing).
- Oral or injectable corticosteroids (short course ≤ 14 days) only for the short term treatment of COPD exacerbations and/or pneumonia.
- Antibiotics (short course ≤ 14 days) for the short term treatment of COPD exacerbations and/or pneumonia.
- Mucolytics such as acetylcysteine.
- Long term oxygen therapy. (To be eligible to enter the study subjects who are on LTOT must be using at a flow rate of ≤ 3 litres/minute at rest. However, oxygen therapy may be adjusted as deemed medically necessary at any time during the study.) Oxygen therapy must be captured on the concomitant medication page of the eCRF. Supplemental oxygen is recommended for patients who exhibit oxyhemoglobin desaturation with rest or exertion (e.g. SaO₂ $\leq 88\%$).
- Maintenance phase of pulmonary rehabilitation treatment (subjects are not allowed to initiate treatment during the study).
- Any COPD medication deemed medically necessary for the short term treatment (≤ 14 days) of a moderate/severe COPD exacerbation or pneumonia.

The following relevant **Non-COPD medications** are permitted during the study:

- Medications for rhinitis (e.g. intranasal corticosteroids, antihistamines, cromolyn, nedocromil, nasal decongestants).
- Topical and ophthalmic corticosteroids.
- Localized corticosteroid injections (e.g. intra-spinal and intra-articular).
- Vaccinations (Influenza vaccine, Pneumonia vaccine, Shingles vaccine, etc.) (Administration of influenza and pneumonia vaccines should be considered based on clinical discretion of the Investigator and local/national guidelines. Current

influenza vaccines and pneumonia vaccines will be captured on the concomitant medication pages of the eCRF).

- Allergy immunotherapy.
- Antibiotics for short-term treatment (≤ 14 days) of acute infections. (Long term treatment with antibiotics is not allowed).
- Systemic and ophthalmic beta-blockers. (Administer with caution as systemic beta-blockers block the pulmonary effect of beta-agonists, and may produce severe bronchospasm in patients with reversible obstructive airways disease. Cardioselective beta-blockers should be considered, although they also should be administered with caution).
- Smoking cessation treatments.
- Cough suppressants.
- Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). (Administer with extreme caution as they may potentiate the effects of beta-agonists on the cardiovascular system, including QTc prolongation).
- Diuretics. (Caution is advised in the co-administration of beta-agonists with non-potassium sparing diuretics as this may result in ECG changes and/or hypokalaemia).
- Use of positive airway pressure for sleep apnoea.
- Oral muscarinic antagonists for the treatment of overactive bladder are permitted but should be used with caution as they may exacerbate medical conditions that are contraindicated for anticholinergics (e.g., narrow angle glaucoma and bladder outflow obstruction).
- CYP3A4 inhibitors (Caution should be exercised when considering the coadministration of long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur).

6.10.2. Prohibited Medications and Non-Drug Therapies

Medications prohibited at specific time intervals prior to Visit 1 (and at any time during the study) are identified in the Exclusion Criteria (Section 5.2).

NOTE: All COPD medications (except for rescue albuterol/salbutamol, mucolytics and oxygen) are prohibited during the randomised period of the study except during the treatment of a moderate/severe COPD exacerbation or pneumonia. In the event of an exacerbation or pneumonia, sites should attempt to follow protocol treatment guidelines (Section 12.7); however, treatment with any medication that the health care provider deems necessary is allowed. Caution is advised in using a LABA or LAMA to treat a subject currently taking study treatment as these additional medications may increase the risk of overdose. If necessary the investigator or other health care personnel may stop the

subjects study treatment temporarily in order to treat the COPD exacerbation. Subjects who require more than two consecutive 14 day courses of treatment (i.e. antibiotics or corticosteroids) should be evaluated for their continuation on study treatment by the investigator in consultation with the GSK medical monitor.

Eligible subjects will be allowed to continue their usual COPD medications during screening and the 2-week run-in period. On the morning of the Screening Visit subjects will refrain from taking their morning dose of their usual COPD medications until instructed to do so by clinic personnel. During the run-in period subjects will continue to use their usual COPD medications with no change in medication or dose.

The number of long-acting bronchodilators taken each day during the run-in period (0, 1 or 2) will be recorded.

On the day before the Randomisation Visit (V2), subjects will take their last dose of their usual COPD medications and will not use any other COPD medications (except for those allowed per protocol: rescue albuterol, oxygen, mucolytics and medications for the treatment of a COPD exacerbation or pneumonia) until the end of the study. Rescue albuterol/salbutamol can be used throughout the study as needed but must be withheld for at least 4 hours prior to conducting spirometry.

COPD Medications and non-drug therapies that are prohibited during the randomized portion of the study:

- Inhaled and systemic corticosteroids (Except for the short term treatment [≤ 14 days] of a COPD exacerbation or pneumonia.) **Note:** Topical and ophthalmic corticosteroids, and localized corticosteroid injections (intra-spinal and intra-articular) are allowed.
- Long and short acting muscarinic antagonists
- Long and short acting β_2 -agonists
- PDE4 inhibitors (roflumilast)
- Theophylline preparations
- Cromoglycate and nedocromil inhalers
- Zafirlukast, montelukast, zileuton
- Acute phase of pulmonary rehabilitation (at any time during the study including run-in)
- Long term systemic antibiotic therapy (antibiotics used for ≤ 14 days are allowed)

7. STUDY ASSESSMENTS AND PROCEDURES

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

7.1. Time and Events Table

Protocol Activity	Pre-Screen	Screen	Treatment				Follow Up	
	Visit 0 Pre-screen	Visit 1 Screening	Visit 2 Randomisation	Visit 3	Visit 4	Visit 5	Early Withdrawal Visit	Safety Follow-up Contact
Study Week		Week -2	Week 0	Week 4	Week 12	Week 24		1 week Fw-up
Window		-3/+8d		-4/+2d	-8/+6d	-8/+6d		-1/+4d
Written Informed Consent ^a	X	X						
Genetic Informed Consent ^b	X	X						
Demography ^c	X	X						
Medical History, including cardiovascular history		X						
COPD and Exacerbation History		X						
Concomitant Medication Assessment	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria		X						
Randomisation Criteria			X					
Smoking History		X						
Smoking status		X				X	X	
Smoking Cessation Counselling		X				X	X	
Register Visit in IRT/ RAMOS NG ^d		X	X	X	X	X	X	
Reversibility Testing ^e		X						
Spirometry			X ^f	X ^f	X ^f	X ^f		
Device training and registration		X	X					
Exacerbation Assessment		X	X	X	X	X	X	X
SGRQ-C ^g			X		X	X		
BDI ^g			X					
TDI ^g					X	X		
CAT ^g		X						
eDevice close out ^h			X			X	X	
Physical examination ⁱ		X				X	X	

Protocol Activity	Pre-Screen	Screen	Treatment				Follow Up	
	Visit 0 Pre-screen	Visit 1 Screening	Visit 2 Randomisation	Visit 3	Visit 4	Visit 5	Early Withdrawal Visit	Safety Follow-up Contact
Study Week		Week -2	Week 0	Week 4	Week 12	Week 24		1 week Fw-up
Window		-3/+8d		-4/+2d	-8/+6d	-8/+6d		-1/+4d
Adverse Events Assessment		X	X	X	X	X	X	X
Vital signs ^j		X		X		X	X	
ECG		X				X ^k	X ^k	
Chest X-ray ^l		X						
Pulse oximetry ^m			X					
Blood draw for PK					X ⁿ	X ^o		
Blood Draw for Genetics research						X ^p		
Haematology/biochemistry ^q		X				X	X	
Urine Pregnancy Test ^r		X		X	X	X	X	
Hepatitis B and C tests		X						
Dispense study treatment			X	X	X			
Administer study treatment in clinic ^s			X	X	X	X	X	
Assess study treatment compliance				X	X	X	X	
Collect study treatment				X	X	X	X	
Dispense albuterol/salbutamol		X	X	X	X			
Collect albuterol/salbutamol			X	X	X	X	X	
Issue/review paper diary ^t		X	X	X	X	X	X	

- Informed consent must be conducted at the Pre-screen Visit prior to performing any study procedures including the changing or withholding of medications. The (IC) may be given at Screening Visit 1 if the subject does not take or has not taken any protocol excluded medications.
- Genetics research consent may be obtained at the same time as the study IC and must be obtained prior to obtaining a genetic blood sample.
- Demography may be captured at either the Pre-screen Visit or Screening Visit (for subjects who do not have a Pre-screen Visit).
- The IRT will be used for randomisation, emergency unblinding and study treatment supply management (Please refer RAMOS NG IRT manual for more information)
- At Screening Visit 1 both pre and post-bronchodilator spirometry will be conducted. Pre-bronchodilator spirometry will be performed prior to the subject taking their morning dose of their usual COPD treatment, between 6am and 11am and after withholding rescue albuterol/salbutamol for ≥4 hours.
- At Visits 2-5 (and the Early Withdrawal Visit), pre-bronchodilator spirometry will be performed prior to taking the morning dose of study treatment, between 6am and 11am and after withholding rescue albuterol/salbutamol for ≥4 hours.

- g. Patient reported assessments should be conducted in the following order and before other study assessments: SGRQ-C, BDI/TDI.
- h. Close out eDevice for any subject who fails to randomize, withdraws early, or completes Visit 5.
- i. Physical examination may include height, weight, blood pressure, temperature, heart rate.
- j. Vital signs must be performed prior to spirometry and prior to taking morning dose of study medication.
- k. ECG to be obtained 15 - 45 minutes post-dose at treatment Visit 5 and Early Withdrawal Visit (if possible). If a subject is not dosed at Early Withdrawal, then an ECG can be taken at any time during the visit
- l. Chest X-ray (PA and lateral) is required at Screening (or historical x-ray obtained within 3 months prior to Screening) and at anytime there is a suspected pneumonia or a mod/severe exacerbation.
- m. Pulse oximetry must be performed at V2 and anytime there is a suspected pneumonia or a moderate or severe exacerbation.
- n. PK subset A: PK samples of 120 subjects at selected sites, to be obtained at two time points at Visit 4: pre-dose and in the window 5 to 15 minutes post-dose.
PK subset B: PK samples of 60 subjects at selected sites, to be obtained and Visit 4: pre-dose, 5-15min, 45-90min, 2.5-4h, 6-8h, 10-12h, 23-24h post-dose.
- o. PK subset A: PK samples of 120 subjects at selected sites, to be obtained at two time points at Visit 5: 5 to 15 minutes post-dose and 45 to 90 minutes post-dose.
- p. The genetics blood sample should be taken at V5 or at any visit after Randomisation (V2).
- q. Haematology and chemistry panels will include liver chemistry, and potassium and glucose levels.
- r. All female subjects of child bearing potential will have a urine pregnancy test at each visit except Visits 2 and follow-up.
- s. Subjects must withhold their morning dose of study treatment at each clinic visit and not take their study treatment dose until instructed to do so by study staff.
- t. Subjects will be issued a paper diary, at screening and other clinic visits (if required) in order to note any changes to concomitant medications and/or incidence of adverse events that may have occurred between clinic visits.

7.2. Screening and Critical Baseline Assessments

No study related procedures may be performed until the informed consent form has been signed by the subject. A pre-screening visit may be required in order to administer the informed consent before any changes are made to the subject's current medical regimen. Selection and modification of the subject's medications prior to study participation is based on the physician's judgment according to sound medical practice, principles, and each subject's needs. A subject's treatment must not be changed merely for the purpose of enabling the subject's participation in the study. The informed consent may be given at the Screening Visit (V1) if the subject does not take or has not taken any protocol excluded medications.

During the pre-screening visit (V0) each subject will have the following procedures performed. The following demographic parameters will be captured:

- Year of birth, sex, race and ethnicity.
- Concomitant medication review.

The additional following critical baseline assessments will be conducted at Screening (V1):

- Medical history including COPD history (comprised of COPD type [emphysema and/or chronic bronchitis]), smoking history, COPD exacerbations history, smoking status and previous and/or current medical conditions.
- Concomitant Medications review (COPD concomitant medications in the 3 months prior to Screening)
- COPD exacerbation assessment (documented history of exacerbation(s) in the 12 months prior to Screening)
- Cardiovascular medical history/risk factors
- Inclusion/Exclusion criteria assessment
- COPD Assessment Test (CAT)
- Physical examination
- Pulse rate, blood pressure measurements
- 12-lead ECG
- Pre- and post-albuterol/salbutamol spirometry (reversibility)
- SAE assessment (if related to study participation)
- Chest X-Ray [or historical radiograph obtained within 3 months prior to Screening (V1)]
- Laboratory assessments (chemistry and hematology, hepatitis and pregnancy testing)

In addition the following procedures must be completed at Screening (V1):

- Smoking cessation counseling
- Electronic device training
- Dispense albuterol/salbutamol

7.2.1. COPD Assessment Test (CAT)

The CAT will be completed by subjects at Screening (V1) using an electronic device, before any other Screening (V1) assessments, in order to assess eligibility.

The COPD Assessment Test (Jones, 2009; Jones, 2012) 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 (no impairment) to 5 (maximum impairment) with a scoring range of 0-40. Higher scores indicate greater disease impact.

7.3. Efficacy

7.3.1. Primary Efficacy Endpoint

- Change from baseline in trough FEV₁ at 24 weeks

Measured using centralised spirometry by fully qualified and trained study site personnel.

7.3.2. Secondary Efficacy Endpoints

- Proportion of Responders based on the SGRQ Total Score at Week 24
- Change from baseline in SGRQ Total Score at Week 24
- Proportion of Responders based on TDI focal score at Week 24
- TDI focal score at Week 24
- Time to first moderate or severe exacerbation

7.3.3. Spirometry and Reversibility Testing

7.3.3.1. Spirometry

Spirometry measurements will be obtained using spirometry equipment that meets or exceeds the minimal performance recommendations of the ATS [Miller, 2005]. All sites will use standardised spirometry equipment provided by an external vendor. All subjects

will have spirometry performed at screening (pre- and post-salbutamol) and pre-dose at each scheduled clinic visit during the treatment period. For FEV₁ and FVC determinations, at least 3 acceptable spirometry efforts (with no more than 8) should be obtained. Acceptable spirometry efforts should have a satisfactory start of test and end of test (*e.g.* a plateau in the volume-time curve) and be free from artefacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons [Miller, 2005].

The largest FEV₁ and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort. Spirometry must be performed as follows:

- Started approximately between 6:00AM and 11:00AM.
- After withholding albuterol/salbutamol for ≥ 4 hours.
- At Screening (V1), before the morning dose of their usual COPD medications.
- At Randomisation (V2) and all treatment visits, before the morning dose of study treatment.
- At Screening (V1), the CAT must be administered prior to spirometry
- At Randomisation (V2), V4 and V5, questionnaires must be completed prior to spirometry (SGRQ-C should be administered first followed by BDI/TDI)
- Subjects should refrain from smoking for 1 hour prior to each pulmonary function test.
- Subjects should abstain from drinking beverages with high levels of caffeine such as tea and coffee for 2 hours prior to each pulmonary function test.

A full description of the timing and conduct of spirometry procedures is provided in the SPM.

7.3.3.2. Reversibility

At Screening (V1), both pre- and post-albuterol/salbutamol spirometry will be obtained. Post albuterol/salbutamol FEV₁ and FEV₁/FVC findings will be used to determine subject eligibility. Reversibility testing will be completed as follows: Following pre-albuterol/salbutamol spirometry (three acceptable spirometry efforts), the subject will self-administer 4 puffs of albuterol/salbutamol MDI using a spacer/valved holding-chamber. Three acceptable spirometry efforts will be obtained approximately 10 to 30 minutes after albuterol/salbutamol administration.

7.3.4. SGRQ-C

The St George's Respiratory Questionnaire -COPD specific (SGRQ-C) will be completed by subjects at Randomisation (V2), Week 12 (V4) and Week 24 (V5).

The SGRQ-C [Meguro, 2007] is a disease-specific questionnaire designed to measure the impact of respiratory disease and its treatment on a COPD patient's HRQoL. As well as producing an overall summary score, scores for the individual domains of symptoms,

activity and impacts are also produced. It has been used in studies of COPD subjects and has been translated and validated for use in most major languages. The SGRQ-C is derived from the original SGRQ, and produces SGRQ scores equivalent to the SGRQ instrument [[Meguro, 2007](#)].

7.3.5. Baseline Dyspnoea Index/Transitional Dyspnoea Index

The BDI is used to measure the severity of dyspnoea in patients at baseline. The TDI measures changes in the patient's dyspnoea from baseline. The scores in both indexes depend on ratings for three different categories: functional impairment; magnitude of task; and magnitude of effort. The BDI will be measured at Randomisation (V2). TDI will be measured at Week 12 (V4) and at Week 24 (V5).

7.3.6. COPD Exacerbations

COPD exacerbations will be identified based on the investigator's clinical judgment.

If the subject experiences a moderate or severe exacerbation, every effort should be made to complete the following assessments within 48 hours of the exacerbation:

- Chest X-ray
- Pulse oximetry

See [Appendix 7](#) (Section 12.7).

7.4. Safety

7.4.1. Safety endpoints

- Incidence of adverse events
- Incidence of adverse events of special interest
- ECG measurements
- Vital signs
- Haematological and clinical chemistry parameters

7.4.2. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in [Appendix 4](#), Section 12.4.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.4.2.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.2.3), at the time points specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4 (Section 12.4.6).
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4 (Section 12.4.6).

7.4.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

7.4.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.5). Further information on follow-up procedures is given in Appendix 4 (Section 12.4).

7.4.2.4. Cardiovascular and Death Events

For any cardiovascular events detailed in [Appendix 4](#), Section 12.4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

7.4.2.5. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation 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.

7.4.3. Adverse Events of Special Interest (AESIs)

AE groups of special interest have been defined as AEs which have specified areas of interest for one or more of class of drugs (ICS, LAMA, LABA). Some AE groups may have subgroups defined.

The following table presents the current special interest AE groups and subgroups. These may be updated prior to conclusion of the study reporting. The final list, including the preferred terms which contribute to each of the groups will be documented *a priori* in the study RAP.

Special interest AE group	Special interest AE subgroup
Cardiovascular effects	Cardiac arrhythmia
	Cardiac failure
	Cardiac ischemia
	Hypertension
	Stroke
Pneumonia and LRTI	Pneumonia
	LRTI excluding pneumonia
Adrenal suppression	
Anticholinergic syndrome	
Corticosteroids associated eye disorders	
Decreased bone mineral density and associated fractures	
Effects on glucose	
Effects on potassium	
Gastrointestinal obstruction	
Hypersensitivity	
Local steroid effects	
Ocular effects	
Tremor	
Urinary retention	

7.4.4. Electrocardiogram (ECG)

Sites will use standardised ECG equipment provided by a centralised external vendor. All ECG measurements will be made with the subject in a supine position having rested in this position for approximately 5 minutes before each reading at Screening (V1) and at Week 24 (V5) or at the Early Withdrawal Visit.

- Single 12-lead ECGs will be obtained at each time point during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

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

All ECGs will be electronically transmitted to an independent cardiologist and evaluated. The independent cardiologist, blinded to treatment assignment, will be responsible for providing measurements of heart rate, QT intervals and an interpretation of all ECGs collected in this study. A hard copy of these results will be sent to the Investigator. The Investigator must provide his/her dated signature on the confirmed report, attesting to his/her review of the independent cardiologist's assessment.

Details of the cardiac monitoring procedures will be provided by the centralised cardiology service provider.

7.4.5. Vital Signs

Vital signs will be performed prior to conducting spirometry and prior to taking the morning dose of study treatment. Vital signs will be collected at Screening (V1), Week 4 (V3), and Week 24 (V5) or at the Early Withdrawal Visit. 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.

7.4.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in [Table 3](#), must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eCRF.

Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in [Table 3](#).

Table 3 Protocol Required Safety Laboratory Assessments

CHEMISTRY	HEMATOLOGY	OTHER
Albumin	Haemoglobin	Hepatitis B surface antigen ¹
Alkaline phosphatase	Hematocrit	Hepatitis C virus antibody ¹
Alanine amino-transferase (ALAT or SGPT)	Platelet count	Urine pregnancy test ²
Aspartate amino-transferase (ASAT or SGOT)	WBC count	
Bilirubin, direct	Neutrophils, absolute	
Bilirubin, indirect	Neutrophils, segs (%)	
Bilirubin, total	Neutrophils, bands (%)	
Calcium	Basophils (%)	
Chloride	Eosinophils (%)	
CO ₂ content/Bicarbonate	Eosinophils, absolute	
Creatinine	Lymphocytes (%)	
Creatine phosphokinase (CPK), total	Monocytes (%)	
Gamma glutamyl transferase (GGT)	RBC count	
Glucose		
Phosphorus		
Potassium		
Protein, total serum		
Sodium		
Urea nitrogen (BUN)		
Uric Acid		

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

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.4.7. Other Safety Assessments

- Physical examinations
- Pneumonia reporting
- Pulse oximetry
- Radiography (CXR)
- Urine pregnancy test (for women of child-bearing potential)
- Medical Problems and Concomitant Medications

7.4.8. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.

7.4.9. Pneumonia

All suspected pneumonias will require confirmation as defined by the presence of new infiltrate(s) on chest x-ray AND at least 2 of the following signs and symptoms:

- Increased cough
- Increased sputum purulence (colour) or production
- Auscultatory findings of adventitious sounds (*e.g.* egophony, bronchial breath sounds, rales, etc.)
- Dyspnoea or tachypnoea
- Fever (oral temperature > 37.5 °C)
- Elevated WBC (>10,000/mm³ or >15% immature forms)
- Hypoxemia (HbO₂ saturation ≤88% or at least 2% lower than baseline value)

All pneumonias must be captured on the AE/SAE page of the eCRF and on the pneumonia page of the eCRF.

The investigators and site staff should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. For all suspected cases of pneumonia, investigators are strongly encouraged to confirm the diagnosis (this includes obtaining a chest x-ray-) and to initiate appropriate therapy as promptly as possible. All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable).

Note: Pulse oximetry should be measured at any time a moderate or severe exacerbation is reported or pneumonia is suspected and recorded in the source documents and on the pneumonia page of the eCRF if applicable.

7.4.10. Pulse oximetry

Pulse oximetry will be conducted at randomisation and recorded in the eCRF. Pulse oximetry should be measured at any time a moderate or severe exacerbation is reported or pneumonia is suspected and recorded in the source documents and on the pneumonia page of the eCRF if applicable.

7.4.11. Radiography (Chest X-Rays)

Confirmation by chest x-ray (posteroanterior and lateral) should be performed as soon as possible and preferably within 48 hours of suspected pneumonia and/or moderate or severe exacerbation. All chest x-rays will be reviewed by the investigator to confirm the presence of new radiographic findings compatible with pneumonia. In all cases, the signs and symptoms that were used to identify the pneumonia must be documented in the source documents and eCRF. Diagnoses of pneumonia must be recorded as adverse events in the eCRF.

7.4.12. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of dosing and until the Follow-up Visit.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in [Appendix 5](#).

7.4.13. Medical Problems and Concomitant Medications

Subjects will be instructed to record any medical problems and the medications used to treat them in a paper diary each day. These entries will be reviewed by the study coordinator at each study visit and recorded in the eCRF as adverse events as appropriate.

7.5. Pharmacokinetics

7.5.1. Blood Sample Collection

Blood samples for PK analysis of FF, UMEC and VI will be collected at the time points indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. A population pharmacokinetics approach will be employed in this study with samples collected in approximately 180 subjects (to achieve approximately 150 subjects treated with FF/UMEC/VI or FF/VI + UMEC). Subjects at selected sites will either be included in subset A or subset B.

PK Subset A (Sparse PK Samples): Approximately 120 subjects will be included, to achieve approximately 100 subjects treated with FF/UMEC/VI or FF/VI + UMEC and providing the required samples. Two 6mL blood samples at each of the two visits will be collected as follows:

- Week 12 (V4): Pre-dose and in the window 5 to 15 minutes post-dose
- Week 24 (V5): In the windows 5 to 15 minutes and 45 to 90 minutes post-dose

PK Subset B (Serial PK Samples): Approximately 60 subjects will be included, to achieve approximately 50 subjects treated with FF/UMEC/VI or FF/VI + UMEC and providing the required samples. Seven 6mL blood samples at one visit will be collected as follows:

- Week 12 (V4): Pre-dose and in the windows 5 to 15 mins and 45 to 90 mins, 2.5 to 4 hours, 6 to 8 hours, 10 to 12 hours and 23 to 24 hours post-dose

Processing, storage and shipping procedures are provided in the SPM.

7.5.2. Sample Analysis

Plasma analysis will be performed under the control of PTS-DMPK/Scinovo, GlaxoSmithKline, the details of which will be included in the SPM. Concentrations of parent compound and metabolites OR compound numbers or names will be determined in plasma OR matrix to be used samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SPM).

Once the plasma OR matrix to be used has been analyzed for parent compound and metabolites OR compound numbers or names any remaining plasma OR matrix to be used may be analyzed for other compound-related metabolites and the results reported under a separate PTS-DMPK/Scinovo, GlaxoSmithKline protocol.

7.6. Genetics

Information regarding genetic research is included in [Appendix 3](#).

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee 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., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- 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.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary objective of this study is to compare FF/UMEC/VI with FF/VI+UMEC in COPD subjects. The primary endpoint is trough FEV₁ at Week 24. The primary analysis is the comparison of this endpoint for FF/UMEC/VI vs. FF/VI+UMEC.

The null hypothesis is that the difference in trough FEV₁ between treatment groups is less than or equal to a pre-specified non-inferiority margin $-\Delta$:

$$H_0: T_1 - T_2 \leq -\Delta$$

The alternative hypothesis is that the difference between treatment groups is greater than the margin.

$$H_1: T_1 - T_2 > -\Delta$$

where T_1 and T_2 are the treatment means for FF/UMEC/VI and FF/VI+UMEC, respectively.

The non-inferiority margin has been set at 50mL, which is half the generally accepted minimal clinically important difference (MCID) for trough FEV₁.

If the lower bound of the two-sided 95% confidence interval around the (FF/UMEC/VI vs. FF/VI+UMEC) treatment difference is above -50mL then FF/UMEC/VI will be considered non-inferior to FF/VI+UMEC.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The sample size calculations use a one-sided 2.5% significance level and an estimate of residual standard deviation (SD) for trough FEV₁ at Week 24 of 220mL. The estimate of SD is based on mixed model repeated measures (MMRM) analyses of previous phase IIIA studies in COPD subjects. A study with 816 evaluable subjects for the primary analysis will have 90% power to determine non-inferiority of FF/UMEC/VI to FF/VI+UMEC based on trough FEV₁ at Week 24, when the margin of non-inferiority is 50mL and the true mean treatment difference is assumed to be 0mL.

It is estimated that approximately 20% of subjects who are randomised will either discontinue study treatment or be excluded from the Adherent population at Week 24, therefore approximately 1020 subjects will be randomised.

However, subjects who provide trough FEV₁ data prior to Week 24 and are in the Adherent population will be included in and contribute to the analysis and so the power of the study may be higher than stated here.

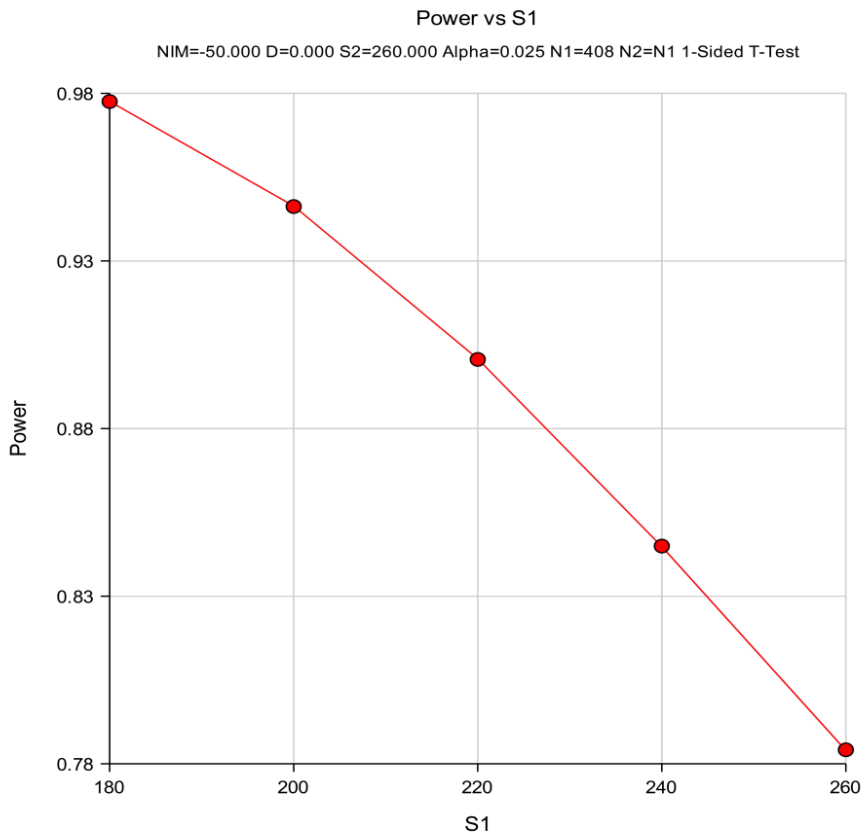
9.2.1.1. Sample Size Sensitivity

If the standard deviation observed in the study is different from the 220 mL used in the sample size calculation, the power to determine non-inferiority based on trough FEV₁ at Week 24 will be affected. [Table 4](#) illustrates the power which would be obtained with various standard deviations, assuming the number of evaluable subjects remains constant at 408 per arm and the non-inferiority margin is 50 mL. [Table 4](#) and [Figure 2](#) illustrate the impact on power of different estimates of standard deviation.

Table 4 Impact on Power of Different Estimates of Standard Deviation

Parameter	SD (mL)	Power for Margin of 50mL
Trough FEV ₁	180	98%
	200	95%
	220	90%
	240	84%
	260	78%

If the SD increased to 260 mL, the study would have 78% power to conclude noninferiority based on a margin of 50 mL.

Figure 2 Impact on Power of Different Estimates of Standard Deviation

S1=standard deviation (mL)

Based on a SD of 220 mL and a sample size of 408 evaluable subjects per arm, the lower confidence bound for the treatment difference would be greater than 0 at an observed treatment difference of 31 mL [detectable effect].

9.2.2. Sample Size Re-estimation or Adjustment

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

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	<ul style="list-style-type: none"> All subjects for whom a record exists in the study database, including screen failures and any subject who was not screened but experienced an SAE between the date of informed consent and the planned date of the Screening visit. 	<ul style="list-style-type: none"> Subject Disposition Reasons for withdrawal prior to randomisation Inclusion, exclusion and randomisation criteria deviations SAEs for non-randomised subjects
Intent-to-treat (ITT)	<ul style="list-style-type: none"> All randomized subjects, excluding those who were randomized in error. A subject who is recorded as a screen or run-in failure and also randomized will be considered to be randomized in error. Any other subject who receives a randomisation number will be considered to have been randomized. Displays will be based on the treatment to which the subject was randomized. 	<ul style="list-style-type: none"> Study Population Efficacy Health-related Quality of Life Inhaler Assessments Safety
Adherent	<ul style="list-style-type: none"> All subjects in the ITT Population who do not have a full protocol deviation considered to impact efficacy. Data following a COPD exacerbation or pneumonia will be excluded from analysis due to the potential impact of the exacerbation or the medications used to treat it Subjects with partial protocol deviations considered to impact efficacy will be included in the Adherent Population but will have their data excluded from analyses from the time of deviation onwards. 	<ul style="list-style-type: none"> Primary treatment comparison of the primary endpoint only

9.4. Key Elements of Analysis Plan

9.4.1. Treatment Comparisons

The primary treatment comparison of FF/UMEC/VI with FF/VI+UMEC will be performed on trough FEV₁ at Week 24, for the Adherent Population.

The treatment comparison of FF/UMEC/VI with FF/VI+UMEC will be performed for the primary endpoint and all other efficacy and health related quality of life endpoints for the ITT Population.

Treatment comparisons will not be adjusted for multiplicity.

9.4.2. Primary Analyses

The “de jure” estimand will be used to demonstrate non-inferiority of FF/UMEC/VI to FF/VI + UMEC.

The primary endpoint of trough FEV₁ at Week 24 will be analysed for the Adherent Population using a mixed model repeated measures (MMRM) analysis, including trough FEV₁ recorded at each of Weeks 4, 12 and 24. The model will include covariates of stratum (number of long-acting bronchodilators per day during the run-in), baseline FEV₁, Week, centre group, treatment and Week by baseline interaction. A Week by treatment interaction term will also be included to allow treatment effects to be estimated at each visit separately. The variance-covariance matrix will be assumed unstructured.

Estimated differences between FF/UMEC/VI and FF/VI+UMEC will be presented together with 95% confidence intervals (CIs) for the difference and p-values.

A “tipping point” sensitivity analysis of trough FEV₁ at Week 24 will be conducted for the Adherent Population. This will explore the impact of missing data by using differing assumptions regarding the mean treatment effect in subjects who discontinue study treatment or have data excluded from Adherent Population analyses. Assumptions will include scenarios where subjects who discontinue FF/UMEC/VI have a lower treatment effect than those who discontinue FF/VI+UMEC. The analysis results will be used to explore the conditions under which the conclusion of non-inferiority no longer holds.

9.4.3. Other Efficacy Analyses

The MMRM analysis will be repeated for the ITT Population.

Full details of the analyses to be performed on the primary and other efficacy endpoints will be given in the RAP.

9.4.4. Safety Analyses

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

Deaths and SAEs will be documented in case narrative format.

Full details of the analyses to be performed on all safety endpoints will be given in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional

assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the Insert the appropriate text, either “CRF” or “PIMS record” for studies conducted at a GSK Phase I unit will serve as the source document.

GSK will monitor the study and site activity to verify 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

10.4. Quality Assurance

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

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.

- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the 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 maintained to allow easy and timely retrieval, 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 these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to 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 and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

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

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

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

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

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
AV	Atrioventricular
BDI	Baseline Dyspnoea Index
Bpm	Beats Per Minute
CAT	COPD Assessment Test
CI	Confidence Intervals
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatinine Phosphokinase
CPRD	Clinical Practice Research Database
CRF	Case Report Form
CT	Computed Tomography
CXR	Chest X-Ray
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FEV1	Forced Expiratory Volume in One Second
FF	Fluticasone Furoate
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma Glutamyl Transferase
GSK	GlaxoSmithKline
GSK573719	Umeclidinium (UMEC)
GW642444	Vilanterol Trifenatate (VI)
GW685698	Fluticasone Furoate (FF)
HRQoL	Health Related Quality of Life
IB	Investigator Brochure
ICS	Inhaled Corticosteroid
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IND	Investigational New Drug
IRB	Independent Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine System

LABA	Long Acting Beta-Agonist
LAMA	Long-acting Muscarinic Receptor Antagonists
LDH	Lactate Dehydrogenase
LTOT	Long Term Oxygen Therapy
MACE	Major Adverse Cardiac Event
mcg	Microgram
MDI	Metered Dose Inhaler
mL	Milliliter
mm	Millimeter
MMRM	Mixed Models Repeated Measures
MSDS	Material Safety Data Sheet
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
PDE4	Phosphodiesterase 4
PA	Posteroanterior
PK	Pharmacokinetic
prn	As required
QD	Once daily
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
SABAs	Short-acting β 2-adrenergic receptor agonists
SAE	Serious Adverse Event
SD	Standard Deviation
SGRQ	St Georges Respiratory Questionnaire
SPM	Study Procedures Manual
TDI	Transitional Dyspnoea Index
ULN	Upper Limit of Normal
UMEC	Umeclidinium
VI	Vilanterol Trifenatate

Trademark Information

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12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

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

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT \geq 8xULN
ALT Increase	ALT \geq 5xULN but <8xULN persists for \geq 2 weeks ALT \geq 3xULN but <5xULN persists for \geq 4 weeks
Bilirubin^{1,2}	ALT \geq 3xULN and bilirubin \geq 2xULN (>35% direct bilirubin)
INR²	ALT \geq 3xULN and INR>1.5, if INR measured
Cannot Monitor	ALT \geq 5xULN but <8xULN and cannot be monitored weekly for \geq 2 weeks ALT \geq 3xULN but <5xULN and cannot be monitored weekly for \geq 4 weeks
Symptomatic³	ALT \geq 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	Follow Up Assessments
<ul style="list-style-type: none"> Immediately discontinue study treatment Report the event to GSK within 24 hours Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE² Perform liver event follow up assessments Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below) 	<ul style="list-style-type: none"> Viral hepatitis serology⁴ Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody⁵. Blood sample for pharmacokinetic (PK) analysis, obtained within 72 hours after last dose⁶ Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).

<ul style="list-style-type: none"> • Do not restart/rechallenge subject with study treatment unless allowed per protocol • If restart/rechallenge not allowed per protocol, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments <p>MONITORING:</p> <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended <p><u>For All other criteria:</u></p> <ul style="list-style-type: none"> • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline 	<ul style="list-style-type: none"> • Fractionate bilirubin, if total bilirubin $\geq 2 \times \text{ULN}$ • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form <p><u>For bilirubin or INR criteria:</u></p> <ul style="list-style-type: none"> • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). NOTE: not required in China • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.
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1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT $\geq 3 \times \text{ULN}$ and bilirubin $\geq 2 \times \text{ULN}$. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT $\geq 3 \times \text{ULN}$ and bilirubin $\geq 2 \times \text{ULN}$ (>35% direct bilirubin) or ALT $\geq 3 \times \text{ULN}$ and INR > 1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: 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
5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment 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.

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	Actions
<p>ALT \geq5xULN and <8xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks.</p> <p>OR</p> <p>ALT \geq3xULN and <5xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks.</p>	<ul style="list-style-type: none"> • Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT \geq5xULN and <8xULN to \geq3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

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12.3. Appendix 3 - Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic aetiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including Fluticasone Furoate (FF)/Umeclidinium (UMEC)/Vilanterol (VI); Umeclidinium (UMEC); and Fluticasone Furoate (FF)/Vilanterol (VI) or any concomitant medicines;
- COPD susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

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

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at V5 or at any visit after Randomisation (V2), after the subject has provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or “coded”) with the same study specific number used to label other samples and data in the study. This number 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).

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 only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

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

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood/saliva being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic 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.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

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

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

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

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

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12.4. Appendix 4: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.4.1. Definition of Adverse Events

Adverse Event Definition:

- An AE is 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.

Events meeting AE definition include:

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

Events NOT meeting definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- 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.

- 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.

12.4.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalisation for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as 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 hospitalisation or prolongation of existing hospitalisation

NOTE:

- In general, hospitalisation 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 hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.
- Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

<ul style="list-style-type: none"> 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
<p>e. Is a congenital anomaly/birth defect</p>
<p>f. Other situations:</p> <ul style="list-style-type: none"> Medical or scientific judgment 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 hospitalisation 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 hospitalisation, or development of drug dependency or drug abuse
<p>g. Is associated with liver injury <u>and</u> impaired liver function defined as:</p> <ul style="list-style-type: none"> ALT \geq 3xULN and total bilirubin* \geq 2xULN (>35% direct), or ALT \geq 3xULN and INR** > 1.5. <p>* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT \geq 3xULN and total bilirubin \geq 2xULN, then the event is still to be reported as an SAE.</p> <p>** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.</p>

12.4.3. Definition of Cardiovascular Events

<p>Cardiovascular Events (CV) Definition:</p>
<p>Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:</p> <ul style="list-style-type: none"> Myocardial infarction/unstable angina Congestive heart failure Arrhythmias Valvulopathy Pulmonary hypertension

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.4.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.4.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort

and not interfering with everyday activities.

- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests

or investigations, histopathological examinations or consultation with other health care professionals.

- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.4.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor or the SAE coordinator
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor or the SAE coordinator by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor or the SAE coordinator
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail

- Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.5.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Oral Contraceptive, either combined or progestogen alone [[Hatcher](#), 2007a]
- Injectable progestogen [[Hatcher](#), 2007a]
- Contraceptive vaginal ring [[Hatcher](#), 2007a]
- Percutaneous contraceptive patches [[Hatcher](#), 2007a]
- Male partner sterilisation with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [[Hatcher](#), 2007a].
- Male condom plus partner use of one of the contraceptive options below:
 - Contraceptive subdermal implant
 - Intrauterine device or intrauterine system
 - Oral Contraceptive, either combined or progestogen alone [[Hatcher](#), 2007a] Injectable progestogen [[Hatcher](#), 2007a]
 - Contraceptive vaginal ring [[Hatcher](#), 2007a]
 - Percutaneous contraceptive patches [[Hatcher](#), 2007a]

This is an all inclusive list of those methods that meet the GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and, correctly and, when applicable, in accordance with the product label. For non-product methods (e.g. male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by the ICH [[ICH](#), M3 (R2) 2009].

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.5.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in [Appendix 4](#) (Section 12.4.6). While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- will discontinue study treatment and be withdrawn from the study

12.6. Appendix 6 - Country Specific Requirements

12.7. Appendix 7 – COPD Exacerbation Identification, Categorization and Treatment Guidelines

12.7.1. Guidelines for Identifying COPD Exacerbations

The following are symptoms used to ascertain an exacerbation of COPD:

Worsening of two or more of the following major symptoms for at least two consecutive days:

- Dyspnea
- Sputum volume
- Sputum purulence (color)

OR

Worsening of any one major symptom together with any one of the following minor symptoms for at least two consecutive days:

- Sore throat
- Colds (nasal discharge and/or nasal congestion)
- Fever (oral temperature > 37.5 °C) without other cause
- Increased cough
- Increased wheeze

Subjects who experience worsening COPD symptoms for greater than 24 hours 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
- Continue to record their symptoms and rescue albuterol/salbutamol
- If the subject seeks emergency/acute care for worsening respiratory symptoms, he/she should request the caring Health Care Provider (HCP) to contact the Investigator as soon as possible.

Subjects with worsening respiratory symptoms will be classified as having:

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

OR

- A Lower Respiratory Tract Infection (LRTI)
- Background variability of COPD
- A non-respiratory related disease

- Other respiratory related disease

Definitions for COPD exacerbations and pneumonia are given in Section 12.7.1.1 and in Section 7.4.9, respectively. 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 recorded in the diary as an AE/SAE in the eCRF. Refer to Section 12.4.1 and Section 12.4.2 for definitions of AE and SAE, respectively.

12.7.1.1. COPD Exacerbation Severity

Each COPD exacerbation will be categorized based on severity as follows:

Mild: Worsening symptoms of COPD that are self-managed by the subject. Mild exacerbations are not associated with the use of corticosteroids or antibiotics.

Moderate: Worsening symptoms of COPD that require treatment with oral/systemic corticosteroids and/or antibiotics.

Severe: Worsening symptoms of COPD that require treatment with in-patient hospitalisation.

Every effort should be made to conduct a chest x-ray within 48 hours of identification of a moderate or severe exacerbation.

Details of an exacerbation should be recorded in the exacerbation page of the eCRF. However, 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 or SAE section of the eCRF and on the Pneumonia page of the eCRF.)

Use of antibiotics for the treatment of upper or lower respiratory tract infections will not be considered a COPD exacerbation unless the subject experiences worsening symptoms of COPD which match the definition of an exacerbation as given above.

12.7.1.2. Treatment of COPD Exacerbations

All medications used for the treatment of exacerbations must be recorded in the source documents and the exacerbation page of the eCRF. All sites should follow the protocol treatment guidelines (as outline below), but any medications deemed medically necessary may be used to treat a COPD exacerbation. However, caution is advised in using a LABA or LAMA to treat a subject currently taking study treatment as these additional medications may increase the risk of overdose. If necessary the Investigator or other health care personnel may stop the subjects study treatment temporarily in order to treat the COPD exacerbation.

12.7.1.3. Guidelines for Treatment with Corticosteroids

If in the opinion of the investigator/treating physician the exacerbation is severe enough to warrant the need for oral or systemic corticosteroids (with or without antibiotics) the following guidelines should be used.

- The duration of treatment with oral/systemic corticosteroids should be \leq 14 days (dose and type according to local practice)
- The duration of treatment with oral/systemic corticosteroids should not exceed 14 days unless approval is given by the sponsor or representative
- Any course of oral/systemic corticosteroids started within 7 days of finishing a previous course will be considered as treatment for a single exacerbation

12.7.1.4. Guidelines for Treatment with Antibiotics

If there is evidence of respiratory infection that in the opinion of the investigator or treating physician warrants the need for antibiotics the following guidelines should be followed:

- The duration of treatment with antibiotics should be 7 to 14 days (dose and type according to local practice). If first line antibiotic treatment fails and additional antibiotics are used, the total duration of antibiotic treatment should not exceed 30 days unless approval is given by the sponsor or representative
- Any course of antibiotics started within 7 days of finishing a previous course will be considered as treatment for a single exacerbation

Use of antibiotics for the treatment of upper or lower respiratory tract infections is not considered a COPD exacerbation unless the subject experiences worsening of symptoms of COPD as described in Section [12.7.1](#).

12.7.1.5. Onset and Resolution of COPD Exacerbations

For each mild, moderate and severe exacerbation, the date of onset and the date of resolution will be recorded in the study source documents and eCRF.

The date of onset is the first day (of at least 2 consecutive days) of worsening symptoms of COPD as described in Section [12.7.1](#).

The date of resolution should be based on when the Investigator and/or subject determines that the COPD symptoms have returned to pre-exacerbation levels or to a new baseline. In determining this resolution date, consideration should be given to diary recorded symptoms and/or study subject evaluation.

12.7.1.6. Guideline for assessing multiple mild exacerbations

Two mild exacerbations can be combined into one, per the Investigator's judgement, if a subject's diary reveals that the two mild COPD exacerbations are separated by no more than three exacerbation free days.

12.7.1.7. Guideline for assessing exacerbations that increase in severity

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

12.8. Appendix 8 – Hair Sample, Scalp & Finger Secretion PK Sub-Study

12.8.1. Introduction

Adherence and compliance to inhaled drug treatment is poor, relative to oral therapies with strong evidence to suggest that over time, compliance remains a challenge for both COPD and asthma (Restrepo, 2008; Tamura, 2007; Laforest, 2010; Yilmaz, 2013; Bryant, 2013; Aguis, 2010; Barbosa, 2013; Breekveldt, 2007; Kardas, 2002; Wilson, 2010). There is currently no robust quantitative or semi-quantitative way of assessing patient compliance to inhaled products. This is primarily due to the small doses (often in micrograms) used during treatment, leading to low systemic exposure and the relatively short timeframe when systemic exposure can be measured using available bioanalytical methods. Normal methods of monitoring drug compliance are poor for inhaled therapies so an alternative approach is being developed.

Testing of orally administered drugs from human head hair is well established in the monitoring of a wide range of drugs including benzodiazepines, opiates, amphetamines and other potential drugs of abuse. A broad spectrum of other pharmaceuticals including orally administered salbutamol and steroids such as stanozolol and nandrolone have also been shown to offer a retrospective analysis of drug use over time (World Health Organisation, 2003; Barbosa, 2013; Porta, 2011; Dominguez-Romero, 2011). The same is not true for drugs taken by the inhaled route, so this study is seeking to find out whether head hair along with finger smears can be used to detect inhaled drugs to assess patient compliance. Sensitive analytical techniques have been developed such as matrix-assisted laser desorption/ionisation (MALDI) (Vulic, 2011) or secondary ion mass spectrometry (SIMS) (Aguis, 2010) with the potential to look at drug use over time. This study will examine the utility of these alternative approaches to detect inhaled drugs.

Human head hair grows at the rate of ~1cm/month, offering the potential to detect and monitor drug deposition in the hair as it grows. Secretions from hair follicles and from the fingers (termed sweat for the purpose of this document) also secrete drugs onto the skin surface (Kuwayama, 2014). The aim of this exploratory sub-study is to establish whether human head hair or human skin sweat samples (scalp or finger smear) can be used to detect and if possible to quantify drug concentrations that have accumulated directly into hair/finger sweat from inhaled respiratory therapies in patients being treated for COPD. Successful detection of inhaled therapies in hair or from sweat over time should allow verification against patient reported adherence to therapy or direct physician assessment of compliance. This sub-study will help inform whether it is possible to collect adherence data in clinical programmes in the future.

12.8.2. Objective

To collect hair samples, and scalp and finger sweat, in a non-invasive way, for PK analysis among COPD subjects taking part in PK subset A, in Study 200812. This sub-study will, therefore be conducted at a selection of sites, in subjects who have also consented to participate in the PK group A. Subjects who consent to participate in this

sub-study, will continue on study treatment and study visits as per the core study (study 200812).

12.8.3. Investigational Plan

This is a hair sample, scalp and finger sweat PK sub-study to collect samples of head hair, and sweat from the scalp and fingers in subjects who have consented and been randomized to study 200812 (Core Study), “A phase IIIb 24-week randomised, double-blind study to compare ‘closed’ triple therapy (FF/UMEC/VI) with ‘open’ triple therapy (FF/VI + UMEC), in subjects with chronic obstructive pulmonary disease (COPD) and they have consented to take part in PK sub-group A (see Section 7.5 for more details).

A subset of subjects randomised to the Core Study will provide blood samples for PK analysis. For the purpose of this sub-study, subjects who are consented and randomized to the Core Study, in PK subgroup A, will provide hair samples along with scalp and finger sweat samples. Subjects will also provide details of any medicines taken in addition to those being administered within the trial in the 6 weeks preceding the sample collection. In addition, the subjects will provide information on any hair treatments they use, or have used (other than simple washing) just prior to the hair sample collection.

Subjects of this sub-study will provide a hair, finger and scalp sweat sample at Visits 2, 4 and 5. Details of the samples being taken at each of these visits are described below:

Hair Sample

A hair sample (the width of a thin pencil) will be taken from the back of the scalp, at a site which is acceptable to the subject, and unlikely to be visible. The hair sample will be taken before study treatment is taken at Visits 2, 4 and 5.

Figure 3 Hair Sample Collection

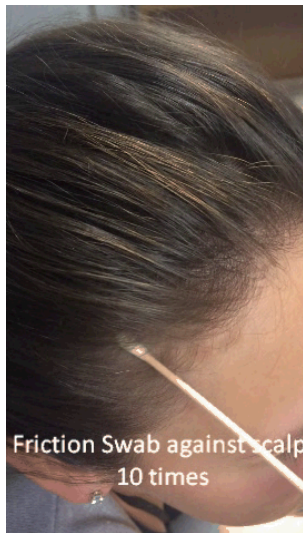


(A pencil width of hair is removed as close to the scalp as possible).

Scalp sweat sample

At the same time, each subject will have a scalp sweat sample taken near the site of the hair sample collection. See [Figure 4](#). The scalp sweat sample will be taken before study treatment is taken at Visits 2, 4 and 5.

Figure 4 Scalp Swab

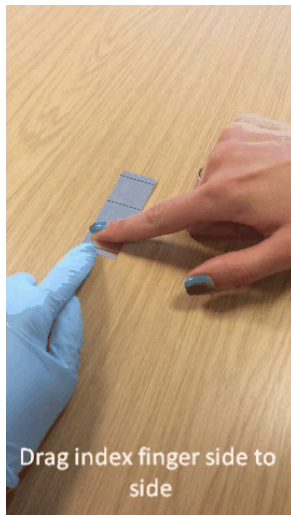


(A scalp swab for a scalp sweat sample will be taken near the same site as the hair sample).

Finger sweat smear

A finger sweat smear will be taken from three separate fingers of one hand (in general: index, 2nd finger and thumb of same hand for each collection). The subject will be required to smear their fingers across an aluminium slide (provided for such purposes), to collect the smear. See [Figure 5](#).

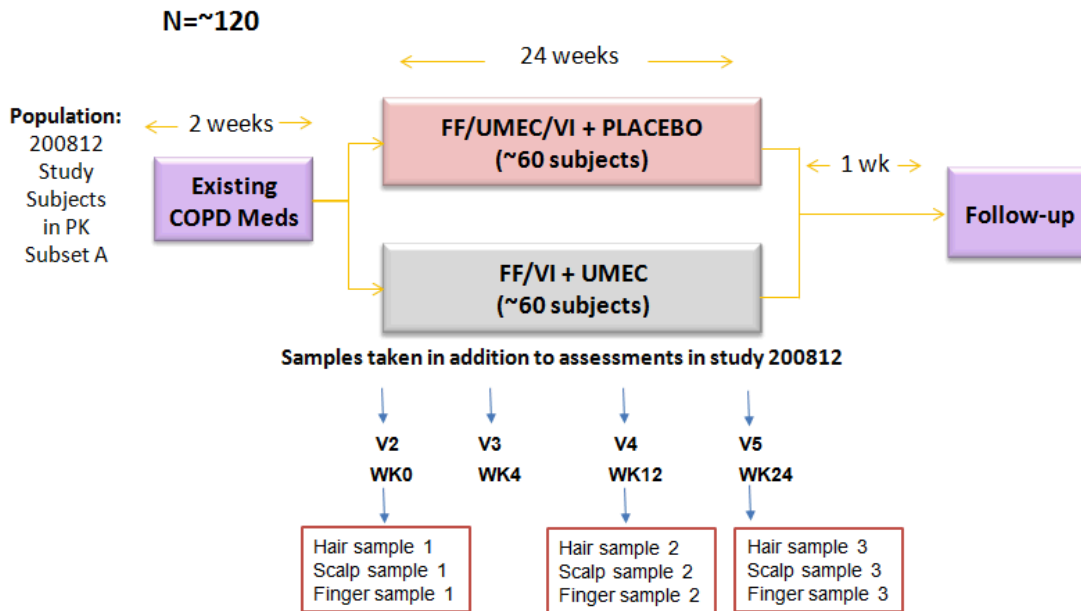
These finger sweat samples will be collected in such a way to ensure that identifiable finger prints are not taken from the subject, therefore ensuring that only a smear is obtained. The finger sweat smear will be taken approximately 15 minutes after hair sampling has been taken in clinic at Visits 2, 4 and 5. Immediately after taking study treatment and 15 minutes before the finger smear is taken, the subject will be required to wash their hands.

Figure 5 Finger Smear Sample

Finger sweat samples will be taken 15 minutes after subjects take their inhaled medication (having washed their hands immediately after dosing with 50:50 water/ethanol).

Both head hair, scalp sweat and finger sweat samples will be used to assess levels of the inhaled drugs the subjects are receiving at scheduled visits starting from Week 0. Samples will be collected at Randomisation (V2), at Week 12 (V4) and Week 24 (V5). Further details on hair, scalp and finger sweat sampling are described in the SPM.

All subjects who participate in this sub-study will be required to provide a separate consent in order to give hair, scalp and finger sweat samples, along with the supporting information on other medication use and hair treatments.

Figure 6 Hair Sample, Scalp & Finger Sweat PK Sub-Study Schematic

12.8.4. Subject Selection and Withdrawal Criteria

12.8.4.1. Inclusion Criteria

Subjects eligible for enrolment in this sub-study must meet both of the following criteria:

1. Informed Consent: A signed and dated written informed consent for the study 200812 (Core Study).
2. Separate Informed Consent for hair, scalp and finger sweat sample sub-study: A signed and dated written informed consent for the sub-study, for hair sample, scalp secretions and finger secretion collection.

12.8.4.2. Exclusion Criteria

There are no exclusion criteria to this sub-study.

12.8.5. Sub-study Withdrawal Criteria

Every effort should be made by the investigator to keep the subject in this sub-study. However a subject may voluntarily withdraw from participation in this sub-study at any time.

In the event that a subject withdraws consent from this Hair Sample, Scalp & Finger Sweat PK Sub-Study, they will still be eligible to continue in the PK sub-study subset A and they can still continue participation in the Core Study.

12.8.6. Potential Risks Associated with Sub-Study Participation

The overall risk to the subject participating in this sub-study is considered minimal. However, there is a small chance of the subject being injured with the scissors used for the hair sample collection. The chance of this happening is very low and any injury that may be sustained is expected to be minor i.e. not requiring treatment.

Wherever possible, the site staff will aim to collect the hair sample from a part of the scalp where it would not be noticeable.

All finger sweat samples will be taken as a smear to ensure that a finger print is not obtained. Therefore, there is no risk of obtaining identifiable finger prints from these samples.

12.9. Appendix 9 – Protocol Changes

Revision History

2015N261999_00	2015-DEC-09	Original
2015N261999_01	2016-JAN-25	Amendment No.: 01 Global
2015N261999_02	2016-FEB-11	Amendment No.: 02 South Korea only
2015N261999_03	2016-JUN-29	Amendment No.: 03 Global (excluding South Korea)

12.9.1. Protocol Amendment 1

Amendment 01 applies to all countries and study centres participating in the 200812 study. Amendment 01 purpose is to correct discrepancies in the Time and Events Table, Appendix 3 - Genetic Research and Appendix 8 – Hair Sample, Scalp & Finger Secretion PK Sub-Study.

The specific areas where changes were made to the protocol are listed below. Wording that has been deleted will be indicated with a strikethrough (ex. ~~Word~~) and new wording will be indicated in Bold type (ex. **Word**).

1. PROTOCOL Synopsis for study 200812 and 4.1. Overall Design:

The following text updated to include the requirement for an early withdrawal study for subjects who stop study treatment early:

Subjects who stop study treatment early will complete **an Early Withdrawal Visit, followed by a Safety Follow-Up a week later** ~~the safety follow-up~~ and **finally** be withdrawn from the study.

7.1. Time and Events Table:

The letters corresponding to the T&E footnotes have been corrected and updated, as detailed below. The scheduled visit for pulse oximetry, and footnote ‘p’ inserted for the genetics blood draw:

Protocol Activity	Pre-Screen	Screen	Treatment				Follow Up	
	Visit 0 Pre-screen	Visit 1 Screening	Visit 2 Randomisation	Visit 3	Visit 4	Visit 5	Early Withdrawal Visit	Safety Follow-up Contact
Study Week		Week -2	Week 0	Week 4	Week 12	Week 24		1 week Fw-up
Window		-3/+8d		-4/+2d	-8/+6d	-8/+6d		-1/+4d
Vital signs ^j		X		X		X	X	
ECG ^k		X				X ^k	X ^k	
Chest X-ray ^l		X						
Pulse oximetry ^m		X	X					
Blood draw for PK					X ⁿ	X ^o		
Blood Draw for Genetics research			X			X ^p		
Haematology/biochemistry ^{p,q}		X				X	X	
Urine Pregnancy Test ^{r,t}		X		X	X	X	X	
Hepatitis B and C tests		X						
Dispense study treatment			X	X	X			
Administer study treatment in clinic ^{r,s}			X	X	X			
Assess study treatment compliance				X	X	X	X	
Collect study treatment				X	X	X	X	
Dispense albuterol/salbutamol		X	X	X	X			
Collect albuterol/salbutamol			X	X	X	X	X	
Issue/review paper diary ^{s,t}		X	X	X	X	X	X	

p. The genetics blood sample should be taken at V5 or at any visit after Randomisation (V2) where there is a scheduled blood draw

q. Haematology and chemistry panels will include liver chemistry, and potassium and glucose levels.

r. All female subjects of child bearing potential will have a urine pregnancy test at each visit except Visits 2 and follow-up.

s. Subjects must withhold their morning dose of study treatment at each clinic visit and not take their study treatment dose until instructed to do so by study staff.

t. Subjects will be issued a paper diary, at screening and other clinic visits (if required) in order to note any changes to concomitant medications and/or incidence of adverse events that may have occurred between clinic visits.

12.3. Appendix 3 - Genetic Research:

The bullet describing the objectives of the genetics research incorrectly references Umeclidinium (UMEC)/Vilanterol (VI). The text has been corrected match the study medication in 200812:

- Response to medicine, including Fluticasone Furoate (FF)/Umeclidinium (UMEC)/Vilanterol (VI); Umeclidinium (UMEC)/~~Vilanterol (VI)~~; and Fluticasone Furoate (FF)/Vilanterol (VI) or any concomitant medicines;

The scheduled collection of the genetics blood sample has been corrected to match the Time and Events Table:

- A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at **V5 or at any visit after Randomisation (V2) where there is a scheduled blood draw** ~~the baseline visit~~, after the subject has ~~been randomized and~~ provided informed consent for genetic research.

12.8. Appendix 8 – Hair Sample, Scalp & Finger Secretion PK Sub-Study:

Text that contradicts timings of sample collections referenced in other parts of the protocol has been removed.

Both head hair, scalp sweat and finger sweat samples will be used to assess levels of the inhaled drugs the subjects are receiving at scheduled visits starting from Week 0. Samples will be collected at Randomisation (V2) ~~prior to first dose of study treatment, at~~ Week 12 (V4) and Week 24 (V5) ~~after the collection of blood PK samples~~. Further details on hair, scalp and finger sweat sampling are described in the SPM.

12.9.2. Country-Specific Protocol Amendment 2 for South Korea

Amendment 02 applies to South Korea. The purpose of Amendment 2 is to include study medication labelling for South Korea and details of study equipment that will be supplied.

12.9.3. Protocol Amendment 3 (excluding South Korea)

Amendment 03 applies to all countries except South Korea. A country-specific amendment for South Korea i.e. Amendment 4 will include required local revisions and information from the Global Amendment 01 and Global Amendment 03.

Amendment 03 purpose is to clarify and correct minor discrepancies in the protocol sections detailed below.

The specific areas where changes were made to the protocol are listed below. Wording that has been deleted will be indicated with a strikethrough (ex. ~~Word~~) and new wording will be indicated in Bold type (ex. **Word**).

5.2. Exclusion Criteria

Exclusion criteria 9 has been updated to reference the views required from the Screening chest x-ray.

9. Abnormal Chest x-ray: Chest x-ray (**posteroanterior and later**) reveals evidence of pneumonia or a clinically significant abnormality not believed to be due to the presence of COPD, or another condition that would hinder the ability to detect an infiltrate on chest x-ray (e.g. significant cardiomegaly, pleural effusion or scarring). All subjects will have a chest x-ray at Screening (V1) [or historical radiograph or CT scan obtained within 3 months prior to Screening (V1)].

7.1. Time and Events Table

The check boxes to register visits in RAMOS have been checked for V1, V3-V5 and the Early Withdrawal Visit and the checkbox to administer study treatment at V5 has been checked. Clarifications have been made to footnote e, k, l and p.

Protocol Activity	Pre-Screen	Screen	Treatment				Follow Up	
	Visit 0 Pre-screen	Visit 1 Screening	Visit 2 Randomisation	Visit 3	Visit 4	Visit 5	Early Withdrawal Visit	Safety Follow-up Contact
Study Week		Week -2	Week 0	Week 4	Week 12	Week 24		1 week Fw-up
Window		-3/+8d		-4/+2d	-8/+6d	-8/+6d		-1/+4d
Written Informed Consent ^a	X	X						
Genetic Informed Consent ^b	X	X						
Demography ^c	X	X						
Medical History, including cardiovascular history		X						
COPD and Exacerbation History		X						
Concomitant Medication Assessment	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria		X						
Randomisation Criteria			X					
Smoking History		X						
Smoking status		X				X	X	
Smoking Cessation Counselling		X				X	X	
Register Visit in IRT/ RAMOS NG ^d		X	X	X	X	X	X	
Reversibility Testing ^e		X						
Spirometry			X ^f	X ^f	X ^f	X ^f		
Device training and registration		X	X					
Exacerbation Assessment		X	X	X	X	X	X	X
SGRQ-C ^g			X		X	X		
BDI ^g			X					
TDI ^g					X	X		
CAT ^g		X						
eDevice close out ^h			X			X	X	
Physical examination ⁱ		X				X	X	

Protocol Activity	Pre-Screen	Screen	Treatment				Follow Up	
	Visit 0 Pre-screen	Visit 1 Screening	Visit 2 Randomisation	Visit 3	Visit 4	Visit 5	Early Withdrawal Visit	Safety Follow-up Contact
Study Week		Week -2	Week 0	Week 4	Week 12	Week 24		1 week Fw-up
Window		-3/+8d		-4/+2d	-8/+6d	-8/+6d		-1/+4d
Adverse Events Assessment		X	X	X	X	X	X	X
Vital signs ^j		X		X		X	X	
ECG		X				X*	X*	
Chest X-ray ^l		X						
Pulse oximetry ^m			X					
Blood draw for PK					X ⁿ	X ^o		
Blood Draw for Genetics research						X ^p		
Haematology/biochemistry ^q		X				X	X	
Urine Pregnancy Test ^r		X		X	X	X	X	
Hepatitis B and C tests		X						
Dispense study treatment			X	X	X			
Administer study treatment in clinic ^s			X	X	X	X	X	
Assess study treatment compliance				X	X	X	X	
Collect study treatment				X	X	X	X	
Dispense albuterol/salbutamol		X	X	X	X			
Collect albuterol/salbutamol			X	X	X	X	X	
Issue/review paper diary ^t		X	X	X	X	X	X	

- Informed consent must be conducted at the Pre-screen Visit prior to performing any study procedures including the changing or withholding of medications. The (IC) may be given at Screening Visit 1 if the subject does not take or has not taken any protocol excluded medications.
- Genetics research consent may be obtained at the same time as the study IC and must be obtained prior to obtaining a genetic blood sample.
- Demography may be captured at either the Pre-screen Visit or Screening Visit (for subjects who do not have a Pre-screen Visit).
- The IRT will be used for randomisation, emergency unblinding and study treatment supply management (Please refer RAMOS NG IRT manual for more information)
- At Screening Visit 1 both pre and post-bronchodilator spirometry will be conducted. ~~Subjects are required to withhold their usual morning dose of their COPD meds including rescue albuterol/salbutamol for the 4 hour period prior to reversibility testing. Pre-bronchodilator spirometry will be performed prior to the subject taking their morning dose of their usual COPD treatment, between 6am and 11am and after withholding rescue albuterol/salbutamol for ≥4 hours.~~
- At Visits 2-5 (and the Early Withdrawal Visit), pre-bronchodilator spirometry will be performed prior to taking the morning dose of study treatment, between 6am and 11am and after withholding rescue albuterol/salbutamol for ≥4 hours.

- g. Patient reported assessments should be conducted in the following order and before other study assessments: SGRQ-C, BDI/TDI.
- h. Close out eDevice for any subject who fails to randomize, withdraws early, or completes Visit 5.
- i. Physical examination may include height, weight, blood pressure, temperature, heart rate.
- j. Vital signs must be performed prior to spirometry and prior to taking morning dose of study medication.
- k. ECG to be obtained 15 - 45 minutes post-dose at treatment Visit 5 and Early Withdrawal Visit (if applicable possible). **If a subject is not dosed at Early Withdrawal, then an ECG can be taken at any time during the visit**
- l. Chest X-ray (**PA and lateral**) is required at Screening (or historical x-ray obtained within 3 months prior to Screening) and at anytime there is a suspected pneumonia or a mod/severe exacerbation.
- m. Pulse oximetry must be performed at V2 and anytime there is a suspected pneumonia or a moderate or severe exacerbation.
- n. PK subset A: PK samples of 120 subjects at selected sites, to be obtained at two time points at Visit 4: pre-dose and in the window 5 to 15 minutes post-dose.
PK subset B: PK samples of 60 subjects at selected sites, to be obtained and Visit 4: pre-dose, 5-15min, 45-90min, 2.5-4h, 6-8h, 10-12h, 23-24h post-dose.
- o. PK subset A: PK samples of 120 subjects at selected sites, to be obtained at two time points at Visit 5: 5 to 15 minutes post-dose and 45 to 90 minutes post-dose.
- p. The genetics blood sample should be taken at V5 or at any visit after Randomisation (V2). ~~where there is a scheduled blood draw.~~
- q. Haematology and chemistry panels will include liver chemistry, and potassium and glucose levels.
- r. All female subjects of child bearing potential will have a urine pregnancy test at each visit except Visits 2 and follow-up.
- s. Subjects must withhold their morning dose of study treatment at each clinic visit and not take their study treatment dose until instructed to do so by study staff.
- t. Subjects will be issued a paper diary, at screening and other clinic visits (if required) in order to note any changes to concomitant medications and/or incidence of adverse events that may have occurred between clinic visits.

7.4.11. Radiography (Chest X-Rays)

The views required for chest x-rays performed for suspected pneumonias and/or moderate/severe exacerbations have been specified in brackets.

Confirmation by chest x-ray (posteroanterior and lateral) should be performed as soon as possible and preferably within 48 hours of suspected pneumonia and/or moderate or severe exacerbation. All chest x-rays will be reviewed by the investigator to confirm the presence of new radiographic findings compatible with pneumonia. In all cases, the signs and symptoms that were used to identify the pneumonia must be documented in the source documents and eCRF. Diagnoses of pneumonia must be recorded as adverse events in the eCRF.

11. References

The reference below for a citation used in Appendix 5 has been added to the reference list.

International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (2009). Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2).

12.3. Appendix 3 – Genetic Research

Text has been updated to reflect the changes to the footnote p in the Time and Events Table.

- A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at V5 or at any visit after Randomisation (V2) ~~where there is a scheduled blood draw~~, after the subject has provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.