TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A 24-week treatment, multi-center, randomized, double-blind, double-dummy, parallel group study to compare Umeclidinium/Vilanterol, Umeclidinium, and Salmeterol in subjects with chronic obstructive pulmonary disease (COPD)

Compound Number: GSK2592356

Development Phase: IV

Effective Date: 18-APR-2017

Protocol Amendment Number: 03

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N277425_00	2016-SEP-13	Original
2016N277425_01	2017-FEB-07	Amendment No. 1
This protocol amendment was created to make the following changes: Regulatory Agency Identifying Number(s): A typographical error in the EudraCT no. corrected. IND no. added Section 4.1and Section 4.4: Typographical errors and inconsistencies corrected Inconsistencies between Section 4.4, Section 7.3.1.5 and Section 7.1revised Section 7.1 Time and Events table: Un-intentional deletion of the ("x") were added to confirm that concomitant medications should be reviewed at every clinic visit was corrected. Increased the visit window Typographical error and inconsistencies corrected as described in Appendix 9, Section 12.9. Section 7.2.2 Critical procedures performed at Screening (Visit 1): To clarify that height and weight are collected at V1 **"**Height and weight" added Section 7.3.2 Spirometry: "At Screening, before the morning dose of usual COPD medication(s)" added. Section 7.3.7: Physical activity monitor (study subset) Inconsistency between Section 1, Section 4.1 and Section 7.3.7 revised		
2016N277425_02	2017-FEB-21	Amendment No. 2 Canada ONLY
This protocol amendment was created to comply with Health Canada guidelines. They require pharmaceutical manufacturers to expeditiously report domestic cases of unusual failure in efficacy (UFIE) for new drugs to the Marketed Health Products Directorate (MHPD) within 15 days of first notification. Changes were made to Section 7.4.1 and Appendix 4.		
2016N277425_03	2017-APR-18	Amendment No. 3
This protocol amendment was created to make the following changes: • Clarifications concerning study design, stratification, permitted and prohibited COPD medications, stopping criteria, visit windows, chest x-rays performed in the context of the protocol and site professional expertise • Rate of COPD exacerbations from tertiary endpoints to exploratory endpoints • Addition of an inclusion criterion specific to France • Integration of Canadian Amendment 2 • Correction of typographical errors and inconsistencies		

SPONSOR SIGNATORY

PPD

18 April 2017

David Lipson, MD
Project Physician Leader

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): IND no. 106616 and 104479, and EudraCT no. 2016-002513-22

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 201749

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

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

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

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 201749

Rationale

The primary purpose of this study is to demonstrate improvements in lung function in subjects treated with Umeclidinium/Vilanterol (UMEC/VI) compared with Umeclidinium (UMEC) for 24 weeks. A further important aspect of the study is to evaluate the effect of UMEC/VI, UMEC, and salmeterol with respect to health-related quality of life (HRQoL), measured through patient reported outcomes (PROs) questionnaires, and lung function. Additional assessments to further evaluate other measures of chronic obstructive pulmonary disease (COPD) efficacy and symptoms control will be performed.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To compare the effect of UMEC/VI (62.5/25 mcg once daily) with UMEC (62.5 mcg once daily) on lung function	• Change from baseline in trough Forced Expiratory Volume in One Second (FEV_1) at week 24
Secondary	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on patient reported outcomes (PROs)	• Change from baseline in self administered computerised (SAC) transient dyspnea index (TDI) • Percentage of TDI responders according to SAC TDI score. A responder is defined as a ≥1 unit improvement in SAC TDI score • Assessment of respiratory daily symptoms over 24 weeks using Evaluating Respiratory Symptoms-COPD (E-RS) and its subscales (breathlessness, cough and sputum and chest symptoms) • Percentage of E-RS responders according to E-RS score (defined as reduction in E-RS score of ≥2 or ≥3.35 units) from baseline • Change from baseline in St George's Respiratory Questionnaire (SGRQ-C) • Percentage of responders according to SGRQ-C total score (defined as a 4 point or greater reduction from

Objectives	Endpoints
	baseline) • Change from baseline in COPD assessment test (CAT) • Percentage of responders according to CAT (defined as a ≥2 unit improvement in score from baseline)
Other	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on other COPD efficacy measures	• Time to first mild, moderate or severe exacerbation • Time to moderate or severe exacerbation • Time to severe exacerbations • Time to clinically important deterioration (CID) composite endpoint • Time to clinically important deterioration composite endpoint excluding FEV_1 • Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the electronic diary (eDiary) over 24 weeks • Inspiratory capacity (IC) • Full Vital capacity (FVC) • Change from baseline in trough FEV_1 • Change from baseline in global impression of disease severity

Objectives	Endpoints
Safety	
• To evaluate safety and tolerability of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) and salmeterol 50 mcg twice daily)	• Incidence of adverse events
Exploratory	
• To explore the effect of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on rate of COPD exacerbation	• Rate of mild, moderate or severe exacerbations • Rate of moderate or severe exacerbation
• To compare albuterol/salbutamol use captured in the eDiary with the electronic metered dose inhaler (eMDI) device	• Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the eMDI device over 24 weeks as data allow
• To explore the effect of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on physical activity	• Change from baseline in physical activity
• To investigate the CID composite endpoint ability to predict short term outcomes	• To compare physical activity levels, ER-S, rescue medication use, exacerbations and mortality in subjects with and without a CID

Overall Design

This is a multi-centre, randomized, double blind, double dummy, 3-arm parallel group study. Eligible subjects will be randomized in a ratio of 1:1:1 to UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA™ dry powder inhaler (DPI) or UMEC (62.5 mcg once daily) administered via the ELLIPTA DPI or salmeterol (50 mcg twice daily (BID)) administered via the DISKUS™ DPI.

There will be a total of 5 clinic visits and one follow-up phone call (Visit 6). A pre-screening visit (Visit 0) may be required in order to administer the informed consent before any changes are made to the subject's current medication regimen. If no changes in medication are required, V0 (pre-screening) and V1 (screening) may be conducted on the same day. Inhaled long-acting muscarinic antagonist (LAMA) or long-acting $beta_2$-agonist (LABA) and/or albuterol/salbutamol as needed (rescue medication) are not exclusionary prior to Screening or during the run-in.

Eligible subjects at Screening Visit 1 will be current or former smokers, at least 6 weeks ICS and ICS/LABA free with an FEV_1 post-albuterol/salbutamol of ≥30% to ≤80% predicted normal and a FEV_1/FVC <0.7 and a CAT score ≥10.

Subjects using inhaled LAMA or LABA medication must withhold their morning dose prior to Screening spirometry. Subjects who meet all other eligibility criteria at Screening will enter a run-in period for 4 weeks. During the run-in period, subjects will continue with their inhaled LAMA or LABA. In addition, subjects will be provided with short acting albuterol/salbutamol as needed for relief of COPD symptoms (rescue medication) throughout the study.

Subjects who experience a moderate or severe COPD exacerbation during the run-in period will be deemed run-in failures. Subjects who experience a mild COPD exacerbation, defined as worsening of symptoms that requires **no** treatment with antibiotics or steroids and is self managed by the patient by an increase of inhaled rescue medication will be able to continue in the study based on the judgment of the investigator and agreement of the sponsor's medical monitor.

At the randomization Visit 2 (Day 1), those subjects who successfully complete the run-in period, as well as meet the other pre-defined eligibility and randomization criteria, will be randomized to one of the 3 treatment arms for 24 weeks.

In addition, a subset of subjects (approximately 150 per treatment arm) will undergo assessment of their physical activity measured through a physical activity monitor (Actigraph GT9X) worn for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3, and for 7 days prior to last clinic Visit (Visit 5).

The occurrence of adverse events (AEs) will be evaluated throughout the study beginning at Visit 2 (Day 1) and until the follow-up contact (Visit 6). Serious adverse events (SAEs) will be collected over the same time period as AEs. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact.

All subjects will be given an electronic diary (eDiary) for use during the run-in, and the treatment period to complete PRO questionnaires, record COPD daily symptoms and the time they take their COPD medications. Daily rescue medication usage (number of inhalations taken in the last 24 h) will also be captured in the eDiary. In addition, and in some countries, rescue medication use will also be captured by the use of electronic metered dose inhaler (eMDI).

At Screening Visit 1, all subjects must be trained on the proper use of their existing COPD medications inhalation devices and instructed to strictly adhere to and record the time they take their COPD medications in the eDiary.

At the randomization Visit 2, all subjects must be trained on the proper use of the ELLIPTA and DISKUS inhalation devices and instructed to strictly adhere to and record the time they take their study medications in the eDiary.

All subjects must be trained on the correct use of the eDiary and instructed to complete the eDiary during the run-in and treatment period.

Subjects will be considered to have completed the study upon completion of the Follow–Up contact by telephone.

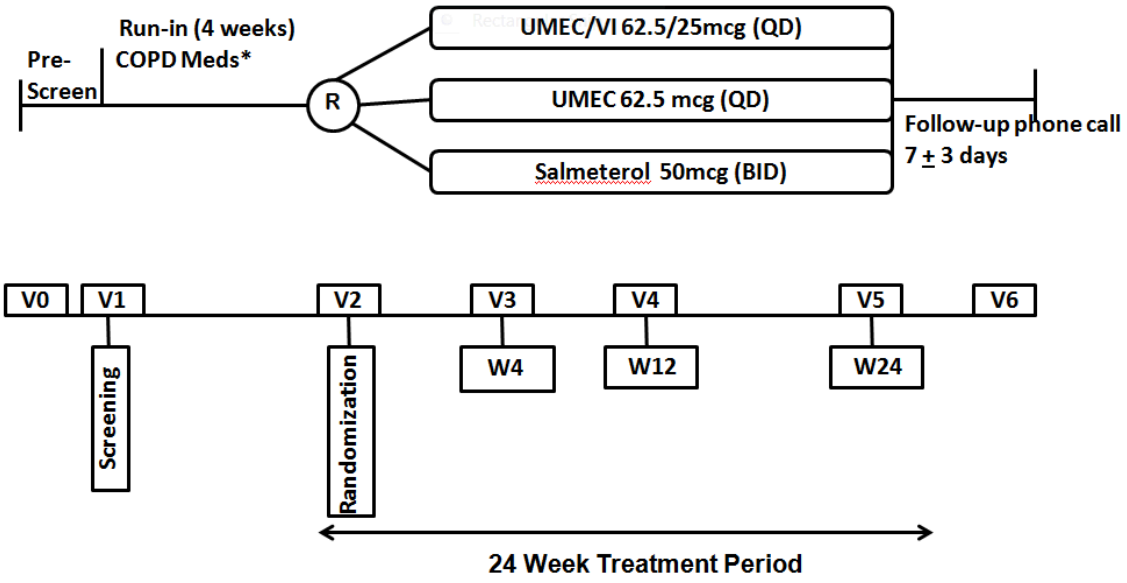
There are no plans to routinely provide any of the study treatments for compassionate use following study completion as the study treatment are commercially available.

Treatment Arms and Duration

Subjects will be stratified based on long-acting bronchodilator usage during the run-in (none or one long-acting bronchodilator per day) and randomized in a ratio of 1:1:1 to either

- UMEC/VI 62.5/25 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- UMEC 62.5 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- Salmeterol 50 mcg twice daily via DISKUS + placebo once daily via ELLIPTA

Study schematic



*Subjects may continue the use of inhaled LAMAs or LABAs and/or study provided albuterol/salbutamol as needed (rescue medication) during the run-in while adhering to the withholding of other COPD medications detailed in the Exclusion Criteria.

Type and Number of Subjects

Approximately 3232 subjects will be screened, such that 2424 subjects will be randomized and approximately 2181 evaluable subjects complete the study.

Analysis

The primary purpose of this study is to demonstrate improvements in lung function for subjects treated with UMEC/VI compared with UMEC for 24 weeks.

The primary endpoint is change from baseline in trough FEV_1 at Week 24.

The null hypothesis is no difference between treatment groups (H0: $\mu T - \mu S = 0$), with the alternative hypothesis that there is a difference between treatment groups (H1: $\mu T - \mu S \neq 0$), where μT is the mean change from baseline for UMEC/VI and μS is the mean change from baseline for UMEC.

The primary endpoint of mean change from baseline in trough FEV_1 at the end of Week 24 will be analysed using Mixed Models repeated Measures (MMRM) analysis. The MMRM analysis will include measurements at Treatment Weeks 4, 12 and 24. Treatment group (a categorical variable) will be fitted as the explanatory variable with appropriate pre-defined variables, stratum (number of bronchodilators per day during run-in) and baseline values, fitted as covariates. Visit (nominal) will be fitted as a categorical variable and visit-by-baseline and visit-by-treatment interaction terms will be included to allow treatment effects to be estimated at each visit separately. The variance covariance matrix

will be assumed to be unstructured (based on previous experience no issues are expected with fitting models with this matrix structure).

The estimated treatment differences between UMEC/VI versus UMEC for each endpoint will be presented with the 95% confidence intervals for the difference and the p-value.

2. INTRODUCTION

2.1. Study Rationale

Chronic obstructive pulmonary disease (COPD) is associated with poor health-related quality of life (HRQoL). Pharmacologic therapy is used to improve lung function, reduce symptoms, frequency and severity of exacerbations, and improve patients HRQoL [GOLD, 2015]. Umeclidinium/Vilanterol (UMEC/VI 62.5/25 mcg) is indicated for the maintenance treatment of COPD that contain long-acting muscarinic antagonist (LAMA) and long-acting beta$_2$-agonist (LABA) bronchodilators. Umeclidinium (UMEC) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Salmeterol has long been used for symptoms management of COPD. However, a direct comparison of these maintenance therapies has not been conducted with respect to HRQoL.

The primary purpose of this study is to demonstrate improvements in lung function for subjects treated with UMEC/VI compared with UMEC for 24 weeks. The effect of UMEC/VI, UMEC, and salmeterol with respect to patient HRQoL measured through patient reported outcomes (PROs) questionnaires, symptoms and lung function will also be evaluated.

2.2. Brief Background

COPD is characterized by an airflow limitation which is not fully reversible, usually progressive and accompanied by a chronic cough, sputum production and dyspnea which can be a major cause of disability and anxiety associated with the disease [Maleki-Yazdi, 2014]

Furthermore, acute exacerbations contribute to the overall severity of disease as these episodes are accompanied by worsened symptoms and are associated with increased decline in lung function and mortality [Wedzicha, 2013; Schmidt, 2014].

Pharmacologic therapy is used to improve lung function, reduce symptoms, reduce the frequency and severity of exacerbations, and also to improve health status and exercise tolerance. Maintenance treatment is recommended primarily through the use of LABAs or LAMAs. COPD treatment guidelines recommend an incremental approach to pharmacological treatment as the disease state worsens, involving the use of combinations of drug classes with different or complementary mechanisms [GOLD, 2015].

UMEC/VI inhalation powder is a combination of UMEC (umeclidinium bromide), a LAMA, and VI (Vilanterol), a LABA, delivered via the ELLIPTA dry powder inhaler

(DPI). UMEC/VI at a dose of 62.5/25mcg once-daily is marketed in the United States (US) and Europe under the trade name ANORO™ ELLIPTA.
UMEC (62.5 mcg) inhalation powder is marketed in the United States (US) and Europe under the trade name INCRUSE™ ELLIPTA. UMEC (62.5mcg) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. UMEC (62.5 mcg) improves forced expiratory volume in one second (FEV_1), dyspnea and HRQoL whether used as monotherapy [Trivedi, 2014; Feldman, 2016] or as an add on to fluticasone propionate and vilanterol (FF/VI) [Siler, 2015]. Salmetrol (50 mcg) DISKUS is a long-acting broncholdilator that has long been used for the maintenance treatment of COPD [Tashkin, 2010].

Clinically important deterioration (CID) is a novel, exploratory composite endpoint which assesses individual deteriorations in lung function and in patient PROs defined by the accepted minimal clinically important difference (MCID), as well as the incidence of moderate to severe exacerbations [Singh, 2016], (Section 7.3.5). CID will be analysed to determine whether UMEC/VI (62.5/25mcg) therapy provides greater clinical stability as compared with UMEC and salmeterol monotherapies.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To compare the effect of UMEC/VI (62.5/25 mcg once daily) with UMEC (62.5 mcg once daily) on lung function	• Change from baseline in trough Forced Expiratory Volume in One Second (FEV_1) at week 24
Secondary	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on patient reported outcomes (PROs)	• Change from baseline in self administered computerised (SAC) transient dyspnea index (TDI) • Percentage of TDI responders according to SAC TDI score. A responder is defined as a ≥1 unit improvement in SAC TDI score • Assessment of respiratory daily symptoms over 24 weeks using Evaluating Respiratory Symptoms-COPD (E-RS) and its subscales (breathlessness, cough and sputum and chest symptoms) • Percentage of E-RS responders according to E-RS score (defined as reduction in E-RS score of ≥2 or ≥3.35 units) from baseline

Objectives	Endpoints
	• Change from baseline in St George's Respiratory Questionnaire (SGRQ-C) • Percentage of responders according to SGRQ-C total score (defined as a 4 point or greater reduction from baseline) • Change from baseline in COPD assessment test (CAT) • Percentage of responders according to CAT (defined as a ≥2 unit improvement in score from baseline)
Other	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on other COPD efficacy measures	• Time to first mild, moderate or severe exacerbation • Time to moderate or severe exacerbation • Time to severe exacerbations • Time to clinically important deterioration (CID) composite endpoint • Time to clinically important deterioration composite endpoint excluding FEV_1 • Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the electronic diary (eDiary) over 24 weeks • Inspiratory capacity (IC) • Full Vital capacity (FVC) • Change from baseline in trough FEV_1 • Change from baseline in global impression of disease severity

Objectives	Endpoints
Safety	
• To evaluate safety and tolerability of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) and salmeterol 50 • mcg twice daily)	• Incidence of adverse events
Exploratory	
• To explore the effect of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on rate of COPD exacerbation	• Rate of mild, moderate or severe exacerbations • Rate of moderate or severe exacerbation
• To compare albuterol/salbutamol use captured in the eDiary with the electronic metered dose inhaler (eMDI) device	• Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the eMDI device over 24 weeks as data allow
• To explore the effect of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on physical activity	• Change from baseline in physical activity
• To investigate the CID composite endpoint ability to predict short term outcomes	• To compare physical activity levels, ER-S, rescue medication use, exacerbations and mortality in subjects with and without a CID

4. STUDY DESIGN

4.1. Overall Design

This is a multi-centre, randomized, double blind, double-dummy, 3-arm parallel group study. Eligible subjects will be randomized in a ratio of 1:1:1 to UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA™ dry powder inhaler, or UMEC (62.5 mcg once daily) administered via the ELLIPTA™ or salmeterol (50 mcg BID) administered via the DISKUS.

There will be a total of 5 clinic visits and one follow-up phone call (Visit 6). A pre-screening visit (Visit 0) may be required in order to administer the informed consent before any changes are made to the subject's current medication regimen. If no changes in medication are required, V0 (pre-screening) and V1 (screening) may be conducted on the same day. Inhaled long-acting muscarinic antagonist (LAMA) or long-acting $beta_2$-agonist (LABA) and/or albuterol/salbutamol as needed (rescue medication) are not exclusionary prior to Screening or during the run-in.

Eligible subjects at Screening Visit 1 will be current or former smokers, at least 6 weeks ICS and ICS/LABA free with an FEV_1 post-albuterol/salbutamol of ≥30% to ≤80% predicted normal and a FEV_1/FVC <0.7 and a CAT score ≥10.

Subjects using inhaled LAMA or LABA medication must withhold their morning dose prior to Screening spirometry. Subjects who meet all other eligibility criteria at Screening will enter a run-in period for 4 weeks. During the run-in period, subjects will continue with their inhaled LAMA or LABA medication. In addition, subjects will be provided with short acting albuterol/salbutamol as needed for relief of COPD symptoms (rescue medication) throughout the study.

Subjects who experience a moderate or severe COPD exacerbation during the run-in period will be deemed run-in failures. Subjects who experience a mild COPD exacerbation, defined as worsening of symptoms that requires **no** treatment with antibiotics or steroids and is self managed by the patient by an increase of inhaled rescue medication, (Appendix 5), will be able to continue in the study based on the judgment of the investigator and agreement of the sponsor's medical monitor.

At the randomization Visit 2 (Day 1), those subjects who successfully complete the run-in period as well as meet the other pre-defined eligibility and randomization criteria will be randomized to one of the 3 treatment arms for 24 weeks.

In addition, a subset of subjects (approximately 150 per treatment arm) will undergo assessment of their physical activity measured through a physical activity monitor (Actigraph GT9X) worn for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3, and for 7 days prior to last clinic Visit (Visit 5).

The occurrence of adverse events (AEs) will be evaluated throughout the study beginning at Visit 2 (Day 1) and until the follow-up contact (Visit 6). Serious adverse events (SAEs) will be collected over the same time period as AEs. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact (Appendix 4).

All subjects will be given an electronic diary (eDiary) for use during the run-in, and the treatment period to complete PRO questionnaires, record COPD daily symptoms, any medical problems experienced during the study and the time they take their COPD medications. Daily rescue medication usage (number of inhalations taken in the last 24h) will also be captured in the eDiary. In addition, and in some countries, rescue medication use will also be captured by the use of electronic metered dose inhaler (eMDI).

At Screening Visit 1, all subjects must be trained on the proper use of their existing COPD medications inhalation devices and instructed to strictly adhere to and record the time they take their COPD medications in the eDiary.

At the randomization Visit 2, all subjects must be trained on the proper use of the ELLIPTA and DISKUS inhalation devices and instructed to strictly adhere to and record the time they take their study medications in the eDiary.

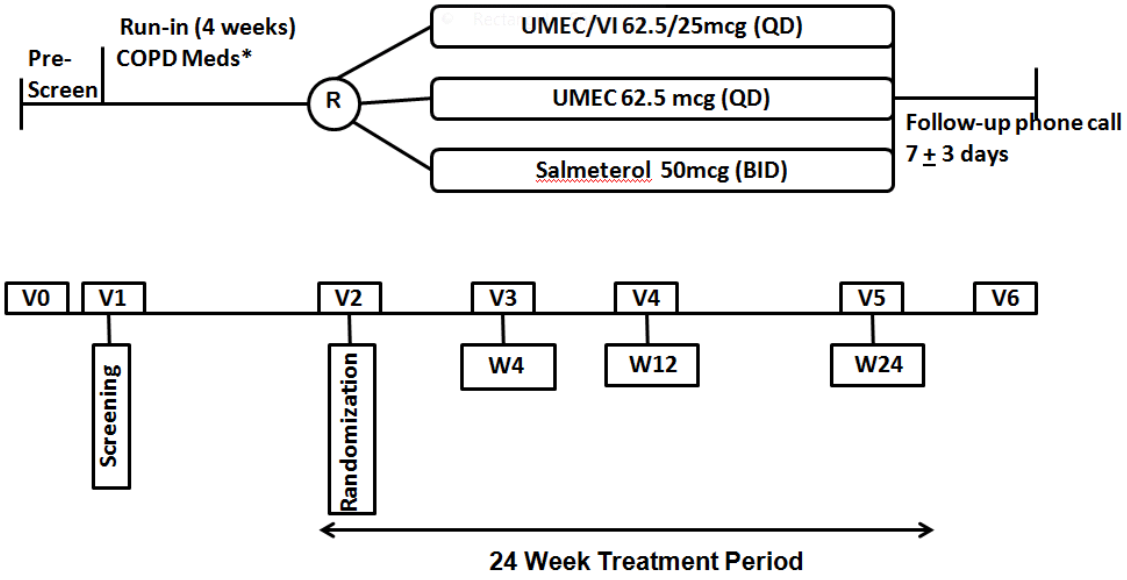
All subjects must be trained on the correct use of the eDiary and instructed to complete the eDiary during the run-in and treatment period.

Subjects will be considered to have completed the study upon completion of the follow – up contact by telephone.

There are no plans to routinely provide any of the study treatments for compassionate use following study completion as the study treatment are commercially available.

The study design schematic is illustrated in Figure 1

Figure 1 Study Schematic



*Subjects may continue the use of inhaled LAMAs or LABAs and/or study provided albuterol/salbutamol as needed (rescue medication) during the run-in while adhering to the withholding of other COPD medications detailed in the Exclusion Criteria.

4.2. Treatment Arms and Duration

Subjects will be stratified based on long-acting bronchodilator usage during the run-in (none or one long-acting bronchodilator per day) and randomized in a ratio of 1:1:1 to either

- UMEC/VI 62.5/25 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- UMEC 62.5 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- Salmeterol 50 mcg twice daily via DISKUS + placebo once daily via ELLIPTA

The total duration of subject participation in the study will be approximately 29 to 35 weeks consisting of 6 weeks pre-screening if necessary, 4 weeks run-in, 24 week treatment and one week follow-up.

4.3. Type and Number of Subjects

Approximately 3232 will be screened globally in approximately 240 sites such that approximately 2424 subjects will be randomized and approximately 2181 evaluable subjects complete the study.

4.4. Design Justification

A randomized, double blinded, parallel group study is a standard, well-established design to evaluate the efficacy and safety of an investigational drug. A salmeterol arm is included to allow a comparison to be made between UMEC/VI, UMEC with salmeterol, a standard practice treatment.

The double-dummy design is appropriate when drugs are of different appearance or different administration regimen which is appropriate in this study where the inhalers used have a different appearance and used once daily and twice daily.

The European Medicines Agency (EMA) COPD Guidelines suggest that duration of 12 to 24 weeks is considered adequate for assessment of response of COPD symptoms to treatment intervention with bronchodilators (EMA COPD guidelines, 2012).

The primary endpoint is trough FEV_1 at week 24. This endpoint is generally considered to be a robust, well established and an objective means to show the efficacy of a bronchodilator [Dahl, 2010; Feldman, 2010].

Other endpoints such SAC TDI, E-RS, SGRQ-C, CAT, Subject Global Rating of Change in global impression of disease severity are captured to allow responder analyses and to provide comparative data on PROs between the treatment groups.

4.5. Dose Justification

This study is intended to evaluate the efficacy of marketed doses of UMEC/VI (62.5/25mcg once daily), UMEC (62.5 mcg once daily) and salmeterol (50mcg twice daily) that are approved for the maintenance treatment of COPD, with respect to PRO measures.

4.6. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with UMEC/VI and UMEC can be found in the investigator's brochures (IB) [GlaxoSmithKline Document Number RM2009/00437/07] and [GlaxoSmithKline Document Number RM2006/00835/09] and in the label information sheets. The current safety profile for UMEC (62.5mcg) and the UMEC/VI (62.5/25mcg) based on data available to date, is comparable with other LABAs and LAMAs. Summary safety data can also be found in the information sheet for salmeterol [Serevent product information, 2003].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
Investigational Product (IP) [UMEC/VI]		
Severe milk protein allergy	Anoro contains Lactose monohydrate (which contains milk protein) as an excipient.	Exclusion criteria have been set for subjects with milk protein allergy.
Cardiovascular effects such as cardiac arrhythmias *e.g.* supraventricular tachycardia and extrasystoles.	Class effects associated with LABAs and LAMA containing therapy. The clinical significance of these arrhythmias is unknown. Clinical experience with UMEC/VI to date in completed studies did not show any association with major cardiovascular events. Data available in the product label for UMEC/VI	Exclusion criteria have been set for subjects with uncontrolled or severe cardiovascular disease according to the principal investigation's (PI) opinion where the potential risk may outweigh the benefit. The PI should also determine the clinical significance of abnormal ECG findings at screening and exclude subjects who would be at undue risk by participating in the trial. Patients with the following abnormalities will be excluded from participation: atrial fibrillation with rapid ventricular rate >120bpm, sustained or nonsustained ventricular tachycardia, or second degree heart block Mobitz type II or third degree heart block (unless pacemaker or defibrillator had been inserted).
Beta agonists and risk of asthma-related death	Long-acting beta agonists such as vilanterol when used alone may increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including vilanterol. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.	Subjects with a current diagnosis of asthma are excluded from participation in the study.
Paradoxical bronchospasm	As with other inhaled medicines, UMEC/VI can produce paradoxical bronchospasm which may be life threatening.	If paradoxical bronchospasm occurs following dosing with UMEC/VI, this treatment should be discontinued immediately and alternative therapy should be instituted.
Use in patients with narrow-angle glaucoma or urinary retention	No association has been found to date, in completed studies with UMEC/VI or UMEC monotherapy, on glaucoma or urinary retention. However, glaucoma or urinary retention	Exclusion criterion states that subjects with medical conditions such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction should only be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	have been observed with other antimuscarinic agents, and could potentially be due to the pharmacology.	included if, in the opinion of the principal investigator, the benefit outweighs the risk.
Use of beta blockers	Beta-adrenergic blockers may weaken or antagonize the effect of $beta_2$-agonists such as vilanterol.	The study permitted medications and non drug therapies section states that concomitant administration with beta-blockers is only permitted if, in the Investigator's opinion, the likely benefit outweighs the potential risk.
Pregnancy	There is no experience to date of pregnancy during the use of UMEC/VI.	The study inclusion criteria ensures that female subjects of child bearing potential must have a negative pregnancy test at screening, and agree to a reliable contraceptive method, used consistently and correctly (i.e. in accordance with the approved product label and the instructions of the physician for the duration of the study). Exclusion criteria include **Pregnancy:** Women who are pregnant or lactating or are planning on becoming pregnant during the study.
Severe hepatic impairment	UMEC/VI has not been studied in severe hepatic impairment.	Exclusion criterion states that subjects severe hepatic impairment should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Investigational product (IP) [UMEC]		
Cardiovascular effects such as cardiac arrhythmia, e.g. atrial fibrillation and tachycardia	A potential class effect associated with anti-muscarinic therapies. Data available to date in the IB for UMEC [GlaxoSmithKline Document Number RM2006/00835/09	Screening electrocardiogram (ECG) criteria to exclude subjects potentially at risk
Narrow-angle glaucoma, urinary retention	A class effect associated with anti-muscarinic therapies. Data available in the IB for UMEC [GlaxoSmithKline Document Number RM2006/00835/09	Exclusion criterion states that subjects with medical conditions such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Paradoxical bronchospasm that may be life threatening	Known effect associated with inhalation therapy	A short-acting inhaled bronchodilator (albuterol/salbutamol) will be provided for use as needed throughout the study. The investigators will be instructed to assess subject's condition to determine their eligibility to

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		continue in the study and the need for alternative therapy.
Severe hepatic impairment	UMEC has not been studied in severe hepatic impairment.	Exclusion criterion states that subjects with severe hepatic impairment should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Pregnancy/Lactation	There is no experience to date of pregnancy during the use of UMEC.	The study inclusion criteria ensure that female subjects enrolled, who are of Child bearing potential, have a negative pregnancy test at screening, and agree to a reliable contraceptive method, used consistently and correctly (i.e. in accordance with the approved product label and the instructions of the physician for the duration of the study). Exclusion criteria states - Pregnancy: Women who are pregnant or lactating or are planning on becoming pregnant during the study.
Study Procedures		
Spirometry procedures	This may cause difficulty breathing, changes in pulse rate and blood pressure, coughing, wheezing, chest tightness or fainting.	Subjects will be monitored during the procedure for these effects and spirometry will be discontinued should these occur.
ECG lead placement	This may cause skin irritation.	It may be necessary to have small patches (about a centimetre in diameter) of hair on the chest shaved to properly attach electrodes to the chest.
Blood sampling procedure (optional pharmacogenetic blood sample)	Giving blood may make subjects feel faint, or experience mild pain, bruising, irritation or redness at the site. In rare cases, they may get an infection	Subjects will be monitored during the blood draw for these effects and should call their study doctor if any of these effects do not resolve
Other		
Side effects of rescue albuterol/salbutamol. Adverse events seen in clinical studies to date are however consistent for the beta$_2$-adrenergic class of compounds	Class effects associated with short acting beta-agonists (SABAs)	Subjects should call their study doctor if they experience any of these symptoms

4.6.2. Benefit Assessment

Subjects will receive single or combination of long-acting bronchodilator therapies approved for maintenance treatment of COPD. Participating subjects in this study will contribute to the process of further characterizing the benefit of these long-acting bronchodilators with respect to PROs and symptoms in the treatment of COPD.

Specific benefits associated with the study design and procedures include the following:

- Subjects will receive treatments approved for the treatment of COPD that have been shown to be effective in the population under study
- All subjects will receive albuterol/salbutamol for use "as needed" for relief of COPD symptoms
- The combination of study procedures of spirometry, CAT, SGRQ, TDI, E-RS will provide the study subjects with a comprehensive evaluation of their symptoms, health status and COPD disease severity. Subjects will also be monitored throughout the study for any worsening of COPD symptoms or decline in general health. Finally smoking cessation counselling will also be provided.

4.6.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with UMEC/VI, UMEC, salmeterol and with study procedures are justified by the anticipated benefits from active treatments that may be afforded to patients with COPD.

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 IBs, [GlaxoSmithKline Document Number RM2006/00835/09], [GlaxoSmithKline Document Number RM2009/00437/07] and product labels.

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

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.

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. **40 years or older** at date of signing informed consent

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. **Outpatient with a diagnosis of COPD** in accordance with the definition of the American Thoracic Society/European Respiratory Society (ATS/ERS) [Celli, 2004].
3. **FEV_1**: Persistent airflow limitations as indicated by: A pre and post-albuterol/salbutamol FEV_1/FVC ratio of <0.70 and a post-albuterol/salbutamol FEV_1 of ≥30% to ≤80% predicted normal values at Screening Visit 1. Predicted values will be based upon the ERS Global Lung Function Initiative [Quanjer, 2012].
4. **CAT score**: A CAT score of ≥10 at Screening Visit 1

Smoking History
5. **Current or former cigarette smokers** with a history of cigarette smoking of ≥ 10 pack-years [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 both equal 10 pack-years)]. Former smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Pipe and/or cigar use cannot be used to calculate pack-year history.

SEX
6. **Male and female** subjects are eligible to participate in the study
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 must be tested. 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) (Appendix 7) from 30 days prior to the first dose of study medication and until [at least five terminal half-lives OR until any continuing pharmacologic effect has ended, whichever is longer] after the last dose of study medication and completion of the follow-up visit. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
7. **Capable of giving signed informed consent** prior to study participation, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION
1. **Asthma**: 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). 2. **Alpha-antitrypsin deficiency:** Subjects with known α1-antitrypsin deficiency as the underlying cause of COPD 3. **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. 4. **Unstable liver disease:** 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). • 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 or within 3 months prior to first dose of study treatment) are acceptable if subject otherwise meets entry

criteria

5. **Unstable or life threatening cardiac disease:** Investigational Product should be used with caution in subjects with severe cardiovascular disease. In the opinion of the investigator, use should only be considered if the benefit is likely to outweigh the risk in conditions such as:
   - 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
6. **12 Lead ECG:** 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. Subjects with the following abnormalities are excluded from participation in the study:
   - Atrial fibrillation with rapid ventricular rate >120 bpm
   - Sustained or non-sustained ventricular tachycardia
   - Second degree heart block Mobitz type II or third degree heart block (unless pacemaker or defibrillator had been inserted)
7. **Antimuscarinic effects:** Subjects with medical conditions such as narrow-angle glaucoma, urinary retention, prostatic hypertrophy, or bladder neck obstruction should be excluded unless, in the opinion of the study physician, the benefit outweighs the risk.
8. **Other disease abnormalities:** Any subject who is considered unlikely to survive the duration of the study period or has any rapidly progressing disease or immediate life-threatening illness (e.g. cancer). In addition, any subject who has any other condition (e.g. neurological condition) that is likely to affect respiratory function should not be included in the study.
9. **Hospitalization:** Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1. **Pneumonia and/or moderate COPD exacerbation** that has not resolved at least 14 days prior to Screening Visit 1 and at least 30 days following the last dose of oral/systemic corticosteroids (if applicable).
10. **Inhaled corticosteroids (ICS):** Had received ICS or ICS/LABA for the treatment of COPD in the 6 weeks prior to Screening Visit 1
11. **Exacerbation:** Had >1 moderate exacerbation in the 12 months prior to Screening Visit 1, or one severe exacerbation requiring hospitalisation in the 12 months prior Screening Visit 1.
12. **Other respiratory tract infections** that have not resolved at least 7 days prior to Screening V1.
13. **Lung Resection:** Subjects with lung volume reduction surgery (including procedures such as endobronchial valves) within the 12 months prior to Screening V1.
14. **Oxygen:** Use of long-term oxygen therapy (LTOT) described as resting oxygen

therapy >3L/min at screening required to maintain adequate oxygenation (*e.g.* S_aO_2 >90%). (Oxygen use ≤3L/min flow is not exclusionary, and patients may adjust oxygen levels up or down as needed during the study.)

CONCOMITANT MEDICATIONS

15. **Medications prior to Screening:** Use of the following medications according to the following defined time intervals prior to Screening (Visit 1) or during the study:

Medication	No use within the following time intervals prior to Screening and thereafter at any time during the study
Inhaled corticosteroids (ICS)	6 weeks
Depot corticosteroids	12 weeks
Systemic, oral or parenteral corticosteroids[a]	6 weeks
Antibiotics (for lower respiratory tract infection)	6 weeks
Phosphodiesterase 4 (PDE_4) Inhibitor (*e.g* roflumilast)	14 days
LABA/Inhaled Corticosteroid (ICS) combination products	6 weeks
LABA/LAMA combination products	2 weeks
Theophyllines	48 hours
Oral beta$_2$-agonists Long-acting Short-acting	 48 hours 12 hours
Inhaled short acting beta$_2$-agonists[b]	4 hours
Inhaled short-acting anticholinergics	4 hours
Inhaled short-acting anticholinergic/short-acting beta$_2$-agonist combination products	4 hours
Any other investigational medication	30 days or within 5 drug half-lives (whichever is longer)

a- Corticosteroids are allowed for the treatment of COPD exacerbations during the double-blind treatment phase of the study. Localized corticosteroid injections (e.g., intra-articular and epidural) are permitted.

b- Use of study provided albuterol/salbutamol is permitted during the study, except in the 4-hour period prior to spirometry testing

16. **Medication prior to spirometry:** Unable to withhold albuterol/salbutamol for the 4 hour period required prior to spirometry testing at each study visit. Unable to withhold morning dose of subject's inhaled LABA or LAMA COPD medication prior to spirometry testing at Screening Visit (Visit 1).

17. **Maintenance use of short-acting bronchodilators**: Regular use (prescribed for daily/ regular use, not for as-needed use) of short-acting bronchodilators (*e.g.* albuterol/salbutamol).

RELEVANT HABITS

18. **Drug or alcohol abuse:** A known or suspected history of alcohol or drug abuse within 2 years prior to Screening Visit 1 that in the opinion of the investigator

would prevent the subject from completing the study procedures.
CONTRAINDICATIONS
19. **Any history of allergy or hypersensitivity** to any anticholinergic/muscarinic receptor antagonist, sympathomimetic, lactose/milk protein or magnesium stearate.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
20. **Pulmonary Rehabilitation program:** Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Screening Visit 1. Subjects who are in the maintenance phase of a pulmonary rehabilitation program are not excluded.
21. **Affiliation with investigator sites:** Is an investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member of the aforementioned that is involved in 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 questionnaires on the electronic diary.

Subjects who fail to meet inclusion and exclusion criteria at the **Screening Visit 1** will be considered screen failures and cannot be **re-screened.**

5.3. Randomization Criteria

In order to be randomized to one of the 3 treatment arms at Visit 2, subjects must have completed the run-in period and must have fulfilled all inclusion and exclusion criteria described in Section 5.1 and Section 5.2. In addition to the following:

REQUIRED CRITERIA FOR RANDOMIZATION AND TREATMENT
1. **COPD Exacerbation**: Subjects must **not** have experienced a moderate or severe COPD exacerbation or a lower respiratory tract infection during run-in or at Day 1 (Visit 2) inclusive. A moderate exacerbation is defined as worsening of symptoms of COPD requiring the use of antibiotics or systemic corticosteroids. A severe exacerbation is defined as worsening symptoms of COPD requiring hospitalization.
2. **CAT score**: A CAT score of ≥10 at Visit 2
3. **Prohibited Medications:** No use of any prohibited medications during the run-in period or at Visit 2, including any ICS or ICS/LABA combination. Subject's inhaled LABA or LAMA medication morning dose must be withheld and discontinued at Visit 2.
4. **Any change to COPD medications:** Including dosage and regimen during the run-in
5. **Completion of electronic diary:** Must have completed the electronic diary for at least 80% of days during the run-in period

Subjects who do not meet the required criteria for randomization at Visit 2 will not be randomized.

5.4. Screening/Baseline/Run-in Failures

Pre-screen, screen and run-in failures are defined as follows:

- Pre-screening failures: A subject, who is assigned a subject number at the Pre-screening Visit 0 but does not have any Screening Visit 1 procedures, will be considered a pre-screen failure.
- Screening failures: Those subjects that complete at least one Screening Visit 1 procedure but do not enter the run-in period.
- Run-in failures: Those subjects that enter the run-in period but are not randomized to any of the study treatment arms.

Subjects who are pre-screen, screen and run-in failure will be recorded in the eCRF. 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 to be recorded in eCRF including demography, screen failure details, eligibility criteria, and serious adverse events (Section 7.4.1).

5.5. Withdrawal/Stopping Criteria

5.5.1. Withdrawal from the Study

Subjects may be withdrawn from the study at any time by the Investigator if it is considered to be detrimental for them to continue in the study. Reasons for withdrawal from study treatment can include: an AE, clinically significant abnormality, lack of efficacy, sponsor terminated study, pregnancy, or for any other reason.

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.

A reason for the withdrawal from the study must be captured in the electronic case report form (eCRF).

Stopping Criteria

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

- **Liver Chemistry:** Meets any of the Liver chemistry stopping criteria (See Section 5.5.3)

  Note: clinical laboratory assessments are not required for this study. However, laboratory samples may be taken for liver event analysis, if clinically indicated by the study investigator.

- **Pregnancy:** Positive pregnancy test (see Appendix 7)

- **Unstable or life threatening cardiac events:** myocardial infarction, hospitalization for unstable angina, stroke, and other cardiovascular events considered life- or intensively health-threatening by the study physician.
- **COPD Exacerbations:** Subjects with two moderate or one severe COPD exacerbation during the study.
- **Withdrawal from study treatment** requires withdrawal from the study.
- **Non-Compliance with Study treatment**: Subjects' compliance with study treatment will be assessed at each study visit. Subjects who are non-compliant should be re-educated on the requirement for treatment compliance. Every effort will be made to keep subjects in the study and to re-educate those subjects who continue to be non-compliant. Subjects who continue to be non-compliant after multiple visit assessments may be permanently discontinued **after consultation with the GSK clinical team.**
- **Non-Compliance with eDiary:** Subjects must be compliant in completing their eDiary between each pair of on-treatment visits. Subjects who are non-compliant should be re-educated on the requirement for daily diary entry compliance. Subjects who continue to be non-compliant after multiple visit assessments may be permanently discontinued **after consultation with the GSK clinical team.**

Subjects withdrawn from study treatment will not be replaced.

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".

5.5.2. Reason for Study Withdrawal

The primary reason for study withdrawal will be recorded in the eCRF. When a subject withdraws consent, the investigator must document the reason (if specified by the subject) in the eCRF.

The primary reason for study withdrawal may include:

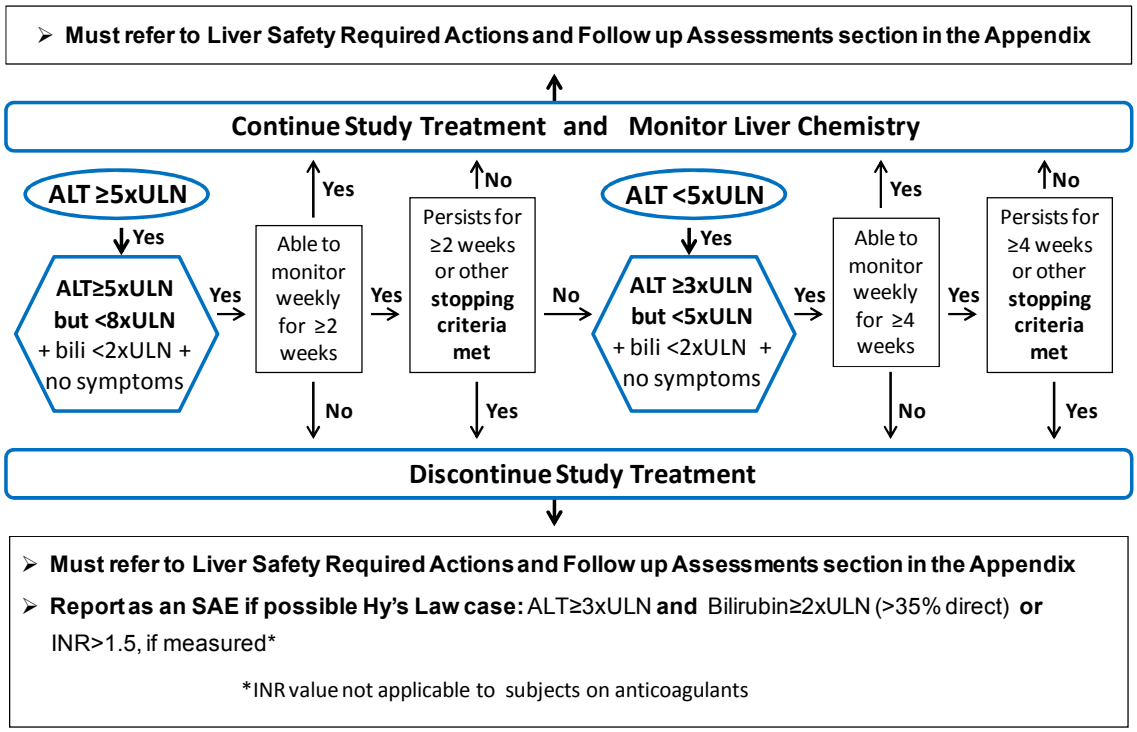
- Adverse event

- Lost to follow-up
- Withdrew consent
  - subject relocated
  - frequency of visits
  - burden of procedures
  - other (specify)
- Protocol deviation
- Lack of efficacy
- COPD exacerbation
- Study closed/terminated
- Subject reached protocol-defined stopping criteria
- Pregnancy
- Investigator discretion

5.5.3. 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

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.

5.5.3.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.6. Follow-up contact

A safety follow-up contact (Visit 6) should be conducted 7±3 days following the completion of Visit 5 or the Early Withdrawal Visit, if applicable.

The following procedures will be performed:

- AE/SAE assessment
- COPD exacerbation assessment
- Concomitant medication assessment limited to any medications used to treat a COPD exacerbation or SAE (if applicable)
- Pregnancy information (if applicable)

Subjects who have successfully completed all on-treatment randomized visits will be discharged from the study upon completion of the safety follow-up contact.

5.7. Subject and Study Completion

A subject will be considered to have completed the study if he/she receives study treatment at Visit 5 (Week 24) and completes the follow-up contact Visit 6.

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.

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

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be

provided to site staff if required by local laws or will otherwise be available from GSK upon request.

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 authorised site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

GlaxoSmithKline (GSK) will provide the study treatments for use in this study.

The following study medications will be used in this study:

- UMEC/VI 62.5/ 25mcg administered via ELLIPTA
- UMEC 62.5 mcg administered via ELLIPTA
- Salmeterol 50 mcg administered via DISKUS
- Placebo via ELLIPTA
- Placebo via DISKUS

Subjects will be instructed to take one dose of medication each morning from the ELLIPTA (one inhalation equals one dose), and one dose in the morning and one in the evening from the DISKUS. Subject instructions and details on how to use the ELLIPTA and DISKUS are provided in the study reference manual (SRM).

A description of the UMEC/VI investigational product administered via the ELLIPTA is provided below in Table 1. The ELLIPTA will contain two, double-foil, laminate, blister strips. The ELLIPTA will provide a total of 30 doses (60 blisters) and will deliver, when actuated, the contents of a single blister simultaneously from each of the two blister strips.

The DISKUS will provide a total of 60 doses and will deliver, when actuated, the contents of a single blister.

A description of the UMEC investigational product administered via the ELLIPTA is provided below in Table 2. A description of placebo inhalation powder via ELLIPTA is shown in Table 3. A description of salmeterol 50mcg and placebo via DISKUS are shown in Table 4 and Table 5 respectively.

Table 1 Description of UMEC/VI Inhalation Powder via ELLIPTA

Formulation	**First strip**	**Second strip**
	Umeclidinium bromide blended with lactose monohydrate and magnesium stearate[1]	Vilanterol trifenatate blended with lactose monohydrate and magnesium stearate[2]
Dosage Form	ELLIPTA Inhaler with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	62.5 mcg	25 mcg
Physical description	White powder	White powder
Route of Administration	Inhaled	

1. Magnesium stearate 0.6% w/w of total drug product
2. Magnesium stearate 1.0% w/w of total drug product

Table 2 Description of UMEC Inhalation Powder via ELLIPTA

Formulation	**First strip**
	Umeclidinium bromide blended with lactose monohydrate and magnesium stearate[1]
Dosage Form	ELLIPTA Inhaler with 30 doses (1 strip with 30 blisters)
Unit Dose Strengths	62.5mcg
Physical description	Dry white powder
Route of Administration	Inhaled

1. Magnesium stearate 0.6% w/w of total drug product

Table 3 Description of Placebo Inhalation powder via ELLIPTA

Formulation	**First strip**	**Second strip**
	Lactose monohydrate blended with magnesium stearate[1]	Lactose monohydrate blended with magnesium stearate[2]
Dosage Form	ELLIPTA Inhaler with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	Not applicable	Not applicable
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	

1. Magnesium stearate 0.6% w/w of total drug product
2. Magnesium stearate 1% w/w of total drug product

Table 4 Description of salmeterol Inhalation powder via DISKUS

Formulation	**First strip**
	Salmeterol Xinafoate blended with lactose monohydrate
Dosage Form	Diskus Inhaler with 60 doses (1 strip with 60 blisters per strip)
Unit Dose Strengths	50 mcg
Physical description	White powder
Route of Administration	Inhaled

Table 5 Description of Placebo inhalation powder via DISKUS

Formulation	Lactose monohydrate
Dosage Form	Diskus Inhaler with 60 doses (1 strip with 60 blisters per strip)
Unit Dose Strengths	Not Applicable
Physical description	White powder
Route of Administration	Inhaled

Albuterol/salbutamol via metered-dose-inhaler (MDI) will be issued for reversibility testing at Visit 1. Albuterol/salbutamol MDI for as needed (prn) use will be issued throughout the study. Albuterol/salbutamol will be sourced from local commercial stock if appropriate.

6.2. Medical Devices

The eMDI devices are provided by GSK and are used in this study to electronically record rescue medication usage. They have US FDA 510(K) clearance to market (Class

II device) and EU CE marketing (Class I device). Description of the eMDI and its use will be provided in the SRM**.**

6.3. Treatment Assignment

Subjects who meet the randomization criteria will be assigned to one of the 3 study treatments in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Once a randomization number is assigned to a subject, it cannot be reassigned to any other subject in the study.

This study will utilize RAMOS NG, which will provide a means for central 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 RAMOS NG to randomize subjects is provided in the SRM.

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. On the other days during the treatment period (i.e. "non-clinic days"), subjects will be instructed to self-administer their study treatment in the morning and evening. Subjects should enter the time they take their study treatment in the eDiary.

Subjects will be randomly assigned to one of the blinded study treatment regimens in equal proportion (ratio of 1:1:1):

- UMEC/VI 62.5/25 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- UMEC 62.5 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- Salmeterol 50 mcg twice daily via DISKUS + placebo once daily via ELLIPTA

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

Study treatment/investigational product will be dispensed at Visits 2, 3 and 4.

In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2 and 60 days from V3 respectively (see Time and event table Section 7.1).

Used study drug and rescue medication will be collected at Visits 3, 4 and 5 or at the Early Withdrawal Visit.

6.4. Planned Dose Adjustments

No dose adjustment is allowed for this study

6.5. Blinding

This will be a double-blind double dummy study 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. 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.

6.6. Packaging and Labeling

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

6.7. Preparation/Handling/Storage/Accountability

No special preparation of the study treatment is required.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer 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 SRM.

All ELLIPTA DPI study treatment should be stored up to 25°C (77°F). Each ELLIPTA DPI 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 investigational product.

Salmeterol DISKUS should be stored up to 25 °C.

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.

6.7.1. Study Treatment Return

All used and unused ELLIPTA and DISKUS inhalers 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 SRM.

Study treatment will be collected at Visit 3, 4 and 5 or at the Early Withdrawal Visit, if applicable.

For any ELLIPTA or DISKUS inhaler that fails to function properly, the subject should return to the clinic as soon as possible to obtain a new inhaler. The site will contact the RAMOS NG 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 RAMOS NG

In addition, any ELLIPTA that fails to function properly must be identified and returned to GSK for testing.

6.8. Compliance with Study Treatment Administration

When subjects self-administer study treatment(s) at home, compliance with study treatment(s) will be assessed through querying the subject during the site visits and through study drug compliance assessed at Visits 2, 3, 4 and 5 documented in the source documents and eCRF. A record of the number of ELLIPTA and DISKUS dispensed and the number of doses inhaled by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays if any will also be recorded in the eCRF.

Compliance with the ELLIPTA inhaler will be determined by reviewing the dose counter on the ELLIPTA. Compliance with the study DISKUS will be determined by reviewing the dose counter on the DISKUS. Subjects should be ≥80% to ≤120% compliant on taking study medication between each pair of on-treatment visits. Subjects who fall outside this range should be re-educated on treatment compliance by their site. This re-education should be documented in the subject's source document. If medication compliance repeatedly falls outside of acceptable ranges, the study sponsor/site monitor must be contacted to discuss subject eligibility for continued participation in the study.

6.9. Treatment of Study Treatment Overdose

An overdose is defined as a dose greater than the total doses described in Section 6.1 and Section 6.8 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 medication, the investigator should use clinical judgment in treating the overdose and contact the study 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 may not be limited to, the approved product label for salmeterol albuterol, UMEC and UMEC/VI or equivalent document provided by GSK.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.10. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study, since the study treatments are commercially available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, post-study treatment.

6.11. Concomitant Medications and Non-Drug Therapies

All COPD medications used within 30 days prior to Pre-Screening (Visit 0) and onwards should be recorded in the eCRF including any changes in medications. Beginning at Visit 1 and throughout the rest of the study, all medications should be recorded in the eCRF including any changes. Study provided albuterol/salbutamol and double-blinded study drug should **not** be recorded in the eCRF. The minimum requirement includes but is not limited to drug name, dose, route and the dates of administration. Medications initiated after completion of Visit 5 or the Early Withdrawal Visit will not be recorded in the eCRF, with the exception of those used to treat a COPD exacerbation or SAE that occurs between Visit 5 (or the Early Withdrawal Visit) and the follow-up contact at Visit 6.

6.11.1. Permitted Medications and Non-Drug Therapies

The following relevant medications are permitted during this study:

- Study-provided albuterol/salbutamol for use as relief medication throughout the run-in and treatment periods
- Mucolytics such as acetylcysteine
- Medications for rhinitis (e.g. intranasal corticosteroids, antihistamines, cromolyn, nedocromil, nasal decongestants)
- Influenza vaccine
- pneumococcal vaccine
- Antibiotics for short term treatment (≤14 days) of acute infections including COPD exacerbations
- Systemic corticosteroids for short term (≤14 consecutive days) treatment of COPD exacerbations
- As-needed supplemental oxygen use provided it is ≤3L/min flow at rest at screening. Patients may adjust oxygen levels as needed during the study.
- Pulmonary rehabilitation program in maintenance phase
- Smoking cessation treatment, including a stable regimen of nicotine replacement
- Use of positive airway pressure/non-invasive ventilation for sleep apnea/sleep disordered breathing (*e.g*. CPAP, BiPAP)
- Localized corticosteroid injections (e.g., intra-articular and epidural)
- 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)
- Immunotherapy injections
- Topical or ophthalmic corticosteroids
- Over-the counter (OTC) cough suppressants
- Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). Administer with caution as they may potentiate the effect of beta-agonists on the vascular system
- Diuretics. Caution is advised in the co-administration of beta agonists with non-potassium sparing diuretics
- Allergy vaccination
- All medications for other disorders as long as the dose remains constant whenever possible and their use would not be expected to affect lung function

6.11.2. Prohibited Medications and Non-Drug Therapies

Use of the medications listed in Table 6 is not permitted during the study

Table 6 Prohibited Medications and Non-Drug Therapies

Medication
Depot corticosteroids
Systemic, oral or parenteral corticosteroids[1]
Inhaled corticosteroids (ICS)[2]
Antibiotics >14 days
LABA/ICS combination products
PDE4 inhibitor (e.g. roflumilast)
Inhaled long acting beta$_2$-agonists (LABA, e.g. salmeterol, formoterol, indacaterol, vilanterol)[3]
Long-acting muscarinic antagonists (LAMA, e.g. tiotropium, aclidinium, glycopyrronium, umeclidinium)[3]
LAMA/LABA combination products except for study drugs
Theophyllines
Oral beta$_2$-agonists
Inhaled short acting beta$_2$-agonists[4]
Inhaled short-acting anticholinergics
Inhaled short-acting anticholinergic/short-acting beta$_2$-agonist combination products
Any other investigational medication

1 Except for the treatment of COPD exacerbations during the study. Localized corticosteroid injections (e.g., intra-articular and epidural) are permitted.
2 Except if during the study use of ICS is deemed necessary for the treatment of subjects' exacerbation.
3 Except for study drug
4 Use of study provided albuterol/salbutamol is permitted during the study, except in the 4-hour period prior to spirometry testing.

The following medications or treatments are also **not** allowed during the study:

- Use of long-term oxygen therapy (LTOT) described as resting oxygen therapy >3L/min only at screening. Oxygen may be titrated to any level deemed necessary during the study.
- Regular use (prescribed for daily/ regular use, not for as-needed use) of short-acting bronchodilators (*e.g.* albuterol/salbutamol)
- Initiation of pulmonary rehabilitation during the study.

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 Section 7.1, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

7.1. Time and Events Table

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-10 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**-70 to -28**	**-28**	**1**	**28**	**84**	**168**		**7 days after V5 or EW Visit**
Window	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**		**±3 days**
Screen/Baseline								
Informed consent	X							
Demography	X							
Medical/COPD history		X						
Smoking history/status		X						
Smoking cessation counselling		X						
Concomitant medication assessment	X	X	X	X	X	X	X	X
Height and weight		X						
Cardiovascular History/family history of premature CV disease])		X						
Screening spirometry (including post bronchodilator testing)[3]		X						
CAT questionnaire		X	X					
Verify Inclusion/Exclusion Criteria		X						
Training on use of inhalers		X	X					
Training on use of eDiary and eMDI		X	X					
Verify randomization Criteria			X					
Register Visit in InForm	X	X	X	X	X	X	X	X
Register Visit in RAMOS NG	X	X	X	X	X	X	X	X

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-10 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**-70 to -28**	**-28**	**1**	**28**	**84**	**168**		**7 days after V5 or EW Visit**
Window	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**		**±3 days**
Efficacy/HRQoL assessments								
Spirometry, including pre-dose FEV_1, trough FEV_1 and inspiratory capacity			X	X	X	X		
SAC BDI questionnaire [4]			X					
SAC TDI questionnaire [4]				X	X	X		
SGRQ-C questionnaire [4]			X	X	X	X		
CAT questionnaire [4]		X	X	X	X	X		
EXACT/ER-S: COPD [5]		→	→	→	→	→		
Patient Global Rating of COPD severity			X	X	X	X		
Patient Global Rating of Change in COPD				X	X	X		
Safety assessments								
Adverse events/Serious adverse events [6]	X	X	X	X	X	X	X	X
COPD exacerbation assessment	X	X	X	X	X	X	X	X
12-Lead ECG		X						
Urine pregnancy test [7]		X	X			X	X	
Pharmacogenetic sample[8]			←	X	→			
Medication/Supplies								
Dispense rescue albuterol/slabutamol. Dispense MDI[9]		X	X	X	X	X		
Assess COPD medication compliance[10] during run-in			X					
Dispense eDiary		X						
Assess compliance with eDiary during run-in			X					
Collect rescue albuterol/slabutamol.			X	X	X	X	X	
Collect eDiary						X	X	
Dispense study treatment[11]			X	X	X			

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-10 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**-70 to -28**	**-28**	**1**	**28**	**84**	**168**		**7 days after V5 or EW Visit**
Window	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**		**±3 days**
Collect study treatment				X	X	X	X	
Assess study treatment compliance during treatment[10]				X	X	X	X	
Study sub-set								
Physical activity monitor[12]		X	X	X		X		
Collect Physical activity monitor						X	X	

1. Pre-screen Visit 0 must be completed prior to Screening Visit1. It can be completed 6 weeks prior or on the same day of V1, if no wash out of exclusionary medications is required.
2. Early Withdrawal Visit: Subjects that withdraw should return to the clinic as soon as possible to complete the Early Withdrawal Visit procedures.
3. Spirometry at screening should be performed as described in (Section 7.2.2.1).
4. SAC BDI, SAC TDI, SGRQ-C, CAT questionnaires will be completed at clinic visits and in the eDiary
5. EXACT/ER-S: COPD is completed daily in the eDiary approximately 2 hours before bed-time, starting on Day 1 of the run-in period.
6. For the start date of collecting AEs and SAEs see (Appendix 4)
7. Pregnancy test: for females for child bearing potential only.
8. Pharmacogenetic sample may be drawn at visit 2 or any visit after.
9. Rescue medication use to be recorded in the eDiary daily **and** in some sites in the eDiary and the eMDI
10. Sites are requested to call subjects every 2 weeks to remind them to take study treatment regularly and to record the time of the morning and evening dose in the eDiary.
11. In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2 and within 60 days from V3 respectively.
12. The Actigraph GT9X should be worn for 7 days from Visit 1, for 7 days from Visit 2, for 7 days from Visit 3 and for 7 days prior to Visit 5.

7.2. Screening and Critical Baseline Assessments

7.2.1. Pre-screening Visit

During the Pre-screening Visit, the study designated personnel must provide informed consent to the study participant. Subjects can perform the Pre-screening Visit (Visit 0) up to 6 weeks prior to or on the same day as the Screening Visit (Visit 1) if subject does not take or has not taken any protocol excluded medications.

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. A subject number will be assigned at the time the informed consent form (ICF) is signed. **No study related procedures may be performed until the informed consent form document has been signed by the subject.**

Once the informed consent is signed and if required, changes can be made to the subject's current medication regimen. The investigator should exercise clinical judgment, and is discouraged from changing medications only for the purpose of the clinical study.

During the pre-screening Visit 0, the following information is collected:

- Demographic parameters: year of birth, gender, race and ethnicity
- Concomitant medications review
- COPD exacerbation assessment

From the pre-screening visit onwards concomitant medications, exacerbations and SAEs (considered as related to study participation) must be reported

7.2.2. Critical procedures performed at Screening (Visit 1)

The following critical assessments will be conducted at Visit 1:

- Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening
- Medical history including COPD (including date of diagnosis and COPD type (emphysema and/or chronic bronchitis), smoking history, COPD exacerbation history, smoking status and previous and/or current medical conditions)
- Concomitant medication review (COPD and non COPD medications in the 3 months prior to Screening).
- Height and weight
- 12-Lead ECG. (Note: ECG is performed at screening Visit 1 to test for eligibility only. See Section 7.4.4).

- Urine pregnancy test if applicable
- Train subject on the use of eDiary
- COPD assessment test (CAT) and patient global rating of COPD severity in eDiary
- Pre- and post-albuterol/salbutamol spirometry (reversibility, see Section 7.2.2.1)
- Inclusion/Exclusion criteria assessment
- Review exacerbations, AEs, (SAEs if related to study participation)
- Train subject on the proper use of their COPD medication inhalation devices
- Instruct subject to take their COPD medications as instructed and to enter the time they take their medication in the eDiary
- Dispense rescue medication

Medical history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.1 and Section 5.2.

Assessment of subject's health status will be made at screening using CAT. PRO questionnaires should be completed by subjects before any other assessments at a clinic visit, in the order specified in Section 7.3.1

7.2.2.1. Albuterol/Salbutamol Reversibility Assessment

At Visit 1, both pre- and post-albuterol/salbutamol spirometry will be obtained to determine subject eligibility. Reversibility assessment should be performed as follows:

- Perform pre-bronchodilator spirometry and record FEV_1 and FVC
- Subject to self-administer 4 Inhalations (4X100µg) of albuterol/salbutamol MDI
- Perform post-bronchodilator spirometry and record FEV_1 and FVC approximately 10 to 30 minutes after albuterol/salbutamol administration

  The results of the spirometry must meet the ATS/ERS criteria [Miller, 2005] for the subject to continue in the study.

7.2.3. Critical procedures performed at first treatment Visit (Baseline V2)

- Review and assess compliance with subject's COPD medications during the run-in period
- Review and assess compliance with completing the eDiary during the run-in period
- Review AEs, SAEs and exacerbations

- Urine pregnancy test, if applicable
- Baseline dyspnea Index, BDI, patient global rating of COPD severity, patient global rating of change in COPD, SGRQ-C and CAT questionnaires in eDiary
- Review randomization criteria (Section 5.3)
- Register and randomize subject in RAMOS NG
- Pre-dose spirometry; IC and FEV_1
- Train subject on the proper use of ELLIPTA and DISKUS inhalers
- Dispense study medication
- Dispense rescue medication
- Optional pharmacogentic sample can be collected at V2 or any visit after.

7.3. Efficacy Assessments

7.3.1. HRQoL assessments: Completion of PRO questionnaires in the Electronic Diary

All subjects will be completing PRO questionnaires in the eDiary.

It is requested that questionnaires are completed before any procedures are performed on the subject.

All questionnaires will be completed using the eDiary at clinic and at home. Adequate time should be allowed to complete all items of the questionnaires and the questionnaires must be reviewed by the investigator or designated study staff for completeness and, if necessary, the subject must be encouraged to complete any missing items. Where more than one questionnaire is to be completed at a visit the order should be as follows:

1. Baseline dyspnea index (Visit 2) then Transient dyspnea index at subsequent visits
2. Patient global rating of COPD severity and global rating of change in COPD
3. St George's respiratory questionnaire
4. COPD Assessment Test

Instructions for completing the questionnaires can be found in the **SRM.**

7.3.1.1. Self Administered Computerised Baseline Dyspnea Index/Transitional Dyspnea Index (SAC BDI/TDI)

The BDI is used to measure the severity of dyspnea in patients at baseline. The TDI measures changes in the patient's dyspnea from baseline. The self-administered computerized version of the BDI/TDI (SAC BDI/TDI)[Mahler, 2004] is used to measure severity of dyspnea in patients at baseline (SAC BDI) on Day 1 (Visit 2) of treatment and change from the baseline (SAC TDI) at Week 4, 12 and 24 (Visits 3, 4 and 5). The

scores in both indexes depend on ratings for three different categories: functional impairment; magnitude of task, and magnitude of effort. SAC BDI/TDI should be completed before performing spirometry.

The SAC BDI/TDI was developed to address issues of potential bias in the interviewer administered (original) BDI/TDI [Mahler, 1984]. The SAC BDI/TDI provides a standardized approach to the measurement of dyspnea, equivalent to the original BDI/TDI with advantages over the interviewer method for grading dyspnea in patients with COPD by standardizing the process for each patient and eliminating individual judgment required by the interviewers when completing the original BDI/TDI. This also removes the need for the same investigator to conduct all interviews with a subject based on the patient's responses. SAC TDI provides a continuous measure of change in dyspnea using a visual analogue scale to record responses.

Details for the completion of the SAC BDI/TDI are provided in the SRM.

7.3.1.2. SGRQ-C

The St George's Respiratory Questionnaire-Chronic Obstructive Pulmonary Disease specific (SGRQ-C) will be completed by subjects at Randomisation (V2, Day 1), at Week 4, 12 and 24.

The SGRQ-C [Meguro, 2007] is a well established, disease-specific questionnaire. It was 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 scores equivalent to the SGRQ instrument [Meguro, 2007].

7.3.1.3. COPD Assessment Test (CAT)

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.

The CAT will be completed in the eDiary by subjects at Screening Visit 1 and Randomisation Visit 2 to assess their eligibility to enter the study. CAT is also completed at Weeks 4, 12 and 24. Additional instructions for completion of the CAT are provided in the SRM.

7.3.1.4. EXACT and the Evaluating Respiratory Symptoms- COPD (E-RS: COPD)

EXACT-PRO is a 14 item patient reported outcome instrument designed to capture information on the occurrence, frequency, severity, and duration of exacerbations of disease in patients with COPD [Leidy, 2011]. EXACT captures information on the severity of the respiratory and systemic manifestations of a COPD exacerbation as reported by the patient. The instrument is to be completed daily (typically 2 hrs before bedtime) using the electronic diary. The daily recording of information allows an assessment of the underlying day to day variability of a patient's symptoms and facilitates the detection of symptom worsening indicative of a COPD exacerbation. The total score for EXACT ranges from 0-100. The entire instrument is intended to be completed in about 3 minutes or less (typically the time required for completion decreases as the patient becomes more familiar with the tool and the electronic diary).

The E-RS: COPD consists of 11 items from the 14 item EXACT instrument [Leidy, 2014]. E-RS: COPD is intended to capture information related to the respiratory symptoms of COPD, i.e. breathlessness, cough, sputum production, chest congestion and chest tightness. The E-RS: COPD has a scoring range of 0-40 higher scores indicate more severe symptoms.

Three subscales of the E-RS are used to describe different symptoms; dyspnea, cough and sputum and chest symptoms.

The EXACT questionnaire will be completed by subjects in the eDiary, at home every night throughout the entire study, starting from Screening V1

7.3.1.5. Subject Global Rating of COPD Severity and Global Rating of Change in COPD

Subjects will complete the Global Rating of COPD Severity at Randomization Visit 2 and visits 3, 4 and 5. This single global question will ask subjects to rate their severity of COPD on a four point scale (mild, moderate, severe, and very severe).

This question should be used immediately before the patient completes other visit specific questionnaires but after completion of SAC TDI questionnaire.

Subjects will also complete a Global Rating of Change in COPD (overall disease) question at Visits 3, 4 and 5. Response options will be on a 7 point Likert scale ranging from much better to much worse. Completing the question at each Visit allows for early detection of response as well as continued response.

7.3.2. 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 standardized spirometry equipment provided by an external vendor.

All subjects will have spirometry performed at Screening to assess eligibility (see Section 7.2.2.1) and at Visits 2, 3, 4 and 5 during the treatment period.

For FEV_1 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 (i.e. a plateau in the volume time curve) and be free from artifacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons [Miller, 2005].

The largest FEV_1 and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort.

Spirometry for FEV_1 and FVC assessments that is not obtained as follows will be considered a protocol deviation:

- Started between 6:00AM and 11:00AM.
- After withholding albuterol/salbutamol (all visits) for ≥4 hours
- At Screening Visit 1, after wash out of medications as specified in the exclusion criteria in Section 5.2 (Concomitant Medications).
- At Screening Visit 1, before subject's morning dose of inhaled LABA or LAMA COPD medication
- At Visit 2 after withholding the morning dose of inhaled LABA or LAMA COPD medication and prior to administration of study medication
- At Visit 3, 4 and 5 after withholding the morning dose of study treatment.
- Pre dose assessment performed prior to dosing.

Subjects should refrain from smoking for 1 hour prior to each pulmonary function test.

Trough FEV_1 measurements for UMEC/VI or UMEC on Weeks 4, 12 and 24 (Visits 3, 4 and 5) should be performed 23 hours and 24 hours after the previous day's dose of study medication recorded in the eDiary. This will also provide trough FEV_1 measurements for the evening dose of salmeterol.

7.3.3. Inspiratory capacity (IC)

Inspiratory capacity (IC) is the volume of gas that can be taken into the lungs in a normal and full inhalation. Starting from the resting inspiratory position it is equal to the tidal volume plus the inspiratory reserve volume. IC has been widely used to assess static and dynamic hyperinflation in patients with COPD.

IC will be measured by spirometry **prior** to forced manoeuvres pre-dose at Visits 2 (30 and 5 min prior to dosing) and at trough at Visits 3, 4, and 5 (23 and 24 hrs post dosing on the previous day). For IC determination the average of at least three acceptable manoeuvres should be recorded. Subjects should be tested while sitting, relaxed and wearing a nose clip. They should be asked to breathe regularly for several breaths until the end-expiratory lung volume is stable (this usually requires at least three tidal manoeuvres) then urged to take a deep breath to Total Lung Capacity (TLC) with no hesitation.

Spirometry for IC determination done in conjunction with FEV_1 and FVC assessments that is not obtained as follows will be considered a protocol deviation:

- Started between 6:00AM and 11:00AM.
- After withholding albuterol/salbutamol (all visits) ≥4 hours
- At Visit 2 after discontinuation of run-in LABA or LAMA COPD medication and prior to administration of study medication
- At Visit 3, 4 and 5 after withholding the morning dose of study drug

7.3.4. COPD Exacerbation

A mild exacerbation is defined as worsening of symptoms that require no treatment with antibiotics or steroids, and is self managed by the patient by an increase of inhaled rescue medications. A moderate COPD exacerbation is defined as worsening symptoms of COPD that require treatment with oral/systemic corticosteroids and/or antibiotics. A severe exacerbation is defined as worsening symptoms of COPD that require in-patient hospitalization or emergency room for longer than 24 hrs.

If a subject experiences a mild, moderate or severe COPD exacerbation, the COPD exacerbation page of the eCRF should be completed. COPD exacerbations should not be recorded as an AE, unless they meet the definition of a SAE. Details of COPD exacerbation identification, categorization and treatment guidelines are described in Appendix 5.

Subjects who experience a mild exacerbation during the run-in period will not be withdrawn from the study. However, subjects who experience moderate or severe exacerbation during the run-in period will be withdrawn from the study and will not be allowed to be re-screened.

Subjects, who experience a mild, moderate or severe exacerbation during the treatment period, will **not** be withdrawn from the study unless the investigator or GSK medical monitor thinks it is best for the patient to withdraw from the study.

Signs and symptoms of COPD included on the electronic diary cards will not be considered AEs and will not be recorded in the eCRF.

The time period for collection of COPD exacerbations will be from the Pre-Screening (Visit 0) until completion of the follow-up contact. If a subject experiences a COPD exacerbation from the time the ICF is signed until randomization, summary information (yes/no status question) will be collected in the eCRF. COPD exacerbations after randomization through follow-up will be recorded on the COPD exacerbation page of the eCRF.

7.3.5. Clinically important deterioration (CID)

Clinically important deterioration (CID) is a composite endpoint defined as:

- A decrease of ≥ 100 mL from baseline in trough FEV_1
- A deterioration in HRQoL defined as ≥ 4 units increase from baseline in SGRQ
- The occurrence of an on-treatment moderate/severe COPD exacerbation

In addition, this study will explore CAT and TDI PROs as part of the composite endpoint.

7.3.6. Rescue albuterol/salbutamol use

Subjects will record the number of daily albuterol/salbutemol puffs they use in the eDiary. In addition, in some countries and selected sites the number of puffs will be collected through the eMDI device (Section 6.2)

7.3.7. Physical activity monitor (study subset)

Physical activity limitation is a common feature of COPD and its measures are highly related to the degree of disease severity [Watz, 2009].

Reduced physical activity levels in COPD is associated with increased morbidity and mortality, sustained disability, depression, and social and physical isolation [Shu-Yi, 2014; Gimeno, 2014]

Improved activity has been identified as an important factor that may modify morbidity and mortality in COPD [Moy, 2012].

The Actigraph GT9X physical activity monitor will be used to measure levels of activity. The activity monitor will be worn by up to approximately 150 subjects per treatment arm for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3 (Week 4) and for 7 days prior to Week 24 (Visit 5).

There will be 4 assessment periods, including a screening assessment in order to provide a reliable estimate of habitual physical activity. Each subject will be given an activity monitor and instruction leaflet at the start of each assessment period. Further details of distribution, operation and retrieval of the monitors will be provided in the **SRM**.

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1)

Safety endpoint includes:

- Incidence of adverse events

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

The definitions of an AE or SAE can be found in Appendix 4.

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

7.4.1.1. 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 7.4.1.3), at the timepoints 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 CRF.
- 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 12.4.4 to Section 12.4.6)

7.4.1.2. 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?

7.4.1.3. 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).

7.4.1.4. Pneumonia Events

Investigators will be required to fill out a pneumonia event specific eCRF within one week of when the pneumonia AE/SAE(s) is first reported.

7.4.1.5. Cardiovascular and Death Events

For any cardiovascular events detailed in (Section 12.4.3) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs 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 CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF 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.

7.4.1.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following disease related events (DREs) are common in subjects with COPD and can be serious/life threatening:

- COPD exacerbation

COPD exacerbations are associated with the disease to be studied and will not be recorded as AEs unless the exacerbation meets the definition of a 'serious' AE. Exacerbations that meet the definition of 'serious' AEs will be recorded on the appropriate eCRF section and should be reported to GSK for all subjects regardless of whether or not they are randomized to study medication. Signs and symptoms of COPD included on the electronic diary will not be considered AEs and will not be recorded in the eCRF

7.4.1.7. 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.

7.4.1.8. Additional Adverse Event (AE) Reporting Requirements for Canadian investigators

Health Canada requires pharmaceutical manufacturers to expeditiously report domestic cases of unusual failure in efficacy (UFIE) for new drugs to the Marketed Health Products Directorate (MHPD) within 15 days of first notification. This regulation applies to marketed drugs, and used as directed per the Canadian prescribing information, including those drugs used in Phase IV (non CTA filed) clinical trials.

Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product. **For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an adverse event),**

In order for GSK to comply this Canadian regulatory requirement, Canadian investigators are required to collect, record and report lack of efficacy events as per the table in Appendix 4 Section 12.4.1.

All paper forms are required to be faxed to GSK Canada's Drug Safety department at PP [redacted] within 24 hrs of first awareness.

7.4.2. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of Screening and until the follow-up contact.
- 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 7.

7.4.3. Medical Device Incidents (Including Malfunctions)

Procedures for documenting medical device incidents are provided in Appendix 6.

7.4.4. Electrocardiogram (ECG)

A Single 12-lead ECG will be obtained at Screening using an ECG machine provided by the investigational site that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

The 12-lead ECG measurement and rhythm strip (10 seconds) will be obtained before spirometry testing. ECG measurement should be obtained after subjects have rested for approximately 5 minutes then the subjects should be placed in the supine position for the ECG measurements. An ECG is only required at Screening Visit 1 for eligibility assessment only.

The investigator, a designated sub-investigator, or other appropriately trained site personnel will be responsible for performing and interpreting the 12-lead ECG at Screening Visit 1. The investigator must provide his/her dated signature on the original paper tracing, attesting to the authenticity of the ECG machine interpretation.

7.5. Genetics

Information regarding genetic research is included in Appendix 3

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, 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.
- CRFs (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 purpose of this study is to demonstrate improvements in lung function for subjects treated with UMEC/VI compared with UMEC for 24 weeks.

The primary endpoint is change from baseline in trough FEV_1 at Week 24.
The null hypothesis is no difference between treatment groups (H0: $\mu T - \mu S = 0$), with the alternative hypothesis that there is a difference between treatment groups (H1: $\mu T - \mu S \neq 0$), where μT is the mean change from baseline for UMEC/VI and μS is the mean change from baseline for UMEC.

9.2. Sample Size Considerations

The primary endpoint is change from baseline in trough FEV_1 at Week 24. As an important aim of the study is to compare UMEC/VI, UMEC and salmeterol with respect to HRQoL the sample size has been calculated to provide sufficient power for the comparison of the primary and secondary endpoint TDI, at Week 24.

The sample size calculations use a two-sided 5% significance level and an estimate of between subject standard deviation for TDI of 2.94 units. The estimate of SD is based on DB2113373 [Donohue, 2013], a study which consisted of treatment arms of UMEC/VI 62.5/25, UMEC 62.5 VI (Vilanterol) 25mcg and placebo and is the value at Day 168 in a subgroup of subjects who were ICS free at screening. Based on these data, 727 evaluable subjects per treatment arm will be required to provide 90% power to detect a statistically significant difference if the true difference is 0.5 units, ½ the MCID, between UMEC/VI and UMEC. The smallest observed effect predicted to result in a statistically significant difference between treatment groups is 0.31 units.

With this number of evaluable subjects per arm, the study will have >99% power assuming a true treatment difference of 80mL between UMEC/VI and UMEC for trough FEV1 at 24 weeks at the two-sided 5% significance level. This calculation uses a SD for trough FEV1 of 240mL, based on prior results for trials comparing dual bronchodilators versus single bronchodilators (Donohue, 2013; Bateman, 2013). The smallest observed effect predicted to result in a statistically significant difference between treatment groups is 25mL.

In order to account a for a 10% withdrawal rate**,** approximately 808 subjects per treatment arm will be randomised.

9.2.1. Sample Size Sensitivity

The assumption of a SD of 2.94 units for the TDI total score is based on estimates from previous studies. The following table presents the power achieved with the proposed sample size of 727 randomised subjects per arm, should the assumption around the SD of the data change.

The actual assumptions used in the sample size calculation are shaded.

Endpoint	Between subject SD	Treatment Difference	Power
TDI	2.54	0.5	96%
	2.74	0.5	94%
	2.94	0.5	90%
	3.14	0.5	86%
	3.34	0.5	81%

9.2.2. Sample Size Re-estimation or Adjustment

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

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	• 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.	• Subject Disposition • Reasons for withdrawal prior to randomisation • Inclusion, exclusion and randomisation criteria deviations • SAEs for non-randomised subjects
Intent-to-treat (ITT)	• All randomized subjects, excluding those who were randomized in error and received at least one dose of study medication. 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 randomization number will be considered to have been randomized. • Displays will be based on the treatment to which the subject was randomized.	• Study Population • Efficacy • Safety
Intent-to-treat ICS free (ITT ICS free)	• All subjects in the ITT Population who have not received ICS.	• Study Population • Efficacy • Safety

9.3.2. Interim Analysis

No interim analysis is planned for the study.

9.4. Key Elements of Analysis Plan

Treatment Comparisons

The primary treatment comparison of UMEC/VI with UMEC will be performed on the ITT population.

The other treatment comparisons of UMEC/VI and UMEC with Salmeterol will be performed on the ITT population and ITT ICS free population.

9.4.1. Primary Analyses

The treatment comparison of primary interest will be UMEC/VI versus UMEC for the primary endpoint of change from baseline in trough FEV_1 at Week 24. The primary analyses will be performed using a mixed model repeated measures (MMRM) analysis and will be based on a two-sided hypothesis testing approach on the ITT Population.

In order to account for multiplicity across treatment comparisons and endpoints, a step-down closed testing procedure will be applied whereby inference for secondary and other endpoints or treatment comparisons are dependent upon statistical significance having been achieved for the primary comparison. If the primary comparison is significant i.e. the associated p-value for UMEC/VI versus UMEC for change from baseline in trough FEV1 at Week 24 is below 0.05, this will allow inference of treatment comparisons (UMEC/VI versus UMEC on all other endpoints, and UMEC/VI versus Salmeterol and UMEC versus Salmeterol on all endpoints including the primary endpoint), which will be declared statistically significant if the associated p-value is below 0.05.

There will be 2 analyses one for one for the German Federal Joint Committee (G-BA) and one for the rest of the world (ROW).

The step-down closed testing procedure only applies to the ROW. For the G-BA statistical inference for secondary and other endpoints or treatment comparisons will not be conditional on achieving statistical significance of the primary comparison.

The primary endpoint of mean change from baseline in trough FEV1 at the end of Week 24 and secondary endpoint change from baseline in TDI score at Week 24 will both be analysed using MMRM analysis. The MMRM analysis for change from baseline in trough FEV1 and TDI will include measurements at Treatment Weeks 4, 12 and 24. Treatment group (a categorical variable) will be fitted as the explanatory variable with appropriate pre-defined variables, stratum (number of bronchodilators per day during run-in) and baseline values, fitted as covariates. Visit (nominal) will be fitted as a categorical variable and visit-by-baseline and visit-by-treatment interaction terms will be included to allow treatment effects to be estimated at each visit separately. The variance covariance matrix will be assumed to be unstructured (based on previous experience no issues are expected with fitting models with this matrix structure).

While missing data are not explicitly imputed in the primary MMRM analyses, there is an underlying assumption that the data are missing at random.

The estimated treatment differences between UMEC/VI versus UMEC for each endpoint will be presented with the 95% confidence intervals for the difference and the p-value.

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

9.4.2. Other Analyses

The MMRM analysis will be repeated for the ITT ICS free population. Estimated differences between UMEC/VI or UMEC and Salmeterol will be presented together with 95% confidence intervals (CIs) for the difference and p-values.

Secondary and other efficacy endpoints and treatment comparisons will be adjusted for multiplicity as per Section 9.4.1.

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

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.

Study site Investigators will be selected to participate in the 201749 study based upon their pulmonology expertise and knowledge of the protocol defined patient population and associated required study assessments.

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 eCRF 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 randomization 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
CAT	COPD Assessment Test
CI	Confidence Intervals
CID	Clinically important deterioration
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine phosphokinase
CRF	Case Report Form
CV	Cardiovascular
DPI	Dry Powder Inhaler
DRE	Disease Related Event
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
eMDI	Electronic Metered Dose Inhaler
E-RS	Evaluating Respiratory Symptoms- COPD Tool
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
IB	Investigator Brochure
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IP	Investigational product
INR	International normalized ratio
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

mcg	Microgram
MCID	Minimal Clinically Important Difference
MDI	Metered Dose Inhaler
mL	Milliliter
mMRC	Modified Medical Research Council
MMRM	Mixed Models Repeated Measures
MSDS	Material Safety Data Sheet
NYHA	New York Heart Association
OTC	Over the Counter
PGx	Pharmacogenetic
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PP	Per Protocol
prn	As required
QTc	QT interval corrected for heart rate
RAP	Reporting and Analysis Plan
SABA	Short Acting Beta-Agonist
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SRT	Safety Review Team
TDI	Transition Dyspnea Index
RAMOS NG	Randomization and medication ordering system new generation
ULN	Upper Limit of Normal
UMEC	Umeclidinium (GSK573719)
UMEC/VI	Umeclidinium & Vilanterol as a fixed dose combination
VI	Vilanterol Trifenate

Trademark Information

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

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

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria - Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥ 8xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 5xULN but <8xULN persists for ≥2 weeks
ALT ≥ 3xULN but <5xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks
ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• 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 SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve , stabilize, or return to within normal ranges. baseline (see MONITORING below)
• Do not restart/rechallenge subject with study treatment. Permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments

MONITORING:
<u>For bilirubin or INR criteria:</u>
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform</td><td>• Viral hepatitis serology[4]
• Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5].
• Blood sample for pharmacokinetic (PK) analysis, obtained within a week after last dose[6]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal</td></tr>
</table>

Liver Chemistry Stopping Criteria - Liver Stopping Event	
liver event follow up assessments within 24 hrs • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within normal ranges. • A specialist or hepatology consultation is recommended **For All other criteria:** • 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 normal ranges.	remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • 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.

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 ≥ 3xULN **and** bilirubin ≥ 2xULN. 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 ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **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 SRM.

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 etiology 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 any concomitant medicines;
- COPD susceptibility, severity, and progression of 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.

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 the baseline visit, after the subject has been randomized and 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 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.

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. **Reporting Specific to Canada**: For a marketed medicinal product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without associated signs or symptoms or clinical sequelae). • 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 <u>meeting</u> 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). • Excluding Canada, "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. • **Reporting Specific to Canada**: "Lack of efficacy" or "failure of expected pharmacological action" will be reported as an AE or SAE as per the table below

Adverse Event criteria	**Electronic case record form (eCRF) only**	**Paper form only**	**Electronic case record form (eCRF) + Paper form**
Non serious	Non drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae	Drug related lack of efficacy reports without associated signs or symptoms or clinical sequelae.	Drug related lack of efficacy with associated signs or symptoms or clinical sequelae
Serious	Non drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae	Drug related lack of efficacy reports without associated signs or symptoms or clinical sequelae.	Drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae

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., hospitalization 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 hospitalization or prolongation of existing hospitalization

NOTE:

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

d. Results in disability/incapacity

NOTE:

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- 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 hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** 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.

12.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial 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 electronic CRF and/or paper form as applicable. 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
- **Reporting Specific to Canada**: For lack of efficacy reports, the paper form will be used to submit to GSK as per the table in Section 12.4.1 above.
- 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
- 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 by telephone.

- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: COPD Exacerbation Identification, Categorization and Treatment Guidelines

12.5.1. 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 usage in their daily eDiary
- 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

12.5.2. COPD Exacerbation Severity

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

> **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 hospitalization or 24 hrs in the emergency room.

Chest X-Ray for pneumonia and/or moderate/severe exacerbation is not mandated but can be performed if required by the investigator as part of standard care of subjects.

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.

12.5.3. 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 outlined 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 IP as these additional medications may increase the risk of overdose. If necessary the PI or other health care personnel may stop the subject's IP temporarily in order to treat the COPD exacerbation.

12.5.4. 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 ≤ 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

12.5.5. 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 not exceed 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

12.5.6. 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 12.5.1.

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.

12.5.7. 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.

12.5.8. 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.

12.6. Appendix 6: Definition of and Procedures for Documenting Medical Device Incidents

12.6.1. Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.2 for the list of GSK medical devices).

Medical Device Incident Definition:

- Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other persons or to a serious deterioration in their state of health.
- Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- an **incident** associated with a device happened and
- the **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.
- A serious deterioration in state of health can include:
- life-threatening illness
- permanent impairment of body function or permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent one of the above
- fetal distress, fetal death or any congenital abnormality or birth defects

Examples of incidents

- a patient, user, care giver or professional is injured as a result of a medical device failure or its misuse
- a patient's treatment is interrupted or compromised by a medical device failure
- misdiagnosis due to medical device failure leads to inappropriate treatment
- a patient's health deteriorates due to medical device failure

12.6.2. Documenting Medical Device Incidents

Medical Device Incident Documenting:
• Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 4. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK. • It is very important that the investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the design to prevent recurrence.

12.7. Appendix 7: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

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

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization 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, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.7.2. 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 fetal 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. 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 be withdrawn from the study

12.8. Appendix 8: Country Specific Requirements

In Canada only, additions were made to Section 7.4.1 and Appendix 4 to comply with Health Canada guidelines concerning the requirement of pharmaceutical manufacturers to expeditiously report domestic cases of unusual failure in efficacy (UFIE) for new drugs to the Marketed Health Products Directorate (MHPD) within 15 days of first notification.

12.9. Appendix 9: Protocol changes

Revision History

2016N277425_00	2016-SEP-13	Original
2016N277425_01	2017-FEB-07	Amendment No. 1
2016N277425_02	2017-FEB-21	Amendment No. 2 Canada only
2016N277425_03	2017-APR-18	Amendment No. 3

12.9.1. Protocol Amendment 1

Scope:

This amendment applies to all sites

Protocol Changes for Amendment No.1 are summarised below.

Strike through text refers to deleted text and underlined refers to added text.

Protocol Changes:

Title
Rationale for change: Correct a typographical error in the title: Umeclidi~~m~~ium to Umeclidinium

Regulatory Agency Identifying Number(s):
Rationale for change: To correct a typographical error of the EudraCT no. and add an IND no.
Revised text:-EudraCT no ~~2016-002513-226,~~ 2016-002513-22 , IND no. 104479

Section 1
Overall Design
Rationale for change: To Correct a typographical error in the last paragraph.
Revised text: ~~Salmeterol~~, salbutamol
"This is a multi-centre, randomized, double blind, double-dummy, 3-arm parallel group study. Eligible subjects will be stratified based on long-acting bronchodilator usage during the run-in (none, one or 2 long-acting bronchodilators per day) and randomized in a ratio of 1:1:1 to UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA inhaler, or UMEC (62.5 mcg once daily) administered via the ELLIPTA or salmeterol (50 mcg BID) administered via the DISKUS.

There will be a total of 5 clinic visits and one follow-up phone call (Visit 6). The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) if subject does not take or has not taken any excluded protocol medications, but must be completed prior to initiating any Visit 1 procedures.

Subjects, who meet all the eligibility criteria at Screening, will enter a run-in period for 4 weeks in order to continue to assess the subject's eligibility for the study. During the run-in period subjects will continue with their inhaled COPD medications (excluding ICS and any exclusionary medications). In addition, subjects will be provided with short acting albuterol/~~salmeterol~~ salbutamol to be used on as needed basis for relief of COPD symptoms (rescue medication) throughout the study".

Section 4.4 Design justification: To be consistent with Section 7.3.1.5 and Section 7.1 the wording has been updated.
Rationale for change: Ensure consistency with Section 7.3.1.5 and Section 7.1 the wording has been changed in paragraph 5.
Revised text: "Other endpoints such SAC TDI, E-RS, SGRQ-C, CAT, Subject Global Rating of COPD Severity and ~~Change in~~ Global Rating ~~impression~~ of Change in COPD ~~disease severity~~ are captured to allow responder analyses and to provide comparative data on PROs between the treatment groups".

Section 7.1 Time and Event table
Rationale for change; to:
Correct an un-intentional deletion of the ("x") in some cells and confirm that concomitant medications should be reviewed at every clinic visit.
Increase the visit window from ~~± 2~~ days to -7/+2
Ensure consistency of wording between Section 7.2 and Table 7.1. "~~Written~~" was deleted
Include height and weight at Screening and correct errors in foot note no.11
"In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2 and within 60 ~~and 90~~ days from V3 ~~and V4~~ respectively"

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 ~~±2~~ -7/+2 days prior Visit 1**	**28 ~~±2~~ -7/+2 days prior Visit 2**	**1~~±2~~ -7/+2 days**	**28 ~~±2~~ -7/+2 days**	**84 ± 2 days**	**168 ~~±2~~ -7/+2 days**		**7~~±2~~ 3 days after V5 or EW Visit**
Screen/Baseline								
~~Written~~ Informed consent	X							
Demography	X							
Medical/COPD history		X						
Smoking history/status		X						
Smoking cessation counselling		X						
Concomitant medication assessment	X	X	X	X	X	X	X	X
Height and weight		X						
Cardiovascular History/family history of premature CV disease])		X						
Screening spirometry (including post bronchodilator testing)[3]		X						
CAT questionnaire		X	X					
Verify Inclusion/Exclusion Criteria		X						
Training on use of inhalers		X	X					
Training on use of eDiary and eMDI		X	X					
Verify randomization Criteria			X					
Register Visit in InForm	X	X	X	X	X	X	X	X
Register Visit in RAMOS NG	X	X	X	X	X	X	X	X

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 ±2 -7/+2 days prior Visit 1**	**28 ± 2 -7/+2 days prior Visit 2**	**1± 2 -7/+2 days**	**28 ±2 -7/+2 days**	**84 ± 2 days**	**168 ±2 -7/+2 days**		**7± 2 3 days after V5 or EW Visit**
Efficacy/HRQoL assessments								
Spirometry, including pre-dose FEV_1, trough FEV_1 and inspiratory capacity			X	X	X	X		
SAC BDI questionnaire [4]			X					
SAC TDI questionnaire [4]				X	X	X		
SGRQ-C questionnaire [4]			X	X	X	X		
CAT questionnaire [4]		X	X	X	X	X		
EXACT/ER-S: COPD [5]		→	→	→	→	→		
Patient Global Rating of COPD severity			X	X	X	X		
Patient Global Rating of Change in COPD				X	X	X		
Safety assessments								
Adverse events/Serious adverse events [6]	X	X	X	X	X	X	X	X
COPD exacerbation assessment	X	X	X	X	X	X	X	X
12-Lead ECG		X						
Urine pregnancy test [7]		X	X			X	X	
Pharmacogenetic sample[8]			←	X	→			
Medication/Supplies								
Dispense rescue albuterol/slabutamol. Dispense MDI[9]		X	X	X	X	X		
Assess COPD medication compliance[10] during run-in			X					
Dispense eDiary		X						
Assess compliance with eDiary during run-in			X					
Collect rescue albuterol/slabutamol.			X	X	X	X	X	
Collect eDiary						X	X	
Dispense study treatment[11]			X	X	X			

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 ~~±2~~ -7/+2 days prior Visit 1**	**28 ~~± 2~~ -7/+2 days prior Visit 2**	**1~~± 2~~ -7/+2 days**	**28 ~~±2~~ -7/+2 days**	**84 ± 2 days**	**168 ~~±2~~ -7/+2 days**		**7~~± 2~~ 3 days after V5 or EW Visit**
Collect study treatment				X	X	X	X	
Assess study treatment compliance during treatment[10]				X	X	X	X	
Study sub-set								
Physical activity monitor[12]		X	X	X		X		
Collect Physical activity monitor						X	X	

1. Pre-screen Visit 0 must be completed prior to Screening Visit1. It can be completed 2 weeks prior or on the same day of V1, if no wash out of exclusionary medications is required.
2. Early Withdrawal Visit: Subjects that withdraw should return to the clinic as soon as possible to complete the Early Withdrawal Visit procedures.
3. Spirometry at screening should be performed as described in (Section 7.2.2.1).
4. SAC BDI, SAC TDI, SGRQ-C, CAT questionnaires will be completed at clinic visits and in the eDiary
5. EXACT/ER-S: COPD is completed daily in the eDiary approximately 2 hours before bed-time, starting on Day 1 of the run-in period.
6. For the start date of collecting AEs and SAEs see (Appendix 4)
7. Pregnancy test: for females for child bearing potential only.
8. Pharmacogenetic sample may be drawn at visit 2 or any visit after.
9. Rescue medication use to be recorded in the eDiary daily **and** in some sites in the eDiary and the eMDI
10. Sites are requested to call subjects every 2 weeks to remind them to take study treatment regularly and to record the time of the morning and evening dose in the eDiary.
11. In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2 and within 60 ~~and 90~~ days from V3 ~~and V4~~ respectively.
12. The Actigraph GT9X should be worn for 7 days from Visit 1, for 7 days from Visit 2, for 7 days from Visit 3 and for 7 days prior to Visit 5.

Section 7.2.2 Critical procedures performed at Screening (Visit 1)
Rationale for change: To clarify that height and weight are collected at V1
Revised text: "Height and weight"

Section 7.3.2 Spirometry
Rationale for change: To further clarify that spirometry at Screening Visit 1 should be performed before subject inhales their usual morning COPD medication(s) a bullet point was added. "At Screening Visit 1, before the morning dose of usual COPD medications"
Revised text:
"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 standardized spirometry equipment provided by an external vendor.

All subjects will have spirometry performed at Screening to assess eligibility (see Section 7.2.2.1) and at Visits 2, 3, 4 and 5 during the treatment period.

For FEV_1 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 (i.e. a plateau in the volume time curve) and be free from artifacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons [Miller, 2005].

The largest FEV_1 and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort.

Spirometry for FEV_1 and FVC assessments that is not obtained as follows will be considered a protocol deviation:

- Started between 6:00AM and 11:00AM.
- After withholding albuterol/salbutamol (all visits) for ≥4 hours
- At Screening Visit 1, after wash out of medications as specified in the exclusion criteria in Section 5.2 (Concomitant Medications).
- At Screening Visit 1, before the morning dose of usual COPD medications
- At Visit 2 after discontinuing inhaled COPD medications and prior the first dose of study treatment
- At Visit 3, 4 and 5 after withholding the morning dose of study treatment.
- Pre dose assessment performed prior dosing.

Subjects should refrain from smoking for 1 hour prior to each pulmonary function test.

Trough FEV_1 measurements for UMC/VI or UMEC on Weeks 4, 12 and 24 (Visits 3, 4 and 5) should be performed 23 hours and 24 hours after the previous day's dose of study medication recorded in the eDiary. This will also provide trough FEV_1 measurements for the evening dose of salmeterol".

8. Physical activity monitor (study subset)

Rationale for changes: Ensure consistency of the wording between Section 1 and Section 4.1 "overall design" and Section 7.3.7.
per treatment arm added to paragraph 4.
Revised Text:
Physical activity monitor (study subset)
"Physical activity limitation is a common feature of COPD and its measures are highly related to the degree of disease severity [Watz, 2009].
Reduced physical activity levels in COPD is associated with increased morbidity and mortality, sustained disability, depression, and social and physical isolation [Shu-Yi, 2014; Gimeno, 2014]

Improved activity has been identified as an important factor that may modify morbidity and mortality in COPD [Moy, 2012].

The Actigraph GT9X physical activity monitor will be used to measure levels of activity. The activity monitor will be worn by up to approximately 150 subjects per treatment arm for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3 (Week 4) and for 7 days prior to Week 24 (Visit 5).

There will be 4 assessment periods, including a screening assessment in order to provide a reliable estimate of habitual physical activity. Each subject will be given an activity monitor and instruction leaflet at the start of each assessment period. Further details of distribution, operation and retrieval of the monitors will be provided in the **SRM"**.

12.9.2. Country-specific Protocol Amendment 2 for Canada

Amendment 02 applies to Canada only. The purpose of Amendment 2 is to comply with Health Canada guidelines. They state that all events associated with lack of efficacy of marketed investigational products must be documented and reported.

Strike through text refers to deleted text and underlined refers to added text.

Section 7.4.1 Adverse Events (AE) and serious Adverse Events (SAEs)
Rationale for change: A new Section added to include information related to documenting events related to lack of efficacy.
Revised text:
"7.4.1.8 Additional Adverse Event (AE) Reporting Requirements for Canadian investigators
Health Canada requires pharmaceutical manufacturers to expeditiously report domestic cases of unusual failure in efficacy (UFIE) for new drugs to the Marketed Health Products Directorate (MHPD) within 15 days of first notification. This regulation applies to marketed drugs, and used as directed per the Canadian prescribing information, including those drugs used in Phase IV (non CTA filed) clinical trials.

Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore

be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product**. For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an adverse event),**

In order for GSK to comply this Canadian regulatory requirement, Canadian investigators are required to collect, record and report lack of efficacy events as per the table in Appendix 4 Section 12.4.1".

All paper forms are required to be faxed to GSK Canada's Drug Safety department at PP [redacted] within 24 hrs of first awareness.

Appendix 4, Section 12.4.1
Rationale for change: To add a small table about reporting of AEs.
Revised text. The table below was added.

Adverse Event criteria	**Electronic case record form (eCRF) only**	**Paper form only**	**Electronic case record form (eCRF) + Paper form**
Non serious	Non drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae	Drug related lack of efficacy reports without associated signs or symptoms or clinical sequelae.	Drug related lack of efficacy with associated signs or symptoms or clinical sequelae
Serious	Non drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae	Drug related lack of efficacy reports without associated signs or symptoms or clinical sequelae.	Drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae

Appendix 4, Section 12.4.4, second bullet point
Revised text:
The investigator will then record all relevant information regarding an AE/SAE in the electronic CRF "and/or paper form as applicable". Added

Section 12.4.6, second bullet point
Revised text:
"For lack of efficacy reports the paper form will be used to submit to GSK as per the table in Section 12.4.1 above". Added

12.9.3. Protocol Amendment 3

Protocol changes for Amendment 03, from protocol changes to amendment 02 (21-Feb-2014)

Scope: This amendment applies to all sites

Amendment 03 Summary and Rationale

Strike through text refers to deleted text and underlined refers to added text.

List of Specific Changes

Section 1 Objective(s)/Endpoint(s) and Section 3 Objective(s)/Endpoint(s)

Rationale for change: Rate of COPD exacerbations endpoints from tertiary to exploratory due to stopping criteria.
Revised text:

Exploratory	
• To explore the effect of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on rate of COPD exacerbation	• Rate of mild, moderate or severe exacerbations • Rate of moderate or severe exacerbation

Section 1. Overall Design
Rationale for change: To clarify study design and content of section to agree with Section 4.1
Revised text:

There will be a total of 5 clinic visits and one follow-up phone call (Visit 6). A pre-screening visit (Visit 0) may be required in order to administer the informed consent before any changes are made to the subject's current medication regimen. If no changes in medication are required, V0 (pre-screening) and V1 (screening) may be conducted on the same day. Inhaled long-acting muscarinic antagonist (LAMA) or long-acting beta$_2$-agonist (LABA) and/or albuterol/salbutamol as needed (rescue medication) are not exclusionary prior to Screening or during the run-in.

Eligible subjects at Screening Visit 1 will be current or former smokers, at least 6 weeks ICS and ICS/LABA free with an FEV_1 post-albuterol/salbutamol of ≥30% to ≤80% predicted normal and a FEV_1/FVC <0.7 and a CAT score ≥10.

Subjects using inhaled LAMA or LABA medication must withhold their morning dose prior to Screening spirometry. Subjects who meet all other eligibility criteria at Screening will enter a run-in period for 4 weeks. During the run-in period, subjects will continue with their inhaled LAMA or LABA. In addition, subjects will be provided with short acting albuterol/salbutamol as needed for relief of COPD symptoms (rescue medication)

throughout the study.~~Eligible subjects at Screening will enter a run-in period for 4 weeks during which they continue taking their inhaled COPD medications (excluding ICS and any exclusionary medications). In addition, subjects will be provided with short acting albuterol/salbutamol to be used on as needed basis (rescue medication) throughout the study.~~

Subjects who experience a moderate or severe COPD exacerbation during the run-in period will be deemed run-in failures. Subjects who experience a mild COPD exacerbation, defined as worsening of symptoms that requires **no** treatment with antibiotics or steroids and is self managed by the patient by an increase of inhaled rescue medication will be able to continue in the study based on the judgment of the investigator and agreement of the sponsor's medical monitor. ~~Subjects experiencing a mild exacerbation, defined as worsening of symptoms that requires **no** treatment with antibiotics or steroids and is self managed by the patient by an increase of inhaled rescue medication, will be allowed to continue in the study.~~

At the randomization Visit 2 (Day 1), those subjects who successfully complete the run-in period as well as meet the other pre-defined eligibility and randomization criteria will ~~discontinue their inhaled COPD medications and will~~ be randomized to one of the 3 treatment arms for 24 weeks.

~~All subjects will be given an eDiary for use during the run-in, and treatment period to complete PRO questionnaires and record medical problems experienced during the study. Subjects will be performing slow and forced spirometry at specific visits.~~

~~There will be a total of 5 clinic visits and one follow-up phone call (Visit 6). The total duration of subject participation in the study will be approximately 29 to 31 weeks consisting of 2 weeks pre-screening if necessary, 4 weeks run-in, 24 week treatment and one week Follow-Up.~~

In addition, a subset of subjects ~~up to 150~~ (approximately 150 per treatment arm) will undergo assessment of their physical activity measured through a physical activity monitor (Actigraph GT9X) worn for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3, and for 7 days prior to last clinic Visit (Visit 5).

The occurrence of adverse events (AEs) will be evaluated throughout the study beginning at Visit 2 (Day 1) and until the follow-up contact (Visit 6). Serious adverse events (SAEs) will be collected over the same time period as AEs. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact.

All subjects will be given an electronic diary (eDiary) for use during the run-in, and the treatment period to complete PRO questionnaires, record COPD daily symptoms and the time they take their COPD medications. Daily rescue medication usage (number of inhalations taken in the last 24 h) will also be captured in the eDiary. In addition, and in

some countries, rescue medication use will also be captured by the use of electronic metered dose inhaler (eMDI).

At Screening Visit 1, all subjects must be trained on the proper use of their existing COPD medications inhalation devices and instructed to strictly adhere to and record the time they take their COPD medications in the eDiary.

At the randomization Visit 2, all subjects must be trained on the proper use of the ELLIPTA and DISKUS inhalation devices and instructed to strictly adhere to and record the time they take their study medications in the eDiary.

All subjects must be trained on the correct use of the eDiary and instructed to complete the eDiary during the run-in and treatment period.

There are no plans to routinely provide any of the study treatments for compassionate use following study completion as the study treatment are commercially available.

Section 1. Treatment Arms and Duration

Rationale for change: clarify stratification and treatment arms
Revised text: Subjects will be stratified based on long-acting bronchodilator usage during the run-in (none or one ~~or 2~~ long-acting bronchodilator~~s~~ per day) and randomized in a ratio of 1:1:1 to either

- UMEC/VI 62.5/25 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- UMEC 62.5 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- Salmeterol 50 mcg twice daily via DISKUS + placebo once daily via ELLIPTA

Rationale for change: Clarify permitted and prohibited Screening and run-in COPD medications
Revised text: *Subjects may continue the use of inhaled LAMAs or LABAs and/or study provided albuterol/salbutamol as needed (rescue medication). ~~Inhaled COPD medications including LABAs, LAMAs or LABA/LAMA combination products are allowed in run-in. ICS alone or in combination with a bronchodilator or any exclusionary medications are not allowed.~~

Section 4.1 Study Design

Rationale for change: To clarify study design
Revised text:

This is a multi-centre, randomized, double blind, double-dummy, 3-arm parallel group study. Eligible subjects will be ~~stratified based on long-acting bronchodilator usage during the run-in (none, one or 2 long-acting bronchodilators per day) and~~ randomized in a ratio of 1:1:1 to UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA™ dry powder inhaler, or UMEC (62.5 mcg once daily) administered via the ELLIPTA™ or salmeterol (50 mcg BID) administered via the DISKUS.

A pre-screening visit (Visit 0) may be required in order to administer the informed consent before any changes are made to the subject's current medication regimen. If no changes in medication are required, V0 (pre-screening) and V1 (screening) may be conducted on the same day. Inhaled long-acting muscarinic antagonist (LAMA) or long-acting beta$_2$-agonist (LABA) medications are not exclusionary prior to Screening or during the run-in. ~~The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) if subject does not take or has not taken any excluded protocol medications, but must be completed prior to initiating any Visit 1 procedures.~~

Eligible subjects at Screening Visit 1 will be current or former smokers, at least 6 weeks ICS and ICS/LABA free with an FEV_1 post-albuterol/salbutamol of ≥30% to ≤80% predicted normal and a FEV_1/FVC <0.7 and a CAT score ≥10.

Subjects using inhaled LAMA or LABA medication must withhold their morning dose prior to Screening spirometry. Subjects who meet all other eligibility criteria at Screening will enter a run-in period for 4 weeks. ~~in order to continue to assess the subject's eligibility for the study~~ During the run-in period, subjects will continue with ~~their inhaled COPD medications (excluding ICS and any exclusionary medications)~~ their inhaled LAMA or LABA medication. In addition, subjects will be provided with short acting albuterol/salbutamol ~~to be used on~~ as needed ~~basis~~ for relief of COPD symptoms (rescue medication) throughout the study.

At the randomization Visit 2 (Day 1) those subjects who successfully complete the run-in period as well as meet the other pre-defined eligibility and randomization criteria ~~will discontinue their inhaled COPD medications and~~ will be randomized to one of the 3 treatment arms for 24 weeks.

In addition, a subset of subjects ~~up to 150~~ (approximately 150 per treatment arm) will undergo assessment of their physical activity measured through a physical activity monitor (Actigraph GT9X) worn for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3, and for 7 days prior to last clinic Visit (Visit 5).

~~During the run-in and treatment period, subjects will be completing PRO questionnaires in the eDiary and performing slow and forced spirometry at specific clinic visits.~~

~~Concurrent use of COPD maintenance medications including LAMAs, LABAs, oral beta-agonists, theophyllines, inhaled corticosteroids, inhaled corticosteroids and LABA combination and phosphodiesterase 4 inhibitors will not be allowed during the study (Section 6.11.2) .~~

*Subjects may continue the use of inhaled LAMAs or LABAs and/or study provided albuterol/salbutamol as needed (rescue medication) during the run-in while adhering to the withholding of other COPD medications detailed in the Exclusion Criteria. ~~Inhaled COPD medications including LABAs, LAMAs or LABA/LAMA combination products are allowed in run-in. ICS alone or in combination with a bronchodilator or any exclusionary medications are not allowed.~~

Section 4.2 Treatment Arms and Duration

Rationale for change: clarify stratification and treatment arms
Revised text: Subjects will be stratified based on long-acting bronchodilator usage during the run-in (none or one ~~or 2~~ long-acting bronchodilator~~s~~ per day) and randomized in a ratio of 1:1:1 to either

- UMEC/VI 62.5/25 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- UMEC 62.5 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- Salmeterol 50 mcg twice daily via DISKUS + placebo once daily via ELLIPTA

Section 4.2 Type and Number of Subjects

Rationale for change: clarify number of sites
Revised text:
Approximately 3232 will be screened globally in approximately 240 ~~205~~ sites such that approximately 2424 subjects will be randomized and approximately 2181 evaluable subjects complete the study.

Section 5.1 Inclusion Criteria
Rationale for change: Addition of inclusion criterion specific to France
Revised text: 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.

Rationale for change: typo
40 years or older at date of signing informed consent ~~at Screening Visit 1~~

Section 5.2 Exclusion Criteria

Rationale for change: typo
Revised text: Pneumonia and/or moderate ~~or severe~~ COPD exacerbation

Rationale for change: clarify prohibited Screening and run-in COPD medications
Revised text:

15. Medications prior to Screening: Use of the following medications according to the following defined time intervals prior to Screening (Visit 1) or during the study:

Medication	No use within the following time intervals prior to Screening and thereafter at any time during the study
Inhaled corticosteroids (ICS)	6 weeks
Depot corticosteroids	12 weeks
Systemic, oral or parenteral corticosteroids[a]	6 weeks
Antibiotics (for lower respiratory tract infection)[b]	6 weeks
Phosphodiesterase 4 (PDE_4) Inhibitor (*e.g* roflumilast)	14 days

LABA/Inhaled Corticosteroid (ICS) combination products	6 weeks
LABA/LAMA combination products	2 weeks
Theophyllines	48 hours
Oral $beta_2$-agonists Long-acting Short-acting	 48 hours 12 hours
Inhaled short acting $beta_2$-agonists[b]	4 hours
Inhaled short-acting anticholinergics	4 hours
Inhaled short-acting anticholinergic/short-acting $beta_2$-agonist combination products	4 hours
Any other investigational medication	30 days or within 5 drug half-lives (whichever is longer)

a- Corticosteroids are allowed for the treatment of COPD exacerbations during the double-blind treatment phase of the study. Localized corticosteroid injections (e.g., intra-articular and epidural) are permitted.
b- Use of study provided albuterol/salbutamol is permitted during the study, except in the 4-hour period prior to spirometry testing

2. Medication prior to spirometry: Unable to withhold albuterol/salbutamol for the 4 hour period required prior to spirometry testing at each study visit. Unable to withhold morning dose of subject's inhaled LABA or LAMA COPD medication prior to spirometry testing at Screening Visit (Visit 1).

Section 5.3 Randomization Criteria

Rationale for change: clarification of prohibited medications at randomization
Revised text: Prohibited Medications: No use of any prohibited medications during the run-in period or at Visit 2, including any ICS or ICS/LABA combination. Subject's inhaled LABA or LAMA medication morning dose must be withheld and discontinued at Visit 2.

Section 5.5.1. Withdrawal from the Study

Rationale for change: Clarify stopping criteria for withdrawal
Revised text:

Stopping Criteria

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

- **Unstable or life threatening cardiac events:** myocardial infarction, hospitalization for unstable angina, stroke, and other cardiovascular events considered life- or intensively health-threatening by the study physician.
- **COPD Exacerbations:** Subjects with two moderate or one severe COPD exacerbation during the study.
- **Withdrawal from study treatment** requires withdrawal from the study.

- **Non-Compliance with Study treatment**: Subjects' compliance with study treatment will be assessed at each study visit. Subjects who are non-compliant should be re-educated on the requirement for treatment compliance. Every effort will be made to keep subjects in the study and to re-educate those subjects who continue to be non-compliant. Subjects who continue to be non-compliant after multiple visit assessments may be permanently discontinued **after consultation with the GSK clinical team.**
- **Non-Compliance with eDiary:** Subjects must be compliant in completing their eDiary between each pair of on-treatment visits. Subjects who are non-compliant should be re-educated on the requirement for daily diary entry compliance. Subjects who continue to be non-compliant after multiple visit assessments may be permanently discontinued **after consultation with the GSK clinical team.**

~~Note: Withdrawal from study treatment requires withdrawal from the study.~~

Section 5.6. Follow-up contact

Rationale for change: typo
Revised text: A safety follow-up contact (Visit 6) should be conducted 7±~~2~~ 3days

Section 6.3 Treatment Assignment

Rationale for change: clarify stratification
Revised text: The randomisation will be stratified based on **long-acting bronchodilator** usage during the run-in (none or~~,~~ one ~~or 2~~ **long-acting bronchodilators~~s~~** per day).

In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2 and 60 ~~and 90~~ days from V3 ~~and V4~~

Section 7.1 Time and Events Table

Rationale for change: clarify Visit windows and correct typo concerning Pre-screen window
Revised text:

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-10 ~~-6~~ to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**-70 to -28 ~~42~~ ~~-7/+2 days prior to Visit 1~~**	**~~-28-7/+2 days prior to Visit 2~~**	**1 ~~-7/+2 days~~**	**28 - ~~7/+2 days~~**	**84 - ~~7/+2 days~~**	**168 ~~-7/+2 days~~**		**~~7±3~~ days after V5 or EW Visit**
Window	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**		**±3 days**

Section 7.1 Time and Events Table

Rationale for change: Correct inconsistency of pre-screen window to Medication withhold periods defined in the Exclusion Criteria

Revised text:

1. Pre-screen Visit 0 must be completed prior to Screening Visit1. It can be completed ~~2~~6 weeks prior or on the same day of V1, if no wash out of exclusionary medications is required.

Section 7.2.1 Pre-screen Visit
Rationale for change: Correct inconsistency of pre-screen window to Medication withhold periods defined in the Exclusion Criteria
Revised text: Subjects can perform the Pre-screening Visit (Visit 0) up to ~~2~~ 6 weeks prior to or on the same day as the Screening Visit (Visit 1) if subject does not take or has not taken any protocol excluded medications.

Section 7.3.1.2 SGRQ-C
Rationale for change: typo
Revised text: The St George's Respiratory Questionnaire-Chronic Obstructive Pulmonary Disease specific (SGRQ-C) will be completed by subjects at Randomisation (V2, Day 1), at Week 4, 12 and 24 ~~or at Early Withdrawal Visit (Where applicable)~~.

Section 7.3.1.5 Subject Global Rating of COPD Severity and Global Rating of Change in COPD

Rationale for change: typo
Revised text: Subjects will complete the Global Rating of COPD Severity at Randomization Visit 2 and visits 3, 4 and 5 ~~or Early Withdrawal Visit.~~

Subjects will also complete a Global Rating of Change in COPD (overall disease) question at Visits 3, 4 and 5~~ or Early Withdrawal Visit~~.

Section 7.3.2 Spirometry

Rationale for change: clarify instructions of COPD medication use prior to Spirometry
Revised text:

- At Screening Visit 1, before ~~the~~ subject's morning dose of ~~usual~~ inhaled LABA or LAMA COPD medication~~s~~
- At Visit 2 after withholding the morning dose of inhaled LABA or LAMA COPD medication and prior to administration of study medication ~~after discontinuing inhaled COPD medication medications and prior the first dose of study treatment~~

Section 7.3.3 Inspiratory capacity (IC)

Rationale for change: clarify instructions of COPD medication use prior to IC maneuver

Revised text:

- At Visit 2 after discontinuation of run-in LABA or LAMA COPD medication and prior to administration of study medication
- At Visit 3, 4 and 5 after withholding the morning dose of study drug

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

Rationale for change: Clarifications concerning site professional expertise
Revised text: Study site Investigators will be selected to participate in the 201749 study based upon their pulmonology expertise and knowledge of the protocol defined patient population and associated required study assessments.

Section 12.4.1 Defining of Adverse Events

Rationale for change: Integration of Canadian Amendment 2 into main protocol
Revised text: **Reporting Specific to Canada**: For a marketed medicinal product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without associated signs or symptoms or clinical sequelae).

- Excluding Canada, "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.
- **Reporting Specific to Canada**: "Lack of efficacy" or "failure of expected pharmacological action" will be reported as an AE or SAE as per the table below

Adverse Event criteria	**Electronic case record form (eCRF) only**	**Paper form only**	**Electronic case record form (eCRF) + Paper form**
Non serious	Non drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae	Drug related lack of efficacy reports without associated signs or symptoms or clinical sequelae.	Drug related lack of efficacy with associated signs or symptoms or clinical sequelae
Serious	Non drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae	Drug related lack of efficacy reports without associated signs or symptoms or clinical sequelae.	Drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae

Section 12.4.6 Reporting of SAEs to GSK

Rationale for change: Integration of Canadian Amendment 2 into main protocol
Revised text: **Reporting Specific to Canada**: For lack of efficacy reports, the paper form will be used to submit to GSK as per the table in Section 12.4.1 above.

Section 12.5.2 COPD Exacerbation Severity

Rationale for change: clarify chest x-rays performed in the context of the protocol
Revised text~~**: Every effort should be made to conduct a chest x-ray within 48 hours of identification of a moderate or severe exacerbation.**~~ Chest X-Ray for pneumonia and/or moderate/severe exacerbation is not mandated but can be performed if required by the investigator as part of standard care of subjects.

Section 12.8 Appendix 8: Country Specific Requirements
Rationale for change: Integration of Canadian Amendment 2 into main protocol
Revised text: In Canada only, additions were made to Section 7.4.1 and Appendix 4 to comply with Health Canada guidelines concerning the requirement of pharmaceutical manufacturers to expeditiously report domestic cases of unusual failure in efficacy (UFIE) for new drugs to the Marketed Health Products Directorate (MHPD) within 15 days of first notification.

~~No country specific requirements exist.~~

TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A 24-week treatment, multi-center, randomized, double-blind, double-dummy, parallel group study to compare Umeclidinium/Vilanterol, Umeclidinium, and Salmeterol in subjects with chronic obstructive pulmonary disease (COPD)

Compound Number:	GSK2592356
Development Phase:	IV
Effective Date:	21-FEB-2017

Protocol Amendment Number: 02

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N277425_00	2016-SEP-13	Original
2016N277425_01	2017-FEB-07	Amendment No. 1
This protocol amendment was created to make the following changes: Regulatory Agency Identifying Number(s): A typographical error in the EudraCT no. corrected. IND no. added Section 4.1and Section 4.4: Typographical errors and inconsistencies corrected Inconsistencies between Section 4.4, Section 7.3.1.5 and Section 7.1revised Section 7.1 Time and event table: Un-intentional deletion of the ("x") were added to confirm that concomitant medications should be reviewed at every clinic visit was corrected. Increased the visit window Typographical error and inconsistencies corrected as described in Appendix 9, Section 12.9. Section 7.2.2 Critical procedures performed at Screening (Visit 1): To clarify that height and weight are collected at V1 **"**Height and weight" added Section 7.3.2 Spirometry: "At Screening, before the morning dose of usual COPD medication(s)" added. Section 7.3.7: Physical activity monitor (study subset) Inconsistency between Section 1, Section 4.1 and Section 7.3.7 revised		
2016N277425_02	2017-FEB-21	Amendment No. 2
This protocol amendment was created to comply with Health Canada guidelines. They require pharmaceutical manufacturers to expeditiously report domestic cases of unusual failure in efficacy (UFIE) for new drugs to the Marketed Health Products Directorate (MHPD) within 15 days of first notification. Changes were made to Section 7.4.1 and Appendix 4.		

SPONSOR SIGNATORY

PPD

21 Feb 2017

David Lipson, MD
Project Physician Leader

Date

PPD

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 201749

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

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

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

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

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1. PROTOCOL SYNOPSIS FOR STUDY 201749

Rationale

The primary purpose of this study is to demonstrate improvements in lung function in subjects treated with Umeclidinium/Vilanterol (UMEC/VI) compared with Umeclidinium (UMEC) for 24 weeks. A further important aspect of the study is to evaluate the effect of UMC/VI, UMEC, and salmeterol with respect to health-related quality of life (HRQoL), measured through patient reported outcomes (PROs) questionnaires, and lung function. Additional assessments to further evaluate other measures of chronic obstructive pulmonary disease (COPD) efficacy and symptoms control will be performed.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To compare the effect of UMEC/VI (62.5/25 mcg once daily) with UMEC (62.5 mcg once daily) on lung function	• Change from baseline in trough Forced Expiratory Volume in One Second (FEV_1) at week 24
Secondary	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on patient reported outcomes (PROs)	• Change from baseline in self administered computerised (SAC) transient dyspnea index (TDI) • Percentage of TDI responders according to SAC TDI score. A responder is defined as a ≥1 unit improvement in SAC TDI score • Assessment of respiratory daily symptoms over 24 weeks using Evaluating Respiratory Symptoms-COPD (E-RS) and its subscales (breathlessness, cough and sputum and chest symptoms) • Percentage of E-RS responders according to E-RS score (defined as reduction in E-RS score of ≥2 or ≥3.35 units) from baseline • Change from baseline in St George's Respiratory Questionnaire (SGRQ-C) • Percentage of responders according to SGRQ-C total score (defined as a 4 point or greater reduction from

Objectives	Endpoints
	baseline) • Change from baseline in COPD assessment test (CAT) • Percentage of responders according to CAT (defined as a ≥2 unit improvement in score from baseline)
Other	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on other COPD efficacy measures	• Rate of mild, moderate or severe exacerbations • Time to first mild, moderate or severe exacerbation • Rate of moderate or severe exacerbation • Time to moderate or severe exacerbation • Time to severe exacerbations • Time to clinically important deterioration (CID) composite endpoint • Time to clinically important deterioration composite endpoint excluding FEV_1 • Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the electronic diary (eDiary) over 24 weeks • Inspiratory capacity (IC) • Full Vital capacity (FVC) • Change from baseline in trough FEV_1 • Change from baseline in global impression of disease severity

Objectives	Endpoints
Safety	
• To evaluate safety and tolerability of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5mcg once daily) and salmeterol 50mcg twice daily)	• Incidence of adverse events
Exploratory	
• To compare albuterol/salbutamol use captured in the eDiary with the electronic metered dose inhaler (eMDI) device	• Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the eMDI device over 24 weeks as data allow
• To explore the effect of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on physical activity	• Change from baseline in physical activity
• To investigate the CID composite endpoint ability to predict short term outcomes	• To compare physical activity levels, ER-S, rescue medication use, exacerbations and mortality in subjects with and without a CID

Overall Design

This is a multi-centre, randomized, double blind, double dummy, 3-arm parallel group study. Eligible subjects will be randomized in a ratio of 1:1:1 to UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA™ dry powder inhaler (DPI), or UMEC (62.5 mcg once daily) administered via the ELLIPTA DPI or salmeterol (50 mcg twice daily (BID)) administered via the DISKUS™ DPI.

Eligible subjects at Screening will enter a run-in period for 4 weeks during which they continue taking their inhaled COPD medications (excluding ICS and any exclusionary medications). In addition, subjects will be provided with short acting albuterol/salbutamol to be used on as needed basis (rescue medication) throughout the study.

Subjects who experience a moderate or severe COPD exacerbation during the run-in period will be deemed run-in failures. Subjects experiencing a mild exacerbation, defined as worsening of symptoms that requires **no** treatment with antibiotics or steroids and is self managed by the patient by an increase of inhaled rescue medication, will be allowed to continue in the study.

At the randomization Visit 2 (Day 1) those subjects who successfully complete the run-in period as well as meet the other pre-defined eligibility and randomization criteria will discontinue their inhaled COPD medications and will be randomized to one of the 3 treatment arms for 24 weeks.

All subjects will be given an eDiary for use during the run-in, and treatment period to complete PRO questionnaires and record medical problems experienced during the study. Subjects will be performing slow and forced spirometry at specific visits.

In addition, a subset of subjects up to 150 per treatment arm will undergo assessment of their physical activity measured through a physical activity monitor (Actigraph GT9X) worn for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3, and for 7 days prior to last clinic Visit (Visit 5).

There will be a total of 5 clinic visits and one follow-up phone call (Visit 6). The total duration of subject participation in the study will be approximately 29 to 31 weeks consisting of 2 weeks pre-screening if necessary, 4 weeks run-in, 24 week treatment and one week Follow-Up.

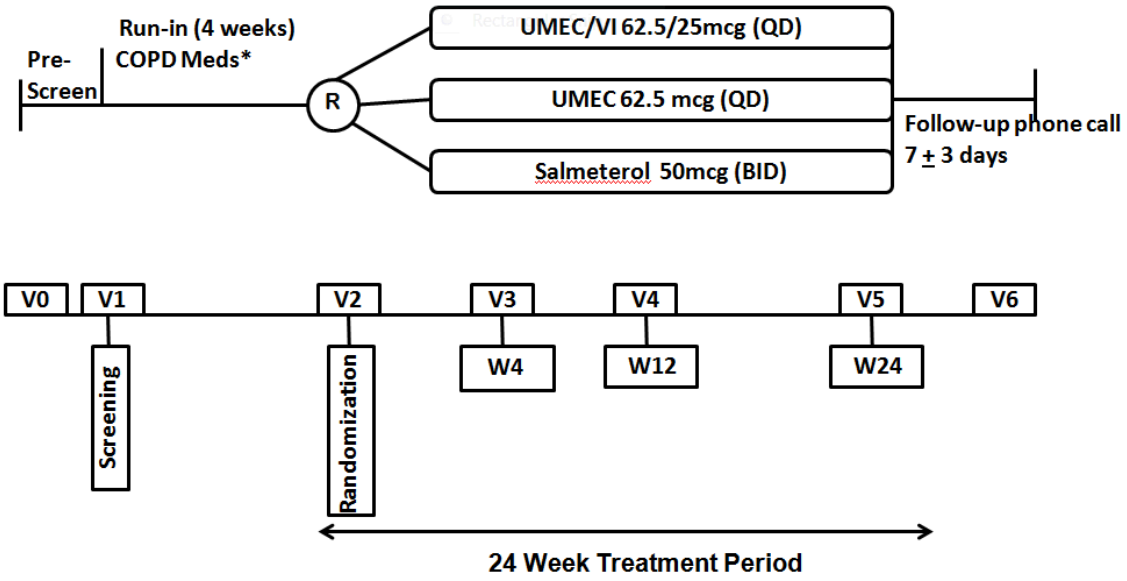
Subjects will be considered to have completed the study upon completion of the Follow–Up contact by telephone.

Treatment Arms and Duration

Subjects will be stratified based on long-acting bronchodilator usage during the run-in (none, one or 2 long-acting bronchodilators per day) and randomized in a ratio of 1:1:1 to either

- UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA DPI) or
- UMEC (62.5 mcg once daily) administered via the ELLIPTA DPI or
- Salmeterol (50 mcg BID) administered via DISKUS

Study schematic



*Inhaled COPD medications including LABAs, LAMAs or LABA/LAMA combination products are allowed in run-in. ICS alone or in combination with a bronchodilator or any exclusionary medications are not allowed.

Type and Number of Subjects

Approximately 3232 subjects will be screened, such that 2424 subjects will be randomized and approximately 2181 evaluable subjects complete the study.

Analysis

The primary purpose of this study is to demonstrate improvements in lung function for subjects treated with UMEC/VI compared with UMEC for 24 weeks.

The primary endpoint is change from baseline in trough FEV_1 at Week 24.

The null hypothesis is no difference between treatment groups (H0: $\mu T - \mu S = 0$), with the alternative hypothesis that there is a difference between treatment groups (H1: $\mu T - \mu S \neq 0$), where μT is the mean change from baseline for UMEC/VI and μS is the mean change from baseline for UMEC.

The primary endpoint of mean change from baseline in trough FEV_1 at the end of Week 24 will be analysed using Mixed Models repeated Measures (MMRM) analysis. The MMRM analysis will include measurements at Treatment Weeks 4, 12 and 24. Treatment group (a categorical variable) will be fitted as the explanatory variable with appropriate pre-defined variables, stratum (number of bronchodilators per day during run-in) and baseline values, fitted as covariates. Visit (nominal) will be fitted as a categorical variable and visit-by-baseline and visit-by-treatment interaction terms will be included to allow treatment effects to be estimated at each visit separately. The variance covariance matrix

will be assumed to be unstructured (based on previous experience no issues are expected with fitting models with this matrix structure).

The estimated treatment differences between UMEC/VI versus UMEC for each endpoint will be presented with the 95% confidence intervals for the difference and the p-value.

2. INTRODUCTION

2.1. Study Rationale

Chronic obstructive pulmonary disease (COPD) is associated with poor health-related quality of life (HRQoL). Pharmacologic therapy is used to improve lung function, reduce symptoms, frequency and severity of exacerbations, and improve patients HRQoL [GOLD, 2015]. Umeclidinium/Vilanterol (UMEC/VI 62.5/25 mcg) is indicated for the maintenance treatment of COPD that contain long-acting muscarinic antagonist (LAMA) and long-acting beta$_2$-agonist (LABA) bronchodilators. Umeclidinium (UMEC) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Salmeterol has long been used for symptoms management of COPD. However, a direct comparison of these maintenance therapies has not been conducted with respect to HRQoL.

The primary purpose of this study is to demonstrate improvements in lung function for subjects treated with UMEC/VI compared with UMEC for 24 weeks. The effect of UMC/VI, UMEC, and salmeterol with respect to patient HRQoL measured through patient reported outcomes (PROs) questionnaires, symptoms and lung function will also be evaluated.

2.2. Brief Background

COPD is characterized by an airflow limitation which is not fully reversible, usually progressive and accompanied by a chronic cough, sputum production and dyspnea which can be a major cause of disability and anxiety associated with the disease [Maleki-Yazdi, 2014]

Furthermore, acute exacerbations contribute to the overall severity of disease as these episodes are accompanied by worsened symptoms and are associated with increased decline in lung function and mortality [Wedzicha, 2013; Schmidt, 2014].

Pharmacologic therapy is used to improve lung function, reduce symptoms, reduce the frequency and severity of exacerbations, and also to improve health status and exercise tolerance. Maintenance treatment is recommended primarily through the use of LABAs or LAMAs. COPD treatment guidelines recommend an incremental approach to pharmacological treatment as the disease state worsens, involving the use of combinations of drug classes with different or complementary mechanisms [GOLD, 2015].

UMEC/VI inhalation powder is a combination of UMEC (umeclidinium bromide), a LAMA, and VI (Vilanterol), a LABA, delivered via the ELLIPTA dry powder inhaler

(DPI). UMEC/VI at a dose of 62.5/25mcg once-daily is marketed in the United States (US) and Europe under the trade name ANORO™ ELLIPTA.
UMEC (62.5 mcg) inhalation powder is marketed in the United States (US) and Europe under the trade name INCRUSE™ ELLIPTA. UMEC (62.5mcg) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. UMEC (62.5 mcg) improves forced expiratory volume in one second (FEV_1), dyspnea and HRQoL whether used as monotherapy [Trivedi, 2014; Feldman, 2016] or as an add on to fluticasone propionate and vilanterol (FF/VI) [Siler, 2015]. Salmetrol (50 mcg) DISKUS is a long-acting broncholdilator that has long been used for the maintenance treatment of COPD [Tashkin, 2010].

Clinically important deterioration (CID) is a novel, exploratory composite endpoint which assesses individual deteriorations in lung function and in patient PROs defined by the accepted minimal clinically important difference (MCID), as well as the incidence of moderate to severe exacerbations [Singh, 2016], (Section 7.3.5). CID will be analysed to determine whether UMEC/VI (62.5/25mcg) therapy provides greater clinical stability as compared with UMEC and salmeterol monotherapies.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To compare the effect of UMEC/VI (62.5/25 mcg once daily) with UMEC (62.5 mcg once daily) on lung function	• Change from baseline in trough Forced Expiratory Volume in One Second (FEV_1) at week 24
Secondary	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on patient reported outcomes (PROs)	• Change from baseline in self administered computerised (SAC) transient dyspnea index (TDI) • Percentage of TDI responders according to SAC TDI score. A responder is defined as a ≥1 unit improvement in SAC TDI score • Assessment of respiratory daily symptoms over 24 weeks using Evaluating Respiratory Symptoms-COPD (E-RS) and its subscales (breathlessness, cough and sputum and chest symptoms) • Percentage of E-RS responders according to E-RS score (defined as reduction in E-RS score of ≥2 or ≥3.35 units) from baseline

Objectives	Endpoints
	• Change from baseline in St George's Respiratory Questionnaire (SGRQ-C) • Percentage of responders according to SGRQ-C total score (defined as a 4 point or greater reduction from baseline) • Change from baseline in COPD assessment test (CAT) • Percentage of responders according to CAT (defined as a ≥2 unit improvement in score from baseline)
Other	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on other COPD efficacy measures	• Rate of mild, moderate or severe exacerbations • Time to first mild, moderate or severe exacerbation • Rate of moderate or severe exacerbation • Time to moderate or severe exacerbation • Time to severe exacerbations • Time to clinically important deterioration (CID) composite endpoint • Time to clinically important deterioration composite endpoint excluding FEV_1 • Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the electronic diary (eDiary) over 24 weeks • Inspiratory capacity (IC) • Full Vital capacity (FVC)

Objectives	Endpoints
	• Change from baseline in trough FEV_1 • Change from baseline in global impression of disease severity
Safety	
• To evaluate safety and tolerability of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5mcg once daily) and salmeterol (50mcg twice daily)	• Incidence of adverse events
Exploratory	
• To compare albuterol/salbutamol use captured in the eDiary with the electronic metered dose inhaler (eMDI) device	• Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the eMDI device over 24 weeks as data allow
• To explore the effect of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on physical activity	• Change from baseline in physical activity
• To investigate the CID composite endpoint ability to predict short term outcomes	• To compare physical activity levels, ER-S, rescue medication use, exacerbations and mortality in subjects with and without a CID

4. STUDY DESIGN

4.1. Overall Design

This is a multi-centre, randomized, double blind, double-dummy, 3-arm parallel group study. Eligible subjects will be stratified based on long-acting bronchodilator usage during the run-in (none, one or 2 long-acting bronchodilators per day) and randomized in a ratio of 1:1:1 to UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA inhaler, or UMEC (62.5 mcg once daily) administered via the ELLIPTA or salmeterol (50 mcg BID) administered via the DISKUS.

There will be a total of 5 clinic visits and one follow-up phone call (Visit 6). The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) if subject does not take or has not taken any excluded protocol medications, but must be completed prior to initiating any Visit 1 procedures.

Subjects, who meet all the eligibility criteria at Screening, will enter a run-in period for 4 weeks in order to continue to assess the subject's eligibility for the study. During the run-in period subjects will continue with their inhaled COPD medications (excluding ICS and

any exclusionary medications). In addition, subjects will be provided with short acting albuterol/salbutamol to be used on as needed basis for relief of COPD symptoms (rescue medication) throughout the study.

Subjects who experience a moderate or severe COPD exacerbation during the run-in period will be deemed run-in failures. Subjects who experience a mild COPD exacerbation, defined as worsening of symptoms that requires **no** treatment with antibiotics or steroids and is self managed by the patient by an increase of inhaled rescue medication, (Appendix 5), will be able to continue in the study based on the judgment of the investigator and agreement of the sponsor's medical monitor.

At the randomization Visit 2 (Day 1) those subjects who successfully complete the run-in period as well as meet the other pre-defined eligibility and randomization criteria will discontinue their inhaled COPD medications and will be randomized to one of the 3 treatment arms for 24 weeks.

During the run-in and treatment period, subjects will be completing PRO questionnaires in the eDiary and performing slow and forced spirometry at specific clinic visits.

In addition, a subset of subjects up to 150 per treatment arm will undergo assessment of their physical activity measured through a physical activity monitor (Actigraph GT9X) worn for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3, and for 7 days prior to last clinic Visit (Visit 5).

Concurrent use of COPD maintenance medications including LAMAs, LABAs, oral beta-agonists, theophyllines, inhaled corticosteroids, inhaled corticosteroids and LABA combination and phosphodiesterase 4 inhibitors will not be allowed during the study (Section 6.11.2) .

The occurrence of adverse events (AEs) will be evaluated throughout the study beginning at Visit 2 (Day 1) and until the follow-up contact (Visit 6). Serious adverse events (SAEs) will be collected over the same time period as AEs. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact (Appendix 4).

All subjects will be given an electronic diary (eDiary) for use during the run-in, and the treatment period to complete PRO questionnaires, record COPD daily symptoms, any medical problems experienced during the study and the time they take their COPD medications. Daily rescue medication usage (number of inhalations taken in the last 24h) will also be captured in the eDiary. In addition, and in some countries, rescue medication use will also be captured by the use of electronic metered dose inhaler (eMDI).

At Screening Visit 1, all subjects must be trained on the proper use of their existing COPD medications inhalation devices and instructed to strictly adhere to and record the time they take their COPD medications in the eDiary.

At the randomization Visit 2, all subjects must be trained on the proper use of the ELLIPTA and DISKUS inhalation devices and instructed to strictly adhere to and record the time they take their study medications in the eDiary.

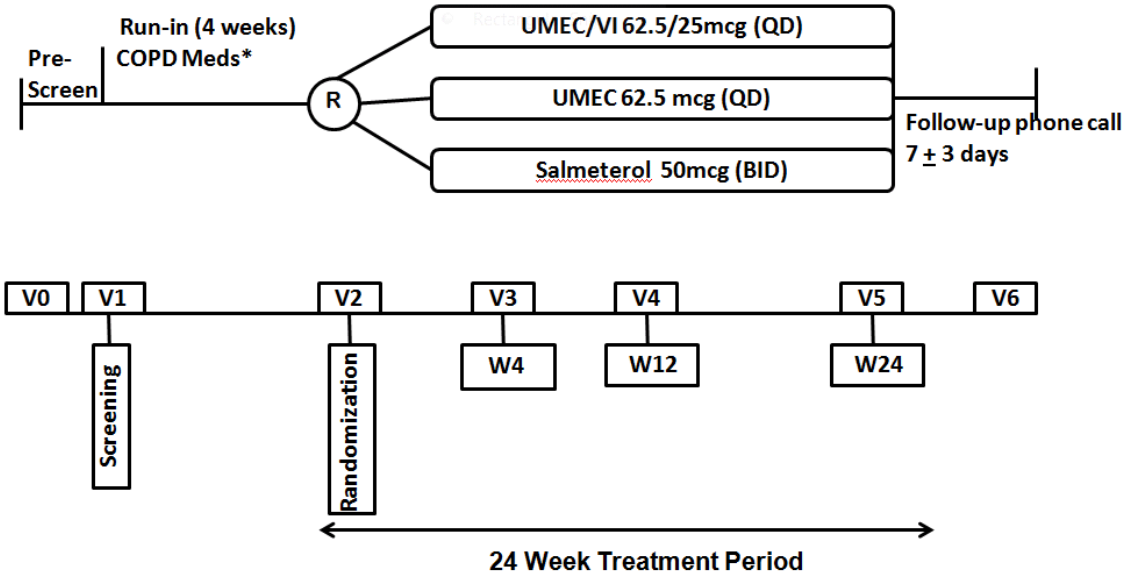
All subjects must be trained on the correct use of the eDiary and instructed to complete the eDiary during the run-in and treatment period.

Subjects will be considered to have completed the study upon completion of the follow – up contact by telephone.

There are no plans to routinely provide any of the study treatments for compassionate use following study completion as the study treatment are commercially available.

The study design schematic is illustrated in Figure 1

Figure 1 Study Schematic



*Inhaled COPD medications including LABAs, LAMAs or LABA/LAMA combination products are allowed in run-in. ICS alone or in combination with a bronchodilator or any exclusionary medications are not allowed.

4.2. Treatment Arms and Duration

Subjects will be stratified based on long-acting bronchodilator usage during the run-in (none, one or 2 long-acting bronchodilators per day) and randomized in a ratio of 1:1:1 to either

- UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA DPI) or
- UMEC (62.5 mcg once daily) administered via the ELLIPTA DPI or
- Salmeterol (50 mcg BID) administered via DISKUS

The total duration of subject participation in the study will be approximately 29 to 31 weeks consisting of 2 weeks pre-screening if necessary, 4 weeks run-in, 24 week treatment and one week follow-up.

4.3. Type and Number of Subjects

Approximately 3232 will be screened globally in approximately 205 sites such that approximately 2424 subjects will be randomized and approximately 2181 evaluable subjects complete the study.

4.4. Design Justification

A randomized, double blinded, parallel group study is a standard, well-established design to evaluate the efficacy and safety of an investigational drug. A salmeterol arm is included to allow a comparison to be made between UMEC/VI, UMEC with salmeterol, a standard practice treatment.

The double-dummy design is appropriate when drugs are of different appearance or different administration regimen which is appropriate in this study where the inhalers used have a different appearance and used once daily and twice daily.

The European Medicines Agency (EMA) COPD Guidelines suggest that duration of 12 to 24 weeks is considered adequate for assessment of response of COPD symptoms to treatment intervention with bronchodilators (EMA COPD guidelines, 2012).

The primary endpoint is trough FEV_1 at week 24. This endpoint is generally considered to be a robust, well established and an objective means to show the efficacy of a bronchodilator [Dahl, 2010; Feldman, 2010].

Other endpoints such SAC TDI, E-RS, SGRQ-C, CAT, Subject Global Rating of Change in global impression of disease severity are captured to allow responder analyses and to provide comparative data on PROs between the treatment groups.

4.5. Dose Justification

This study is intended to evaluate the efficacy of marketed doses of UMEC/VI (62.5/25mcg once daily), UMEC (62.5 mcg once daily) and salmeterol (50mcg twice daily) that are approved for the maintenance treatment of COPD, with respect to PRO measures.

4.6. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with UMEC/VI and UMEC can be found in the investigator's brochures (IB) [GlaxoSmithKline Document Number RM2009/00437/07] and [GlaxoSmithKline Document Number RM2006/00835/09] and in the label information sheets. The current safety profile for UMEC (62.5mcg) and the UMEC/VI (62.5/25mcg) based on data available to date, is comparable with other LABAs and LAMAs. Summary safety data can also be found in the information sheet for salmeterol [Serevent product information, 2003].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
Investigational Product (IP) [UMEC/VI]		
Severe milk protein allergy	Anoro contains Lactose monohydrate (which contains milk protein) as an excipient.	Exclusion criteria have been set for subjects with milk protein allergy.
Cardiovascular effects such as cardiac arrhythmias *e.g.* supraventricular tachycardia and extrasystoles.	Class effects associated with LABAs and LAMA containing therapy. The clinical significance of these arrhythmias is unknown. Clinical experience with UMEC/VI to date in completed studies did not show any association with major cardiovascular events. Data available in the product label for UMEC/VI	Exclusion criteria have been set for subjects with uncontrolled or severe cardiovascular disease according to the principal investigation's (PI) opinion where the potential risk may outweigh the benefit. The PI should also determine the clinical significance of abnormal ECG findings at screening and exclude subjects who would be at undue risk by participating in the trial. Patients with the following abnormalities will be excluded from participation: atrial fibrillation with rapid ventricular rate >120bpm, sustained or nonsustained ventricular tachycardia, or second degree heart block Mobitz type II or third degree heart block (unless pacemaker or defibrillator had been inserted).
Beta agonists and risk of asthma-related death	Long-acting beta agonists such as vilanterol when used alone may increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including vilanterol. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.	Subjects with a current diagnosis of asthma are excluded from participation in the study.
Paradoxical bronchospasm	As with other inhaled medicines, UMEC/VI can produce paradoxical bronchospasm which may be life threatening.	If paradoxical bronchospasm occurs following dosing with UMEC/VI, this treatment should be discontinued immediately and alternative therapy should be instituted.
Use in patients with narrow-angle glaucoma or urinary retention	No association has been found to date, in completed studies with UMEC/VI or UMEC monotherapy, on glaucoma or urinary retention. However, glaucoma or urinary retention	Exclusion criterion states that subjects with medical conditions such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction should only be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	have been observed with other antimuscarinic agents, and could potentially be due to the pharmacology.	included if, in the opinion of the principal investigator, the benefit outweighs the risk.
Use of beta blockers	Beta-adrenergic blockers may weaken or antagonize the effect of $beta_2$-agonists such as vilanterol.	The study permitted medications and non drug therapies section states that concomitant administration with beta-blockers is only permitted if, in the Investigator's opinion, the likely benefit outweighs the potential risk.
Pregnancy	There is no experience to date of pregnancy during the use of UMEC/VI.	The study inclusion criteria ensures that female subjects of child bearing potential must have a negative pregnancy test at screening, and agree to a reliable contraceptive method, used consistently and correctly (i.e. in accordance with the approved product label and the instructions of the physician for the duration of the study). Exclusion criteria include **Pregnancy:** Women who are pregnant or lactating or are planning on becoming pregnant during the study.
Severe hepatic impairment	UMEC/VI has not been studied in severe hepatic impairment.	Exclusion criterion states that subjects severe hepatic impairment should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Investigational product (IP) [UMEC]		
Cardiovascular effects such as cardiac arrhythmia, e.g. atrial fibrillation and tachycardia	A potential class effect associated with anti-muscarinic therapies. Data available to date in the IB for UMEC [GlaxoSmithKline Document Number RM2006/00835/09	Screening electrocardiogram (ECG) criteria to exclude subjects potentially at risk
Narrow-angle glaucoma, urinary retention	A class effect associated with anti-muscarinic therapies. Data available in the IB for UMEC [GlaxoSmithKline Document Number RM2006/00835/09	Exclusion criterion states that subjects with medical conditions such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Paradoxical bronchospasm that may be life threatening	Known effect associated with inhalation therapy	A short-acting inhaled bronchodilator (albuterol/salbutamol) will be provided for use as needed throughout the study. The investigators will be instructed to assess subject's condition to determine their eligibility to

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		continue in the study and the need for alternative therapy.
Severe hepatic impairment	UMEC has not been studied in severe hepatic impairment.	Exclusion criterion states that subjects with severe hepatic impairment should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Pregnancy/Lactation	There is no experience to date of pregnancy during the use of UMEC.	The study inclusion criteria ensure that female subjects enrolled, who are of Child bearing potential, have a negative pregnancy test at screening, and agree to a reliable contraceptive method, used consistently and correctly (i.e. in accordance with the approved product label and the instructions of the physician for the duration of the study). Exclusion criteria states - Pregnancy: Women who are pregnant or lactating or are planning on becoming pregnant during the study.
Study Procedures		
Spirometry procedures	This may cause difficulty breathing, changes in pulse rate and blood pressure, coughing, wheezing, chest tightness or fainting.	Subjects will be monitored during the procedure for these effects and spirometry will be discontinued should these occur.
ECG lead placement	This may cause skin irritation.	It may be necessary to have small patches (about a centimetre in diameter) of hair on the chest shaved to properly attach electrodes to the chest.
Blood sampling procedure (optional pharmacogenetic blood sample)	Giving blood may make subjects feel faint, or experience mild pain, bruising, irritation or redness at the site. In rare cases, they may get an infection	Subjects will be monitored during the blood draw for these effects and should call their study doctor if any of these effects do not resolve
Other		
Side effects of rescue albuterol/salbutamol. Adverse events seen in clinical studies to date are however consistent for the beta$_2$-adrenergic class of compounds	Class effects associated with short acting beta-agonists (SABAs)	Subjects should call their study doctor if they experience any of these symptoms

4.6.2. Benefit Assessment

Subjects will receive single or combination of long-acting bronchodilator therapies approved for maintenance treatment of COPD. Participating subjects in this study will contribute to the process of further characterizing the benefit of these long-acting bronchodilators with respect to PROs and symptoms in the treatment of COPD.

Specific benefits associated with the study design and procedures include the following:

- Subjects will receive treatments approved for the treatment of COPD that have been shown to be effective in the population under study
- All subjects will receive albuterol/salbutamol for use "as needed" for relief of COPD symptoms
- The combination of study procedures of spirometry, CAT, SGRQ, TDI, E-RS will provide the study subjects with a comprehensive evaluation of their symptoms, health status and COPD disease severity. Subjects will also be monitored throughout the study for any worsening of COPD symptoms or decline in general health. Finally smoking cessation counselling will also be provided.

4.6.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with UMEC/VI, UMEC, salmeterol and with study procedures are justified by the anticipated benefits from active treatments that may be afforded to patients with COPD.

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 IBs, [GlaxoSmithKline Document Number RM2006/00835/09], [GlaxoSmithKline Document Number RM2009/00437/07] and product labels.

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

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. **40 years or older** at date of signing informed consent at Screening Visit 1

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. **Outpatient with a diagnosis of COPD** in accordance with the definition of the American Thoracic Society/European Respiratory Society (ATS/ERS) [Celli, 2004]. 3. **FEV_1**: Persistent airflow limitations as indicated by: A pre and post-albuterol/salbutamol FEV_1/FVC ratio of <0.70 and a post-albuterol/salbutamol FEV_1 of ≥30% to ≤80% predicted normal values at Screening Visit 1. Predicted values will be based upon the ERS Global Lung Function Initiative [Quanjer, 2012]. 4. **CAT score**: A CAT score of ≥10 at Screening Visit 1

Smoking History
5. **Current or former cigarette smokers** with a history of cigarette smoking of ≥ 10 pack-years [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 both equal 10 pack-years)]. Former smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Pipe and/or cigar use cannot be used to calculate pack-year history.

SEX
6. **Male and female** subjects are eligible to participate in the study 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 must be tested. 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) (Appendix 7) from 30 days prior to the first dose of study medication and until [at least five terminal half-lives OR until any continuing pharmacologic effect has ended, whichever is longer] after the last dose of study medication and completion of the follow-up visit. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
7. **Capable of giving signed informed consent** prior to study participation, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION
1. **Asthma**: 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). 2. **Alpha-antitrypsin deficiency:** Subjects with known α1-antitrypsin deficiency as the underlying cause of COPD 3. **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. 4. **Unstable liver disease:** 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). • 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 or within 3 months prior to first dose of study treatment) are acceptable if subject otherwise meets entry criteria 5. **Unstable or life threatening cardiac disease:** Investigational Product should be used with caution in subjects with severe cardiovascular disease. In the opinion of the investigator, use should only be considered if the benefit is likely to

outweigh the risk in conditions such as:

- 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

6. **12 Lead ECG:** 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. Subjects with the following abnormalities are excluded from participation in the study:

- Atrial fibrillation with rapid ventricular rate >120 bpm
- Sustained or non-sustained ventricular tachycardia
- Second degree heart block Mobitz type II or third degree heart block (unless pacemaker or defibrillator had been inserted)

7. **Antimuscarinic effects:** Subjects with medical conditions such as narrow-angle glaucoma, urinary retention, prostatic hypertrophy, or bladder neck obstruction should be excluded unless, in the opinion of the study physician, the benefit outweighs the risk.

8. **Other disease abnormalities:** Any subject who is considered unlikely to survive the duration of the study period or has any rapidly progressing disease or immediate life-threatening illness (e.g. cancer). In addition, any subject who has any other condition (e.g. neurological condition) that is likely to affect respiratory function should not be included in the study.

9. **Hospitalization:** Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1. **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).

10. **Inhaled corticosteroids (ICS):** Had received ICS or ICS/LABA for the treatment of COPD in the 6 weeks prior to Screening Visit1

11. **Exacerbation:** Had >1 moderate exacerbation in the 12 months prior Screening Visit1, or one severe exacerbation requiring hospitalisation in the 12 months prior Screening Visit 1.

12. **Other respiratory tract infections** that have not resolved at least 7 days prior to Screening V1.

13. **Lung Resection:** Subjects with lung volume reduction surgery (including procedures such as endobronchial valves) within the 12 months prior to Screening V1.

14. **Oxygen:** Use of long-term oxygen therapy (LTOT) described as resting oxygen therapy >3L/min at screening required to maintain adequate oxygenation (*e.g.* S_aO_2 >90%). (Oxygen use ≤3L/min flow is not exclusionary, and patients may adjust oxygen levels up or down as needed during the study.)

CONCOMITANT MEDICATIONS

1. **Medications prior to Screening:** Use of the following medications according to the following defined time intervals prior to Screening (Visit 1):

Medication	No use within the following time intervals prior to Screening
Inhaled corticosteroids (ICS)	6 weeks
Depot corticosteroids	12 weeks
Systemic, oral or parenteral corticosteroids[a]	6 weeks
Antibiotics (for lower respiratory tract infection)	6 weeks
Phosphodiesterase 4 (PDE_4) Inhibitor (*e.g* roflumilast)	14 days
LABA/Inhaled Corticosteroid (ICS) combination products	6 weeks
Theophyllines	48 hours
Oral $beta_2$-agonists Long-acting Short-acting	 48 hours 12 hours
Inhaled short acting $beta_2$-agonists[b]	4 hours
Inhaled short-acting anticholinergics	4 hours
Inhaled short-acting anticholinergic/short-acting $beta_2$-agonist combination products	4 hours
Any other investigational medication	30 days or within 5 drug half-lives (whichever is longer)

a- Localized corticosteroid injections (e.g., intra-articular and epidural) are permitted.

b- Use of study provided albuterol/salbutamol is permitted during the study, except in the 4-hour period prior to spirometry testing

2. **Medication prior to spirometry:** Unable to withhold albuterol/salbutamol for the 4 hour period required prior to spirometry testing at each study visit.
3. **Maintenance use of short-acting bronchodilators**: Regular use (prescribed for daily/ regular use, not for as-needed use) of short-acting bronchodilators (*e.g*. albuterol/salbutamol).

RELEVANT HABITS

1. **Drug or alcohol abuse:** A known or suspected history of alcohol or drug abuse within 2 years prior to Screening Visit 1 that in the opinion of the investigator would prevent the subject from completing the study procedures.

CONTRAINDICATIONS

1. **Any history of allergy or hypersensitivity** to any anticholinergic/muscarinic receptor antagonist, sympathomimetic, lactose/milk protein or magnesium stearate.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
1. **Pulmonary Rehabilitation program:** Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Screening Visit 1. Subjects who are in the maintenance phase of a pulmonary rehabilitation program are not excluded.
2. **Affiliation with investigator sites:** Is an investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member of the aforementioned that is involved in this study
3. **Inability to read:** In the opinion of the investigator, any subject who is unable to read and/or would not be able to complete questionnaires on the electronic diary.

Subjects who fail to meet inclusion and exclusion criteria at the **Screening Visit 1** will be considered screen failures and cannot be **re-screened.**

5.3. Randomization Criteria

In order to be randomized to one of the 3 treatment arms at Visit 2, subjects must have completed the run-in period and must have fulfilled all inclusion and exclusion criteria described in Section 5.1 and Section 5.2. In addition to the following:

REQUIRED CRITERIA FOR RANDOMIZATION AND TREATMENT
1. **COPD Exacerbation**: Subjects must **not** have experienced a moderate or severe COPD exacerbation or a lower respiratory tract infection during run-in or at Day 1 (Visit 2) inclusive. A moderate exacerbation is defined as worsening of symptoms of COPD requiring the use of antibiotics or systemic corticosteroids. A severe exacerbation is defined as worsening symptoms of COPD requiring hospitalization.
2. **CAT score**: A CAT score of ≥10 at Visit 2
3. **Prohibited Medications:** No use of any prohibited medications during the run-in period or at Visit 2, including any ICS or ICS/LABA combination
4. **Any change to COPD medications:** Including dosage and regimen during the run-in
5. **Completion of electronic diary:** Must have completed the electronic diary for at least 80% of days during the run-in period

Subjects who do not meet the required criteria for randomization at Visit 2 will not be randomized.

5.4. Screening/Baseline/Run-in Failures

Pre-screen, screen and run-in failures are defined as follows:

- Pre-screening failures: A subject, who is assigned a subject number at the Pre-screening Visit 0 but does not have any Screening Visit 1 procedures, will be considered a pre-screen failure.

- Screening failures: Those subjects that complete at least one Screening Visit 1 procedure but do not enter the run-in period.
- Run-in failures: Those subjects that enter the run-in period but are not randomized to any of the study treatment arms.

Subjects who are pre-screen, screen and run-in failure will be recorded in the eCRF. 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 to be recorded in eCRF including demography, screen failure details, eligibility criteria, and serious adverse events (Section 7.4.1).

5.5. Withdrawal/Stopping Criteria

5.5.1. Withdrawal from the Study

Subjects may be withdrawn from the study at any time by the Investigator if it is considered to be detrimental for them to continue in the study. Reasons for withdrawal from study treatment can include: an AE, clinically significant abnormality, lack of efficacy, sponsor terminated study, pregnancy, or for any other reason.

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.

A reason for the withdrawal from the study must be captured in the electronic case report form (eCRF).

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

- **Liver Chemistry:** Meets any of the Liver chemistry stopping criteria (See Section 5.5.3)

  Note: clinical laboratory assessments are not required for this study. However, laboratory samples may be taken for liver event analysis, if clinically indicated by the study investigator.

- **Pregnancy:** Positive pregnancy test (see Appendix 7)

Subjects withdrawn from study treatment will not be replaced.

Note: Withdrawal from study treatment requires withdrawal from the study.

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".

5.5.2. Reason for Study Withdrawal

The primary reason for study withdrawal will be recorded in the eCRF. When a subject withdraws consent, the investigator must document the reason (if specified by the subject) in the eCRF.

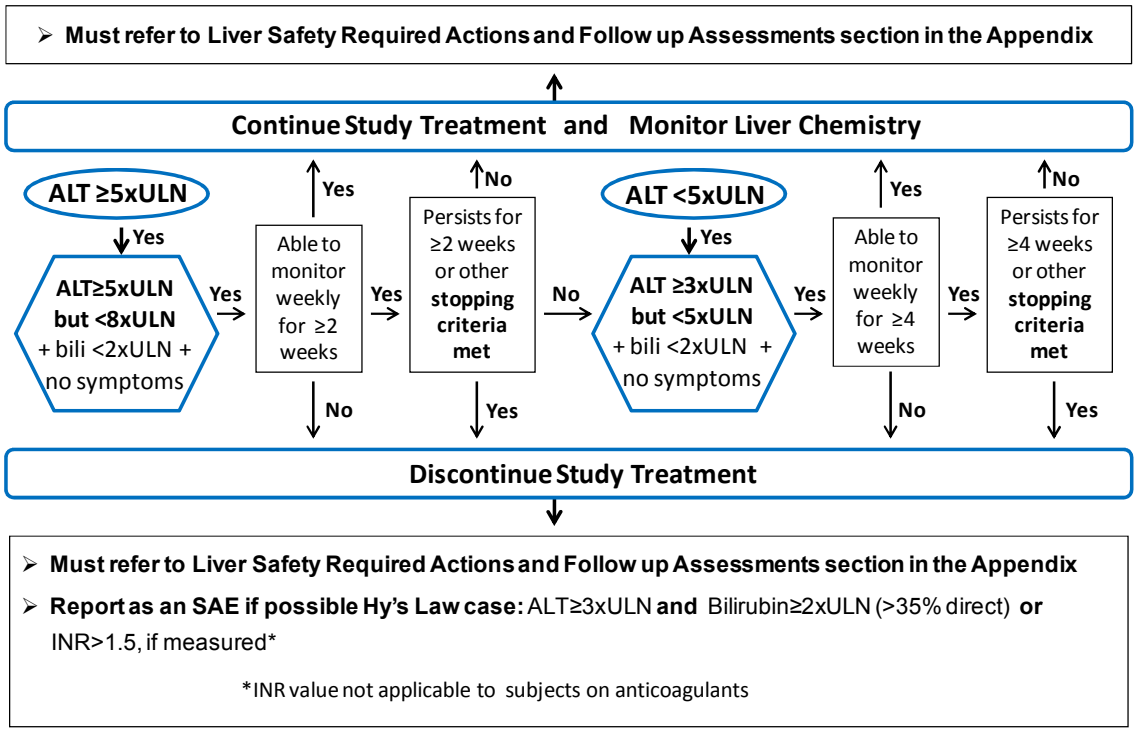
The primary reason for study withdrawal may include:

- Adverse event
- Lost to follow-up
- Withdrew consent
  - subject relocated
  - frequency of visits
  - burden of procedures
  - other (specify)
- Protocol deviation
- Lack of efficacy
- COPD exacerbation
- Study closed/terminated
- Subject reached protocol-defined stopping criteria
  - Liver event
- Pregnancy
- Investigator discretion

5.5.3. 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

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.

5.5.3.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.6. Follow-up contact

A safety follow-up contact (Visit 6) should be conducted 7±2 days following the completion of Visit 5 or the Early Withdrawal Visit, if applicable.

The following procedures will be performed:

- AE/SAE assessment
- COPD exacerbation assessment
- Concomitant medication assessment limited to any medications used to treat a COPD exacerbation or SAE (if applicable)
- Pregnancy information (if applicable)

Subjects who have successfully completed all on-treatment randomized visits will be discharged from the study upon completion of the safety follow-up contact.

5.7. Subject and Study Completion

A subject will be considered to have completed the study if he/she receives study treatment at Visit 5 (Week 24) and completes the follow-up contact Visit 6.

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.

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

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

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 authorised site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

GlaxoSmithKline (GSK) will provide the study treatments for use in this study.

The following study medications will be used in this study:

- UMEC/VI 62.5/ 25mcg administered via ELLIPTA
- UMEC 62.5 mcg administered via ELLIPTA
- Salmeterol 50 mcg administered via DISKUS
- Placebo via ELLIPTA
- Placebo via DISKUS

Subjects will be instructed to take one dose of medication each morning from the ELLIPTA (one inhalation equals one dose), and one dose in the morning and one in the evening from the DISKUS). Subject instructions and details on how to use the ELLIPTA and DISKUS are provided in the study reference manual (SRM).

A description of the UMEC/VI investigational product administered via the ELLIPTAis provided below in Table 1. The ELLIPTA will contain two, double-foil, laminate, blister strips. The ELLIPTA will provide a total of 30 doses (60 blisters) and will deliver, when actuated, the contents of a single blister simultaneously from each of the two blister strips.

The DISKUS will provide a total of 60 doses and will deliver, when actuated, the contents of a single blister.

A description of the UMEC investigational product administered via the ELLIPTA is provided below in Table 2. A description of placebo inhalation powder via ELLIPTA is shown in Table 3. A description of salmeterol 50mcg and placebo via DISKUS are shown in Table 4 and Table 5 respectively.

Table 1 Description of UMEC/VI Inhalation Powder via ELLIPTA

Formulation	**First strip**	**Second strip**
	Umeclidinium bromide blended with lactose monohydrate and magnesium stearate[1]	Vilanterol trifenatate blended with lactose monohydrate and magnesium stearate[2]
Dosage Form	ELLIPTA Inhaler with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	62.5 mcg	25 mcg
Physical description	White powder	White powder
Route of Administration	Inhaled	

1. Magnesium stearate 0.6% w/w of total drug product
2. Magnesium stearate 1.0% w/w of total drug product

Table 2 Description of UMEC Inhalation Powder via ELLIPTA

Formulation	**First strip**
	Umeclidinium bromide blended with lactose monohydrate and magnesium stearate[1]
Dosage Form	ELLIPTA Inhaler with 30 doses (1 strip with 30 blisters)
Unit Dose Strengths	62.5mcg
Physical description	Dry white powder
Route of Administration	Inhaled

1. Magnesium stearate 0.6% w/w of total drug product

Table 3 Description of Placebo inhalation powder via ELLIPTA

Formulation	**First strip**	**Second strip**
	Lactose monohydrate blended with magnesium stearate[1]	Lactose monohydrate blended with magnesium stearate[2]
Dosage Form	ELLIPTA Inhaler with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	Not applicable	Not applicable
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	

1. Magnesium stearate 0.6% w/w of total drug product
2. Magnesium stearate 1% w/w of total drug product

Table 4 Description of salmeterol Inhalation powder via DISKUS

Formulation	**First strip**
	Salmeterol Xinafoate blended with lactose monohydrate
Dosage Form	Diskus Inhaler with 60 doses (1 strip with 60 blisters per strip)
Unit Dose Strengths	50 mcg
Physical description	White powder
Route of Administration	Inhaled

Table 5 Description of Placebo inhalation powder via DISKUS

Formulation	Lactose monohydrate
Dosage Form	Diskus Inhaler with 60 doses (1 strip with 60 blisters per strip)
Unit Dose Strengths	Not Applicable
Physical description	White powder
Route of Administration	Inhaled

Albuterol/salbutamol via metered-dose-inhaler (MDI) will be issued for reversibility testing at Visit 1. Albuterol/salbutamol MDI for as needed (prn) use will be issued throughout the study. Albuterol/salbutamol will be sourced from local commercial stock if appropriate.

6.2. Medical Devices

The eMDI devices are provided by GSK and are used in this study to electronically record rescue medication usage. They have US FDA 510(K) clearance to market (Class II device) and EU CE marking (Class I device). Description of the eMDI and its use will be provided in the **SRM.**

6.3. Treatment Assignment

Subjects who meet the randomization criteria will be assigned to one of the 3 study treatments in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Once a randomization number is assigned to a subject, it cannot be reassigned to any other subject in the study.

This study will utilize RAMOS NG, which will provide a means for central 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 RAMOS NG to randomize subjects is provided in the SRM.

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. On the other days during the treatment period (i.e. “non-clinic days”), subjects will be instructed to self-administer their study treatment

in the morning and evening. Subjects should enter the time they take their study treatment in the eDiary.

Subjects will be randomly assigned to one of the blinded study treatment regimens in equal proportion (ratio of 1:1:1):

- UMEC/VI 62.5/25 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- UMEC 62.5 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- Salmeterol 50 mcg twice daily via DISKUS + placebo once daily via ELLIPTA

The randomisation will be stratified based on **long-acting bronchodilator** usage during the run-in (none, one or 2 **long-acting bronchodilators** per day).

Study treatment/investigational product will be dispensed at Visits 2, 3 and 4.

In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2, 60 and 90 days from V3 and V4 respectively (see Time and event table Section 7.1).

Used study drug and rescue medication will be collected at Visits 3, 4 and 5 or at the Early Withdrawal Visit.

6.4. Planned Dose Adjustments

No dose adjustment is allowed for this study

6.5. Blinding

This will be a double-blind double dummy study 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. 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.

6.6. Packaging and Labeling

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

6.7. Preparation/Handling/Storage/Accountability

No special preparation of the study treatment is required.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer 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 SRM.

All ELLIPTA DPI study treatment should be stored up to 25°C (77°F). Each All ELLIPTA DPI 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 investigational product.

Salmeterol DISKUS should be stored up to 25 °C.

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.

6.7.1. Study Treatment Return

All used and unused ELLIPTA and DISKUS inhalers 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 SRM.

Study treatment will be collected at Visit 3, 4 and 5 or at the Early Withdrawal Visit, if applicable.

For any ELLIPTA or DISKUS inhaler that fails to function properly, the subject should return to the clinic as soon as possible to obtain a new inhaler. The site will contact the RAMOS NG 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 RAMOS NG

In addition, any ELLIPTA that fails to function properly must be identified and returned to GSK for testing.

6.8. Compliance with Study Treatment Administration

When subjects self-administer study treatment(s) at home, compliance with study treatment(s) will be assessed through querying the subject during the site visits and through study drug compliance assessed at Visits 2, 3, 4 and 5 documented in the source documents and eCRF. A record of the number of ELLIPTA and DISKUS dispensed and the number of doses inhaled by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays if any will also be recorded in the eCRF.

Compliance with the ELLIPTA inhaler will be determined by reviewing the dose counter on the ELLIPTA. Compliance with the study DISKUS will be determined by reviewing the dose counter on the DISKUS. Subjects should be ≥80% to ≤120% compliant on taking study medication between each pair of on-treatment visits. Subjects who fall outside this range should be re-educated on treatment compliance by their site. This re-education should be documented in the subject's source document. If medication compliance repeatedly falls outside of acceptable ranges, the study sponsor/site monitor must be contacted to discuss subject eligibility for continued participation in the study.

6.9. Treatment of Study Treatment Overdose

An overdose is defined as a dose greater than the total doses described in Section 6.1 and Section 6.8 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 medication, the investigator should use clinical judgment in treating the overdose and contact the study 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 may not be limited to, the approved product label for salmeterol albuterol, UMEC and UMEC/VI or equivalent document provided by GSK.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.10. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study, since the study treatments are commercially available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, post-study treatment.

6.11. Concomitant Medications and Non-Drug Therapies

All COPD medications used within 30 days prior to Pre-Screening (Visit 0) and onwards should be recorded in the eCRF including any changes in medications. Beginning at Visit 1 and throughout the rest of the study, all medications should be recorded in the eCRF including any changes. Study provided albuterol/salbutamol and double-blinded study drug should **not** be recorded in the eCRF. The minimum requirement includes but is not limited to drug name, dose, route and the dates of administration. Medications initiated after completion of Visit 5 or the Early Withdrawal Visit will not be recorded in the eCRF, with the exception of those used to treat a COPD exacerbation or SAE that occurs between Visit 5 (or the Early Withdrawal Visit) and the follow-up contact atVisit 6.

6.11.1. Permitted Medications and Non-Drug Therapies

The following relevant medications are permitted during this study:

- Study-provided albuterol/salbutamol for use as relief medication throughout the run-in and treatment periods
- Mucolytics such as acetylcysteine
- Medications for rhinitis (e.g. intranasal corticosteroids, antihistamines, cromolyn, nedocromil, nasal decongestants)
- Influenza vaccine
- pneumococcal vaccine
- Antibiotics for short term treatment (≤14 days) of acute infections including COPD exacerbations
- Systemic corticosteroids for short term (≤14 consecutive days) treatment of COPD exacerbations

- As-needed supplemental oxygen use provided it is ≤3L/min flow at rest at screening. Patients may adjust oxygen levels as needed during the study.
- Pulmonary rehabilitation program in maintenance phase
- Smoking cessation treatment, including a stable regimen of nicotine replacement
- Use of positive airway pressure/non-invasive ventilation for sleep apnea/sleep disordered breathing (*e.g*. CPAP, BiPAP)
- Localized corticosteroid injections (e.g., intra-articular and epidural)
- 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)
- Immunotherapy injections
- Topical or ophthalmic corticosteroids
- Over-the counter (OTC) cough suppressants
- Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). Administer with caution as they may potentiate the effect of beta-agonists on the vascular system
- Diuretics. Caution is advised in the co-administration of beta agonists with non-potassium sparing diuretics
- Allergy vaccination
- All medications for other disorders as long as the dose remains constant whenever possible and their use would not be expected to affect lung function

6.11.2. Prohibited Medications and Non-Drug Therapies

Use of the medications listed in Table 6 is not permitted during the study

Table 6 Prohibited Medications and Non-Drug Therapies

Medication
Depot corticosteroids
Systemic, oral or parenteral corticosteroids[1]
Inhaled corticosteroids (ICS)[2]
Antibiotics >14 days
LABA/ICS combination products
PDE4 inhibitor (e.g. roflumilast)
Inhaled long acting $beta_2$-agonists (LABA, e.g. salmeterol, formoterol, indacaterol, vilanterol)
Long-acting muscarinic antagonists (LAMA, e.g. tiotropium, aclidinium, glycopyrronium, umeclidinium[3])
LAMA/LABA combination products except for study drugs
Theophyllines
Oral $beta_2$-agonists
Inhaled short acting $beta_2$-agonists[4]
Inhaled short-acting anticholinergics
Inhaled short-acting anticholinergic/short-acting $beta_2$-agonist combination products
Any other investigational medication

1 Except for the treatment of COPD exacerbations during the study. Localized corticosteroid injections (e.g., intra-articular and epidural) are permitted.
2 Except if during the study use of ICS is deemed necessary for the treatment of subjects' exacerbation.
3 Expect for study drug
4 Use of study provided albuterol/salbutamol is permitted during the study, except in the 4-hour period prior to spirometry testing.

The following medications or treatments are also **not** allowed during the study:

- Use of long-term oxygen therapy (LTOT) described as resting oxygen therapy >3L/min only at screening. Oxygen may be titrated to any level deemed necessary during the study.
- Regular (prescribed for daily/regular use, not for as-needed use) therapy with albuterol/salbutamol.
- Initiation of pulmonary rehabilitation during the study.

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 Section 7.1, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

7.1. Time and Events Table

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 -7/+2 days prior Visit 1**	**28 -7/+2 days prior Visit 2**	**1 -7/+2 days**	**28 -7/+2 days**	**84 -7/+2 days**	**168 -7/+2 days**		**7±3 days after V5 or EW Visit**
Screen/Baseline								
Written informed consent	X							
Demography	X							
Medical/COPD history		X						
Smoking history/status		X						
Smoking cessation counselling		X						
Concomitant medication assessment	X	X	X	X	X	X	X	X
Height and weight		X						
Cardiovascular History/family history of premature CV disease])		X						
Screening spirometry (including post bronchodilator testing)[3]		X						
CAT questionnaire		X	X					
Verify Inclusion/Exclusion Criteria		X						
Training on use of inhalers		X	X					
Training on use of eDiary and eMDI		X	X					
Verify randomization Criteria			X					
Register Visit in InForm	X	X	X	X	X	X	X	X
Register Visit in RAMOS NG	X	X	X	X	X	X	X	X

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 -7/+2 days prior Visit 1**	**28 -7/+2 days prior Visit 2**	**1 -7/+2 days**	**28 -7/+2 days**	**84 -7/+2 days**	**168 -7/+2 days**		**7±3 days after V5 or EW Visit**
Efficacy/HRQoL assessments								
Spirometry, including pre-dose FEV_1, trough FEV_1 and inspiratory capacity			X	X	X	X		
SAC BDI questionnaire [4]			X					
SAC TDI questionnaire [4]				X	X	X		
SGRQ-C questionnaire [4]			X	X	X	X		
CAT questionnaire [4]		X	X	X	X	X		
EXACT/ER-S: COPD [5]		→	→	→	→	→		
Patient Global Rating of COPD severity			X	X	X	X		
Patient Global Rating of Change in COPD				X	X	X		
Safety assessments								
Adverse events/Serious adverse events [6]	X	X	X	X	X	X	X	X
COPD exacerbation assessment	X	X	X	X	X	X	X	X
12-Lead ECG		X						
Urine pregnancy test [7]		X	X			X	X	
Pharmacogenetic sample[8]			←	←	X	→	→	
Medication/Supplies								
Dispense rescue albuterol/slabutamol. Dispense MDI[9]		X	X	X	X	X		
Assess COPD medication compliance[10] during run-in			X					
Dispense eDiary		X						
Assess compliance with eDiary during run-in			X					
Collect rescue albuterol/slabutamol.			X	X	X	X	X	
Collect eDiary						X	X	
Dispense study treatment[11]			X	X	X			
Collect study treatment				X	X	X	X	

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 -7/+2 days prior Visit 1**	**28 -7/+2 days prior Visit 2**	**1 -7/+2 days**	**28 -7/+2 days**	**84 -7/+2 days**	**168 -7/+2 days**		**7±3 days after V5 or EW Visit**
Assess study treatment compliance during treatment[10]				X	X	X	X	
Study sub-set								
Physical activity monitor[12]		X	X	X		X		
Collect Physical activity monitor						X	X	

1. Pre-screen Visit 0 must be completed prior to Screening Visit1. It can be completed 2 weeks prior or on the same day of V1, if no wash out of exclusionary medications is required.
2. Early Withdrawal Visit: Subjects that withdraw should return to the clinic as soon as possible to complete the Early Withdrawal Visit procedures.
3. Spirometry at screening should be performed as described in (Section 7.2.2.1).
4. SAC BDI, SAC TDI, SGRQ-C, CAT questionnaires will be completed at clinic visits and in the eDiary
5. EXACT/ER-S: COPD is completed daily in the eDiary approximately 2 hours before bed-time, starting on Day 1 of the run-in period.
6. For the start date of collecting AEs and SAEs see (Appendix 4)
7. Pregnancy test: for females for child bearing potential only.
8. Pharmacogenetic sample may be drawn at visit 2 or any visit after.
9. Rescue medication use to be recorded in the eDiary daily **and** in some sites in the eDiary and the eMDI
10. Sites are requested to call subjects every 2 weeks to remind them to take study treatment regularly and to record the time of the morning and evening dose in the eDiary.
11. In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2 and within 60 days from V3 respectively.
12. The Actigraph GT9X should be worn for 7 days from Visit 1, for 7 days from Visit 2, for 7 days from Visit 3 and for 7 days prior to Visit 5.

7.2. Screening and Critical Baseline Assessments

7.2.1. Pre-screening Visit

During the Pre-screening Visit, the study designated personnel must provide informed consent to the study participant. Subjects can perform the Pre-screening Visit (Visit 0) up to 2 weeks prior to or on the same day as the Screening Visit (Visit 1) if subject does not take or has not taken any protocol excluded medications.

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. A subject number will be assigned at the time the informed consent form (ICF) is signed. **No study related procedures may be performed until the informed consent form document has been signed by the subject.**

Once the informed consent is signed and if required, changes can be made to the subject's current medication regimen. The investigator should exercise clinical judgment, and is discouraged from changing medications only for the purpose of the clinical study.

During the pre-screening Visit 0, the following information is collected:

- Demographic parameters: year of birth, gender, race and ethnicity
- Concomitant medications review
- COPD exacerbation assessment

From the pre-screening visit onwards concomitant medications, exacerbations and SAEs (considered as related to study participation) must be reported

7.2.2. Critical procedures performed at Screening (Visit 1)

The following critical assessments will be conducted at Visit 1:

- Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening
- Medical history including COPD (including date of diagnosis and COPD type (emphysema and/or chronic bronchitis), smoking history, COPD exacerbation history, smoking status and previous and/or current medical conditions)
- Concomitant medication review (COPD and non COPD medications in the 3 months prior to Screening).
- Height and weight
- 12-Lead ECG. (Note: ECG is performed at screening Visit 1 to test for eligibility only. See Section 7.4.4).

- Urine pregnancy test if applicable
- Train subject on the use of eDiary
- COPD assessment test (CAT) and patient global rating of COPD severity in eDiary
- Pre- and post-albuterol/salbutamol spirometry (reversibility, see Section 7.2.2.1)
- Inclusion/Exclusion criteria assessment
- Review exacerbations, AEs, (SAEs if related to study participation)
- Train subject on the proper use of their COPD medication inhalation devices
- Instruct subject to take their COPD medications as instructed and to enter the time they take their medication in the eDiary
- Dispense rescue medication

Medical history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.1 and Section 5.2.

Assessment of subject's health status will be made at screening using CAT. PRO questionnaires should be completed by subjects before any other assessments at a clinic visit, in the order specified in Section 7.3.1

7.2.2.1. Albuterol/Salbutamol Reversibility Assessment

At Visit 1, both pre- and post-albuterol/salbutamol spirometry will be obtained to determine subject eligibility. Reversibility assessment should be performed as follows:

- Perform pre-bronchodilator spirometry and record FEV_1 and FVC
- Subject to self-administer 4 Inhalations (4X100µg) of albuterol/salbutamol MDI
- Perform post-bronchodilator spirometry and record FEV_1 and FVC approximately 10 to 30 minutes after albuterol/salbutamol administration

  The results of the spirometry must meet the ATS/ERS criteria [Miller, 2005] for the subject to continue in the study.

7.2.3. Critical procedures performed at first treatment Visit (Baseline V2)

- Review and assess compliance with subject's COPD medications during the run-in period
- Review and assess compliance with completing the eDiary during the run-in period
- Review AEs, SAEs and exacerbations

- Urine pregnancy test, if applicable
- Baseline dyspnea Index, BDI, patient global rating of COPD severity, patient global rating of change in COPD, SGRQ-C and CAT questionnaires in eDiary
- Review randomization criteria (Section 5.3)
- Register and randomize subject in RAMOS NG
- Pre-dose spirometry; IC and FEV_1
- Train subject on the proper use of ELLIPTA and DISKUS inhalers
- Dispense study medication
- Dispense rescue medication
- Optional pharmacogentic sample can be collected at V2 or any visit after.

7.3. Efficacy Assessments

7.3.1. HRQoL assessments: Completion of PRO questionnaires in the Electronic Diary

All subjects will be completing PRO questionnaires in the eDiary.

It is requested that questionnaires are completed before any procedures are performed on the subject.

All questionnaires will be completed using the eDiary at clinic and at home. Adequate time should be allowed to complete all items of the questionnaires and the questionnaires must be reviewed by the investigator or designated study staff for completeness and, if necessary, the subject must be encouraged to complete any missing items. Where more than one questionnaire is to be completed at a visit the order should be as follows:

1. Baseline dyspnea index (Visit 2) then Transient dyspnea index at subsequent visits
2. Patient global rating of COPD severity and global rating of change in COPD
3. St George's respiratory questionnaire
4. COPD Assessment Test

Instructions for completing the questionnaires can be found in the **SRM.**

7.3.1.1. Self Administered Computerised Baseline Dyspnea Index/Transitional Dyspnea Index (SAC BDI/TDI)

The BDI is used to measure the severity of dyspnea in patients at baseline. The TDI measures changes in the patient's dyspnea from baseline. The self-administered computerized version of the BDI/TDI (SAC BDI/TDI)[Mahler, 2004] is used to measure severity of dyspnea in patients at baseline (SAC BDI) on Day 1 (Visit 2) of treatment and change from the baseline (SAC TDI) at Week 4, 12 and 24 (Visits 3, 4 and 5). The

scores in both indexes depend on ratings for three different categories: functional impairment; magnitude of task, and magnitude of effort. SAC BDI/TDI should be completed before performing spirometry.

The SAC BDI/TDI was developed to address issues of potential bias in the interviewer administered (original) BDI/TDI [Mahler, 1984]. The SAC BDI/TDI provides a standardized approach to the measurement of dyspnea, equivalent to the original BDI/TDI with advantages over the interviewer method for grading dyspnea in patients with COPD by standardizing the process for each patient and eliminating individual judgment required by the interviewers when completing the original BDI/TDI. This also removes the need for the same investigator to conduct all interviews with a subject based on the patient's responses. SAC TDI provides a continuous measure of change in dyspnea using a visual analogue scale to record responses.

Details for the completion of the SAC BDI/TDI are provided in the SRM.

7.3.1.2. SGRQ-C

The St George's Respiratory Questionnaire-Chronic Obstructive Pulmonary Disease specific (SGRQ-C) will be completed by subjects at Randomisation (V2, Day 1), at Week 4, 12 and 24 or at the Early Withdrawal Visit (where applicable).

The SGRQ-C [Meguro, 2007] is a well established, disease-specific questionnaire. It was 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 scores equivalent to the SGRQ instrument [Meguro, 2007].

7.3.1.3. COPD Assessment Test (CAT)

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.

The CAT will be completed in the eDiary by subjects at Screening Visit 1 and Randomisation Visit 2 to assess their eligibility to enter the study. CAT is also completed at Weeks 4, 12 and 24. Additional instructions for completion of the CAT are provided in the **SRM.**

7.3.1.4. EXACT and the Evaluating Respiratory Symptoms- COPD (E-RS: COPD)

EXACT-PRO is a 14 item patient reported outcome instrument designed to capture information on the occurrence, frequency, severity, and duration of exacerbations of disease in patients with COPD [Leidy, 2011]. EXACT captures information on the severity of the respiratory and systemic manifestations of a COPD exacerbation as reported by the patient. The instrument is to be completed daily (typically 2 hrs before bedtime) using the electronic diary. The daily recording of information allows an assessment of the underlying day to day variability of a patient's symptoms and facilitates the detection of symptom worsening indicative of a COPD exacerbation. The total score for EXACT ranges from 0-100. The entire instrument is intended to be completed in about 3 minutes or less (typically the time required for completion decreases as the patient becomes more familiar with the tool and the electronic diary).

The E-RS: COPD consists of 11 items from the 14 item EXACT instrument [Leidy, 2014]. E-RS: COPD is intended to capture information related to the respiratory symptoms of COPD, i.e. breathlessness, cough, sputum production, chest congestion and chest tightness. The E-RS: COPD has a scoring range of 0-40 higher scores indicate more severe symptoms.

Three subscales of the E-RS are used to describe different symptoms; dyspnea, cough and sputum and chest symptoms.

The EXACT questionnaire will be completed by subjects in the eDiary, at home every night throughout the entire study, starting from Screening V1

7.3.1.5. Subject Global Rating of COPD Severity and Global Rating of Change in COPD

Subjects will complete the Global Rating of COPD Severity at Randomization Visit 2 and visits 3, 4 and 5 or Early Withdrawal Visit. This single global question will ask subjects to rate their severity of COPD on a four point scale (mild, moderate, severe, and very severe).

This question should be used immediately before the patient completes other visit specific questionnaires but after completion of SAC TDI questionnaire.

Subjects will also complete a Global Rating of Change in COPD (overall disease) question at Visits 3, 4 and 5 or Early Withdrawal Visit. Response options will be on a 7 point Likert scale ranging from much better to much worse. Completing the question at each Visit allows for early detection of response as well as continued response.

7.3.2. 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 standardized spirometry equipment provided by an external vendor.

All subjects will have spirometry performed at Screening to assess eligibility (see Section 7.2.2.1) and at Visits 2, 3, 4 and 5 during the treatment period.

For FEV_1 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 (i.e. a plateau in the volume time curve) and be free from artifacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons [Miller, 2005].

The largest FEV_1 and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort.

Spirometry for FEV_1 and FVC assessments that is not obtained as follows will be considered a protocol deviation:

- Started between 6:00AM and 11:00AM.
- After withholding albuterol/salbutamol (all visits) for ≥4 hours
- At Screening Visit 1, after wash out of medications as specified in the exclusion criteria in Section 5.2 (Concomitant Medications).
- At Screening Visit 1, before the morning dose of usual COPD medications
- At Visit 2 after discontinuing inhaled COPD medications and prior the first dose of study treatment
- At Visit 3, 4 and 5 after withholding the morning dose of study treatment.
- Pre dose assessment performed prior dosing.

Subjects should refrain from smoking for 1 hour prior to each pulmonary function test.

Trough FEV_1 measurements for UMC/VI or UMEC on Weeks 4, 12 and 24 (Visits 3, 4 and 5) should be performed 23 hours and 24 hours after the previous day's dose of study medication recorded in the eDiary. This will also provide trough FEV_1 measurements for the evening dose of salmeterol.

7.3.3. Inspiratory capacity (IC)

Inspiratory capacity (IC) is the volume of gas that can be taken into the lungs in a normal and full inhalation. Starting from the resting inspiratory position it is equal to the tidal volume plus the inspiratory reserve volume. IC has been widely used to assess static and dynamic hyperinflation in patients with COPD.

IC will be measured by spirometry **prior** to forced manoeuvres pre-dose at Visits 2 (30 and 5 min prior to dosing) and at trough at Visits 3, 4, and 5 (23 and 24 hrs post dosing on the previous day). For IC determination the average of at least three acceptable manoeuvres should be recorded. Subjects should be tested while sitting, relaxed and wearing a nose clip. They should be asked to breathe regularly for several breaths until the end-expiratory lung volume is stable (this usually requires at least three tidal manoeuvres) then urged to take a deep breath to Total Lung Capacity (TLC) with no hesitation.

Spirometry for IC determination done in conjunction with FEV_1 and FVC assessments that is not obtained as follows will be considered a protocol deviation:

- Started between 6:00AM and 11:00AM.
- After withholding albuterol/salbutamol (all visits) ≥4 hours
- At Visit 2 after discontinuation of run-in medication
- At Visit 3, 4 and 5 after withholding the morning dose of study drug

7.3.4. COPD Exacerbation

A mild exacerbation is defined as worsening of symptoms that require no treatment with antibiotics or steroids, and is self managed by the patient by an increase of inhaled rescue medications. A moderate COPD exacerbation is defined as worsening symptoms of COPD that require treatment with oral/systemic corticosteroids and/or antibiotics. A severe exacerbation is defined as worsening symptoms of COPD that require in-patient hospitalization or emergency room for longer than 24 hrs.

If a subject experiences a mild, moderate or severe COPD exacerbation, the COPD exacerbation page of the eCRF should be completed. COPD exacerbations should not be recorded as an AE, unless they meet the definition of a SAE. Details of COPD exacerbation identification, categorization and treatment guidelines are described in Appendix 5.

Subjects who experience a mild exacerbation during the run-in period will not be withdrawn from the study. However, Subjects who experience moderate or severe exacerbation during the run-in period will be withdrawn from the study and will not be allowed to be re-screened.

Subjects who experience a mild, moderate or severe exacerbation during the treatment period, will **not** be withdrawn from the study unless the investigator or GSK medical monitor think it is best for the patient to withdraw from the study.

Signs and symptoms of COPD included on the electronic diary cards will not be considered AEs and will not be recorded in the eCRF.

The time period for collection of COPD exacerbations will be from the Pre-Screening (Visit 0) until completion of the follow-up contact. If a subject experiences a COPD exacerbation from the time the ICF is signed until randomization, summary information (yes/no status question) will be collected in the eCRF. COPD exacerbations after randomization through follow-up will be recorded on the COPD exacerbation page of the eCRF.

7.3.5. Clinically important deterioration (CID)

Clinically important deterioration (CID) is a composite endpoint defined as:

- A decrease of ≥ 100 mL from baseline in trough FEV_1

- A deterioration in HRQoL defined as ≥ 4 units increase from baseline in SGRQ
- The occurrence of an on-treatment moderate/severe COPD exacerbation

In addition, this study will explore CAT and TDI PROs as part of the composite endpoint.

7.3.6. Rescue albuterl/salbutamol use

Subjects will record the number of daily albuterol/salbutemol puffs they use in the eDiary. In addition, in some countries and selected sites the number of puffs will be collected through the eMDI device (Section 6.2)

7.3.7. Physical activity monitor (study subset)

Physical activity limitation is a common feature of COPD and its measures are highly related to the degree of disease severity [Watz, 2009].

Reduced physical activity levels in COPD is associated with increased morbidity and mortality, sustained disability, depression, and social and physical isolation [Shu-Yi, 2014; Gimeno, 2014]

Improved activity has been identified as an important factor that may modify morbidity and mortality in COPD [Moy, 2012].

The Actigraph GT9X physical activity monitor will be used to measure levels of activity. The activity monitor will be worn by up to approximately 150 subjects per treatment arm for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3 (Week 4) and for 7 days prior to Week 24 (Visit 5).

There will be 4 assessment periods, including a screening assessment in order to provide a reliable estimate of habitual physical activity. Each subject will be given an activity monitor and instruction leaflet at the start of each assessment period. Further details of distribution, operation and retrieval of the monitors will be provided in the **SRM**.

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1)

Safety endpoint includes:

- Incidence of adverse events

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

The definitions of an AE or SAE can be found in Appendix 4.

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

7.4.1.1. 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 7.4.1.3), at the timepoints 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 CRF.
- 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 12.4.4 to Section 12.4.6)

7.4.1.2. 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?

7.4.1.3. 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).

7.4.1.4. Pneumonia Events

Investigators will be required to fill out a pneumonia event specific eCRF within one week of when the pneumonia AE/SAE(s) is first reported.

7.4.1.5. Cardiovascular and Death Events

For any cardiovascular events detailed in (Section 12.4.3) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs 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 CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF 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.

7.4.1.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following disease related events (DREs) are common in subjects with COPD and can be serious/life threatening:

- COPD exacerbation

COPD exacerbations are associated with the disease to be studied and will not be recorded as AEs unless the exacerbation meets the definition of a 'serious' AE. Exacerbations that meet the definition of 'serious' AEs will be recorded on the appropriate eCRF section and should be reported to GSK for all subjects regardless of whether or not they are randomized to study medication. Signs and symptoms of COPD included on the electronic diary will not be considered AEs and will not be recorded in the eCRF

7.4.1.7. 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.

7.4.1.8. Additional Adverse Event (AE) Reporting Requirements for Canadian investigators

Health Canada requires pharmaceutical manufacturers to expeditiously report domestic cases of unusual failure in efficacy (UFIE) for new drugs to the Marketed Health Products Directorate (MHPD) within 15 days of first notification. This regulation applies to marketed drugs, and used as directed per the Canadian prescribing information, including those drugs used in Phase IV (non CTA filed) clinical trials.

Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product. **For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an adverse event),**

In order for GSK to comply this Canadian regulatory requirement, Canadian investigators are required to collect, record and report lack of efficacy events as per the table in Appendix 4 Section12.4.1.

All paper forms are required to be faxed to GSK Canada's Drug Safety department at PP [redacted] within 24 hrs of first awareness.

7.4.2. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of Screening and until the follow-up contact.
- 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 7.

7.4.3. Medical Device Incidents (Including Malfunctions)

Procedures for documenting medical device incidents are provided in Appendix 6.

7.4.4. Electrocardiogram (ECG)

A Single 12-lead ECG will be obtained at Screening using an ECG machine provided by the investigational site that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

The 12-lead ECG measurement and rhythm strip (10 seconds) will be obtained before spirometry testing. ECG measurement should be obtained after subjects have rested for approximately 5 minutes then the subjects should be placed in the supine position for the ECG measurements. An ECG is only required at Screening Visit 1 for eligibility assessment only.

The investigator, a designated sub-investigator, or other appropriately trained site personnel will be responsible for performing and interpreting the 12-lead ECG at Screening Visit 1. The investigator must provide his/her dated signature on the original paper tracing, attesting to the authenticity of the ECG machine interpretation.

7.5. Genetics

Information regarding genetic research is included in Appendix 3

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, 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.
- CRFs (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 purpose of this study is to demonstrate improvements in lung function for subjects treated with UMEC/VI compared with UMEC for 24 weeks.

The primary endpoint is change from baseline in trough FEV_1 at Week 24.
The null hypothesis is no difference between treatment groups (H0: $\mu T - \mu S = 0$), with the alternative hypothesis that there is a difference between treatment groups (H1: $\mu T - \mu S \neq 0$), where μT is the mean change from baseline for UMEC/VI and μS is the mean change from baseline for UMEC.

9.2. Sample Size Considerations

The primary endpoint is change from baseline in trough FEV_1 at Week 24. As an important aim of the study is to compare UMEC/VI, UMEC and salmeterol with respect to HRQoL the sample size has been calculated to provide sufficient power for the comparison of the primary and secondary endpoint TDI, at Week 24.

The sample size calculations use a two-sided 5% significance level and an estimate of between subject standard deviation for TDI of 2.94 units. The estimate of SD is based on DB2113373 [Donohue, 2013], a study which consisted of treatment arms of UMEC/VI 62.5/25, UMEC 62.5 VI (Vilanterol) 25mcg and placebo and is the value at Day 168 in a subgroup of subjects who were ICS free at screening. Based on these data, 727 evaluable subjects per treatment arm will be required to provide 90% power to detect a statistically significant difference if the true difference is 0.5 units, ½ the MCID, between UMEC/VI and UMEC. The smallest observed effect predicted to result in a statistically significant difference between treatment groups is 0.31 units.

With this number of evaluable subjects per arm, the study will have >99% power assuming a true treatment difference of 80mL between UMEC/VI and UMEC for trough FEV1 at 24 weeks at the two-sided 5% significance level. This calculation uses a SD for trough FEV1 of 240mL, based on prior results for trials comparing dual bronchodilators versus single bronchodilators (Donohue, 2013; Bateman, 2013). The smallest observed effect predicted to result in a statistically significant difference between treatment groups is 25mL.

In order to account a for a 10% withdrawal rate**,** approximately 808 subjects per treatment arm will be randomised.

9.2.1. Sample Size Assumptions

9.2.2. Sample Size Sensitivity

The assumption of a SD of 2.94 units for the TDI total score is based on estimates from previous studies. The following table presents the power achieved with the proposed sample size of 727 randomised subjects per arm, should the assumption around the SD of the data change.

The actual assumptions used in the sample size calculation are shaded.

Endpoint	Between subject SD	Treatment Difference	Power
TDI	2.54	0.5	96%
	2.74	0.5	94%
	2.94	0.5	90%
	3.14	0.5	86%
	3.34	0.5	81%

9.2.3. Sample Size Re-estimation or Adjustment

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

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	• 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.	• Subject Disposition • Reasons for withdrawal prior to randomisation • Inclusion, exclusion and randomisation criteria deviations • SAEs for non-randomised subjects
Intent-to-treat (ITT)	• All randomized subjects, excluding those who were randomized in error and received at least one dose of study medication. 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 randomization number will be considered to have been randomized. • Displays will be based on the treatment to which the subject was randomized.	• Study Population • Efficacy • Safety
Intent-to-treat ICS free (ITT ICS free)	• All subjects in the ITT Population who have not received ICS.	• Study Population • Efficacy • Safety

9.3.2. Interim Analysis

No interim analysis is planned for the study.

9.4. Key Elements of Analysis Plan

Treatment Comparisons

The primary treatment comparison of UMEC/VI with UMEC will be performed on the ITT population.

The other treatment comparisons of UMEC/VI and UMEC with Salmeterol will be performed on the ITT population and ITT ICS free population.

9.4.1. Primary Analyses

The treatment comparison of primary interest will be UMEC/VI versus UMEC for the primary endpoint of change from baseline in trough FEV_1 at Week 24. The primary analyses will be performed using a mixed model repeated measures (MMRM) analysis and will be based on a two-sided hypothesis testing approach on the ITT Population.

In order to account for multiplicity across treatment comparisons and endpoints, a step-down closed testing procedure will be applied whereby inference for secondary and other endpoints or treatment comparisons are dependent upon statistical significance having been achieved for the primary comparison. If the primary comparison is significant i.e. the associated p-value for UMEC/VI versus UMEC for change from baseline in trough FEV1 at Week 24 is below 0.05, this will allow inference of treatment comparisons (UMEC/VI versus UMEC on all other endpoints, and UMEC/VI versus Salmeterol and UMEC versus Salmeterol on all endpoints including the primary endpoint), which will be declared statistically significant if the associated p-value is below 0.05.

There will be 2 analyses one for one for the German Federal Joint Committee (G-BA) and one for the rest of the world (ROW).

The step-down closed testing procedure only applies to the ROW. For the G-BA statistical inference for secondary and other endpoints or treatment comparisons will not be conditional on achieving statistical significance of the primary comparison.

The primary endpoint of mean change from baseline in trough FEV1 at the end of Week 24 and secondary endpoint change from baseline in TDI score at Week 24 will both be analysed using MMRM analysis. The MMRM analysis for change from baseline in trough FEV1 and TDI will include measurements at Treatment Weeks 4, 12 and 24. Treatment group (a categorical variable) will be fitted as the explanatory variable with appropriate pre-defined variables, stratum (number of bronchodilators per day during run-in) and baseline values, fitted as covariates. Visit (nominal) will be fitted as a categorical variable and visit-by-baseline and visit-by-treatment interaction terms will be included to allow treatment effects to be estimated at each visit separately. The variance covariance matrix will be assumed to be unstructured (based on previous experience no issues are expected with fitting models with this matrix structure).

While missing data are not explicitly imputed in the primary MMRM analyses, there is an underlying assumption that the data are missing at random.

The estimated treatment differences between UMEC/VI versus UMEC for each endpoint will be presented with the 95% confidence intervals for the difference and the p-value.

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

9.4.2. Other Analyses

The MMRM analysis will be repeated for the ITT ICS free population. Estimated differences between UMEC/VI or UMEC and Salmeterol will be presented together with 95% confidence intervals (CIs) for the difference and p-values.

Secondary and other efficacy endpoints and treatment comparisons will be adjusted for multiplicity as per Section 9.4.1.

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

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 eCRF 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 randomization 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
CAT	COPD Assessment Test
CI	Confidence Intervals
CID	Clinically important deterioration
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine phosphokinase
CRF	Case Report Form
CV	Cardiovascular
DPI	Dry Powder Inhaler
DRE	Disease Related Event
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
eMDI	Electronic Metered Dose Inhaler
E-RS	Evaluating Respiratory Symptoms- COPD Tool
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
IB	Investigator Brochure
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IP	Investigational product
INR	International normalized ratio
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

mcg	Microgram
MCID	Minimal Clinically Important Difference
MDI	Metered Dose Inhaler
mL	Milliliter
mMRC	Modified Medical Research Council
MMRM	Mixed Models Repeated Measures
MSDS	Material Safety Data Sheet
NYHA	New York Heart Association
OTC	Over the Counter
PGx	Pharmacogenetic
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PP	Per Protocol
prn	As required
QTc	QT interval corrected for heart rate
RAP	Reporting and Analysis Plan
SABA	Short Acting Beta-Agonist
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SRT	Safety Review Team
TDI	Transition Dyspnea Index
RAMOS NG	Randomization and medication ordering system new generation
ULN	Upper Limit of Normal
UMEC	Umeclidinium (GSK573719)
UMEC/VI	Umeclidinium & Vilanterol as a fixed dose combination
VI	Vilanterol Trifenate

Trademark Information

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

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

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 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**
• 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 SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve , stabilize, or return to within normal ranges. baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment. Permanently discontinue stud**y treatment and may continu**e subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained within a week after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal

Liver Chemistry Stopping Criteria - Liver Stopping Event	
liver event follow up assessments within 24 hrs • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within normal ranges. • A specialist or hepatology consultation is recommended **For All other criteria:** • 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 normal ranges.	remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • 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.

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 ≥ 3xULN **and** bilirubin ≥ 2xULN. 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 ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **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 SRM.

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 etiology 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 any concomitant medicines;
- COPD susceptibility, severity, and progression of 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.

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 the baseline visit, after the subject has been randomized and 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 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.

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. For a marketed medicinal product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without associated signs or symptoms or clinical sequelae).
- 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 <u>meeting</u> 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" will be reported as an AE or SAE as per the table below

Adverse Event criteria	**Electronic case record form (eCRF) only**	**Paper form only**	**Electronic case record form (eCRF) + Paper form**
Non serious	Non drug related lack of efficacy reports with associated signs or symptoms or clinical	Drug related lack of efficacy reports without associated signs or symptoms or	Drug related lack of efficacy with associated signs or symptoms or

	sequelae	clinical sequelae.	clinical sequelae
Serious	Non drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae	Drug related lack of efficacy reports without associated signs or symptoms or clinical sequelae.	Drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae

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., hospitalization 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 hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are

AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in disability/incapacity

NOTE:

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- 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 hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** 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.

12.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias

- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial 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 electronic CRF and/or paper form as applicable. 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
- For lack of efficacy reports, the paper form will be used to submit to GSK as per the table in Section 12.4.1 above. 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
- 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 by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: COPD Exacerbation Identification, Categorization and Treatment Guidelines

12.5.1. 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 usage in their daily eDiary
- 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

12.5.2. COPD Exacerbation Severity

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

> **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 hospitalization or 24 hrs in the emergency room.

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.

12.5.3. 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 outlined 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 IP as these additional medications may increase the risk of overdose. If necessary the PI or other health care personnel may stop the subject's IP temporarily in order to treat the COPD exacerbation.

12.5.4. 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 ≤ 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

12.5.5. 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 not exceed 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

12.5.6. 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 12.5.1.

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.

12.5.7. 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.

12.5.8. 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.

12.6. Appendix 6: Definition of and Procedures for Documenting Medical Device Incidents

12.6.1. Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.2 for the list of GSK medical devices).

Medical Device Incident Definition:

- Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other persons or to a serious deterioration in their state of health.
- Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- an **incident** associated with a device happened and
- the **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.
- A serious deterioration in state of health can include:
- life-threatening illness
- permanent impairment of body function or permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent one of the above
- fetal distress, fetal death or any congenital abnormality or birth defects

Examples of incidents

- a patient, user, care giver or professional is injured as a result of a medical device failure or its misuse
- a patient's treatment is interrupted or compromised by a medical device failure
- misdiagnosis due to medical device failure leads to inappropriate treatment
- a patient's health deteriorates due to medical device failure

12.6.2. Documenting Medical Device Incidents

Medical Device Incident Documenting:
• Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 4. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK. • It is very important that the investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the design to prevent recurrence.

12.7. Appendix 7: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

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

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization 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, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.7.2. 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 fetal 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. 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 be withdrawn from the study

12.8. Appendix 8: Country Specific Requirements

No country-specific requirements exist.

12.9. Appendix 9: protocol changes

Revision History

2016N277425_00	2016-SEP-13	Original
2016N277425_01	2017-FEB-07	Amendment No. 1
2016N277425_02	2017-FEB-21	Amendment No. 2 Canada only

Protocol Amendment 1

Scope:

This amendment applies to all sites

Protocol Changes for Amendment No.1 are summarised below.

Strike through text refers to deleted text and underlined refers to added text.

Protocol Changes:

Title
Rationale for change: Correct a typographical error in the title: Umeclidi~~m~~ium to Umeclidinium

Regulatory Agency Identifying Number(s):
Rationale for change: To correct a typographical error of the EudraCT no. and add an IND no.
Revised text:-EudraCT no ~~2016-002513-226,~~ 2016-002513-22 , IND no. 104479

Section 1
Overall Design
Rationale for change: To Correct a typographical error in the last paragraph.
Revised text: ~~Salmeterol~~, salbutamol
"This is a multi-centre, randomized, double blind, double-dummy, 3-arm parallel group study. Eligible subjects will be stratified based on long-acting bronchodilator usage during the run-in (none, one or 2 long-acting bronchodilators per day) and randomized in a ratio of 1:1:1 to UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA inhaler, or UMEC (62.5 mcg once daily) administered via the ELLIPTA or salmeterol (50 mcg BID) administered via the DISKUS.

There will be a total of 5 clinic visits and one follow-up phone call (Visit 6). The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) if subject does not take or has not taken any excluded protocol medications, but must be completed prior to initiating any Visit 1 procedures.

Subjects, who meet all the eligibility criteria at Screening, will enter a run-in period for 4 weeks in order to continue to assess the subject's eligibility for the study. During the run-in period subjects will continue with their inhaled COPD medications (excluding ICS and any exclusionary medications). In addition, subjects will be provided with short acting albuterol/~~salmeterol~~ salbutamol to be used on as needed basis for relief of COPD symptoms (rescue medication) throughout the study".

Section 4.4 Design justification: To be consistent with Section 7.3.1.5 and Section 7.1 the wording has been updated.
Rationale for change: Ensure consistency with Section 7.3.1.5 and Section 7.1 the wording has been changed in paragraph 5.
Revised text: "Other endpoints such SAC TDI, E-RS, SGRQ-C, CAT, Subject Global Rating of COPD Severity and ~~Change in~~ Global Rating ~~impression~~ of Change in COPD ~~disease severity~~ are captured to allow responder analyses and to provide comparative data on PROs between the treatment groups".

Section 7.1 Time and Event table
Rationale for change; to:
Correct an un-intentional deletion of the ("x") in some cells and confirm that concomitant medications should be reviewed at every clinic visit.
Increase the visit window from ~~± 2~~ days to -7/+2
Ensure consistency of wording between Section 7.2 and Table 7.1. "~~Written~~" was deleted
Include height and weight at Screening and correct errors in foot note no.11
"In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2 and within 60 ~~and 90~~ days from V3 ~~and V4~~ respectively"

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 ~~±2~~ -7/+2 days prior Visit 1**	**28 ~~± 2~~ -7/+2 days prior Visit 2**	**1~~± 2~~ -7/+2 days**	**28 ~~±2~~ -7/+2 days**	**84 ± 2 days**	**168 ~~±2~~ -7/+2 days**		**7~~± 2~~ 3 days after V5 or EW Visit**
Screen/Baseline								
~~Written~~ Informed consent	X							
Demography	X							
Medical/COPD history		X						
Smoking history/status		X						
Smoking cessation counselling		X						
Concomitant medication assessment	X	X	X	X	X	X	X	X
Height and weight		X						
Cardiovascular History/family history of premature CV disease])		X						
Screening spirometry (including post bronchodilator testing)[3]		X						
CAT questionnaire		X	X					
Verify Inclusion/Exclusion Criteria		X						
Training on use of inhalers		X	X					
Training on use of eDiary and eMDI		X	X					
Verify randomization Criteria			X					
Register Visit in InForm	X	X	X	X	X	X	X	X
Register Visit in RAMOS NG	X	X	X	X	X	X	X	X

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 ±2 -7/+2 days prior Visit 1**	**28 ± 2 -7/+2 days prior Visit 2**	**1± 2 -7/+2 days**	**28 ±2 -7/+2 days**	**84 ± 2 days**	**168 ±2 -7/+2 days**		**7± 2 3 days after V5 or EW Visit**
Efficacy/HRQoL assessments								
Spirometry, including pre-dose FEV_1, trough FEV_1 and inspiratory capacity			X	X	X	X		
SAC BDI questionnaire [4]			X					
SAC TDI questionnaire [4]				X	X	X		
SGRQ-C questionnaire [4]			X	X	X	X		
CAT questionnaire [4]		X	X	X	X	X		
EXACT/ER-S: COPD [5]		→	→	→	→	→		
Patient Global Rating of COPD severity			X	X	X	X		
Patient Global Rating of Change in COPD				X	X	X		
Safety assessments								
Adverse events/Serious adverse events [6]	X	X	X	X	X	X	X	X
COPD exacerbation assessment	X	X	X	X	X	X	X	X
12-Lead ECG		X						
Urine pregnancy test [7]		X	X			X	X	
Pharmacogenetic sample[8]			←	X	→			
Medication/Supplies								
Dispense rescue albuterol/slabutamol. Dispense MDI[9]		X	X	X	X	X		
Assess COPD medication compliance[10] during run-in			X					
Dispense eDiary		X						
Assess compliance with eDiary during run-in			X					
Collect rescue albuterol/slabutamol.			X	X	X	X	X	
Collect eDiary						X	X	
Dispense study treatment[11]			X	X	X			

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 ~~±2~~ -7/+2 days prior Visit 1**	**28 ~~± 2~~ -7/+2 days prior Visit 2**	**1~~± 2~~ -7/+2 days**	**28 ~~±2~~ -7/+2 days**	**84 ± 2 days**	**168 ~~±2~~ -7/+2 days**		**7~~± 2~~ 3 days after V5 or EW Visit**
Collect study treatment				X	X	X	X	
Assess study treatment compliance during treatment[10]				X	X	X	X	
Study sub-set								
Physical activity monitor[12]		X	X	X		X		
Collect Physical activity monitor						X	X	

1. Pre-screen Visit 0 must be completed prior to Screening Visit1. It can be completed 2 weeks prior or on the same day of V1, if no wash out of exclusionary medications is required.
2. Early Withdrawal Visit: Subjects that withdraw should return to the clinic as soon as possible to complete the Early Withdrawal Visit procedures.
3. Spirometry at screening should be performed as described in (Section 7.2.2.1).
4. SAC BDI, SAC TDI, SGRQ-C, CAT questionnaires will be completed at clinic visits and in the eDiary
5. EXACT/ER-S: COPD is completed daily in the eDiary approximately 2 hours before bed-time, starting on Day 1 of the run-in period.
6. For the start date of collecting AEs and SAEs see (Appendix 4)
7. Pregnancy test: for females for child bearing potential only.
8. Pharmacogenetic sample may be drawn at visit 2 or any visit after.
9. Rescue medication use to be recorded in the eDiary daily **and** in some sites in the eDiary and the eMDI
10. Sites are requested to call subjects every 2 weeks to remind them to take study treatment regularly and to record the time of the morning and evening dose in the eDiary.
11. In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2 and within 60 ~~and 90~~ days from V3 ~~and V4~~ respectively.
12. The Actigraph GT9X should be worn for 7 days from Visit 1, for 7 days from Visit 2, for 7 days from Visit 3 and for 7 days prior to Visit 5.

Section 7.2.2 Critical procedures performed at Screening (Visit 1)
Rationale for change: To clarify that height and weight are collected at V1
Revised text: "Height and weight"

Section 7.3.2 Spirometry
Rationale for change: To further clarify that spirometry at Screening Visit 1 should be performed before subject inhales their usual morning COPD medication(s) a bullet point was added. "At Screening Visit 1, before the morning dose of usual COPD medications"
Revised text:
"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 standardized spirometry equipment provided by an external vendor.

All subjects will have spirometry performed at Screening to assess eligibility (see Section 7.2.2.1) and at Visits 2, 3, 4 and 5 during the treatment period.

For FEV_1 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 (i.e. a plateau in the volume time curve) and be free from artifacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons [Miller, 2005].

The largest FEV_1 and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort.

Spirometry for FEV_1 and FVC assessments that is not obtained as follows will be considered a protocol deviation:

- Started between 6:00AM and 11:00AM.
- After withholding albuterol/salbutamol (all visits) for ≥4 hours
- At Screening Visit 1, after wash out of medications as specified in the exclusion criteria in Section 5.2 (Concomitant Medications).
- At Screening Visit 1, before the morning dose of usual COPD medications
- At Visit 2 after discontinuing inhaled COPD medications and prior the first dose of study treatment
- At Visit 3, 4 and 5 after withholding the morning dose of study treatment.
- Pre dose assessment performed prior dosing.

Subjects should refrain from smoking for 1 hour prior to each pulmonary function test.

Trough FEV_1 measurements for UMC/VI or UMEC on Weeks 4, 12 and 24 (Visits 3, 4 and 5) should be performed 23 hours and 24 hours after the previous day's dose of study medication recorded in the eDiary. This will also provide trough FEV_1 measurements for the evening dose of salmeterol".

8. Physical activity monitor (study subset)

Rationale for changes: Ensure consistency of the wording between Section 1 and Section 4.1 "overall design" and Section 7.3.7.
per treatment arm added to paragraph 4.
Revised Text:
Physical activity monitor (study subset)
"Physical activity limitation is a common feature of COPD and its measures are highly related to the degree of disease severity [Watz, 2009].
Reduced physical activity levels in COPD is associated with increased morbidity and mortality, sustained disability, depression, and social and physical isolation [Shu-Yi, 2014; Gimeno, 2014]

Improved activity has been identified as an important factor that may modify morbidity and mortality in COPD [Moy, 2012].

The Actigraph GT9X physical activity monitor will be used to measure levels of activity. The activity monitor will be worn by up to approximately 150 subjects per treatment arm for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3 (Week 4) and for 7 days prior to Week 24 (Visit 5).

There will be 4 assessment periods, including a screening assessment in order to provide a reliable estimate of habitual physical activity. Each subject will be given an activity monitor and instruction leaflet at the start of each assessment period. Further details of distribution, operation and retrieval of the monitors will be provided in the **SRM"**.

Country-specific Protocol Amendment 2 for Canada

Amendment 02 applies to Canada only. The purpose of Amendment 2 is to comply with Health Canada guidelines. They sate that all events associated with lack of efficacy of marketed investigational products must be documented and reported.

Strike through text refers to deleted text and underlined refers to added text.

Section 7.4.1 Adverse Events (AE) and serious Adverse Events (SAEs)
Rationale for change: A new Section added to include information related to documenting events related to lack of efficacy.
Revised text:
"7.4.1.8 Additional Adverse Event (AE) Reporting Requirements for Canadian investigators
Health Canada requires pharmaceutical manufacturers to expeditiously report domestic cases of unusual failure in efficacy (UFIE) for new drugs to the Marketed Health Products Directorate (MHPD) within 15 days of first notification. This regulation applies to marketed drugs, and used as directed per the Canadian prescribing information, including those drugs used in Phase IV (non CTA filed) clinical trials.

Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore

be any unfavourable and unintended sign (including an abnormal laboratory finding) symptom or disease (new or exacerbated) temporally associated with the use of a Medicinal Product**. For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an adverse event),**

In order for GSK to comply this Canadian regulatory requirement, Canadian investigators are required to collect, record and report lack of efficacy events as per the table in Appendix 4 Section 12.4.1".

All paper forms are required to be faxed to GSK Canada's Drug Safety department at PP within 24 hrs of first awareness.

Appendix 4, Section 12.4.1
Rationale for change: To add a small table about reporting of AEs.
Revised text. The table below was added.

Adverse Event criteria	**Electronic case record form (eCRF) only**	**Paper form only**	**Electronic case record form (eCRF) + Paper form**
Non serious	Non drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae	Drug related lack of efficacy reports without associated signs or symptoms or clinical sequelae.	Drug related lack of efficacy with associated signs or symptoms or clinical sequelae
Serious	Non drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae	Drug related lack of efficacy reports without associated signs or symptoms or clinical sequelae.	Drug related lack of efficacy reports with associated signs or symptoms or clinical sequelae

Appendix 4, Section 12.4.4, second bullet point
Revised text:
The investigator will then record all relevant information regarding an AE/SAE in the electronic CRF "and/or paper form as applicable". Added

Section 12.4.6, second bullet point
Revised text:
"For lack of efficacy reports the paper form will be used to submit to GSK as per the table in Section 12.4.1 above". Added

TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A 24-week treatment, multi-center, randomized, double-blind, double-dummy, parallel group study to compare Umeclidinium/Vilanterol, Umeclidinium, and Salmeterol in subjects with chronic obstructive pulmonary disease (COPD)

Compound Number: GSK2592356

Development Phase: IV

Effective Date: 07-FEB-2017

Protocol Amendment Number: 01

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N277425_00	2016-SEP-13	Original
2016N277425_01	2017-FEB-07	Amendment No. 1

This protocol amendment was created to make the following changes:

Regulatory Agency Identifying Number(s): A typographical error in the EudraCT no. corrected. IND no. added

Section 4.1 and Section 4.4: Typographical errors and inconsistencies corrected

Inconsistencies between Section 4.4, Section 7.3.1.5 and Section 7.1 revised

Section 7.1 Time and event table:
Un-intentional deletion of the ("x") were added to confirm that concomitant medications should be reviewed at every clinic visit was corrected.
Increased the visit window
Typographical error and inconsistencies corrected as described in Appendix 9, Section 12.9.

Section 7.2.2 Critical procedures performed at Screening (Visit 1): To clarify that height and weight are collected at V1 **"**Height and weight" added

Section 7.3.2 Spirometry: "At Screening, before the morning dose of usual COPD medication(s)" added.

Section 7.3.7: Physical activity monitor (study subset)
Inconsistency between Section 1, Section 4.1 and Section 7.3.7 revised

SPONSOR SIGNATORY

PPD

7 Feb 2017

David Lipson, MD Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	Telephone: PPD PPD	Cell: PPD	Fax: PPD	GlaxoSmithKline Stockley Park West, 1-3 Ironbridge Road, Heathrow, Uxbridge, Middlesex, UB11 1BT, United Kingdom
Secondary Medical Monitor		PPD MD Telphone: PPD PPD	Cell:	Fax:	GlaxoSmithKline Stockley Park West, 1-3 Ironbridge Road, Heathrow, Uxbridge, Middlesex, UB11 1BT, United Kingdom
SAE contact information		Telephone: PPD PPD	Cell: PPD	Fax: PPD	GlaxoSmithKline Stockley Park West, 1-3 Ironbridge Road, Heathrow, Uxbridge, Middlesex, UB11 1BT, United Kingdom

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact

person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): IND no. 106616 and 104479, and EudraCT no. 2016-002513-22

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 201749

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

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

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

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 201749

Rationale

The primary purpose of this study is to demonstrate improvements in lung function in subjects treated with Umeclidinium/Vilanterol (UMEC/VI) compared with Umeclidinium (UMEC) for 24 weeks. A further important aspect of the study is to evaluate the effect of UMC/VI, UMEC, and salmeterol with respect to health-related quality of life (HRQoL), measured through patient reported outcomes (PROs) questionnaires, and lung function. Additional assessments to further evaluate other measures of chronic obstructive pulmonary disease (COPD) efficacy and symptoms control will be performed.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To compare the effect of UMEC/VI (62.5/25 mcg once daily) with UMEC (62.5 mcg once daily) on lung function	• Change from baseline in trough Forced Expiratory Volume in One Second (FEV_1) at week 24
Secondary	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on patient reported outcomes (PROs)	• Change from baseline in self administered computerised (SAC) transient dyspnea index (TDI) • Percentage of TDI responders according to SAC TDI score. A responder is defined as a ≥1 unit improvement in SAC TDI score • Assessment of respiratory daily symptoms over 24 weeks using Evaluating Respiratory Symptoms-COPD (E-RS) and its subscales (breathlessness, cough and sputum and chest symptoms) • Percentage of E-RS responders according to E-RS score (defined as reduction in E-RS score of ≥2 or ≥3.35 units) from baseline • Change from baseline in St George's Respiratory Questionnaire (SGRQ-C) • Percentage of responders according to SGRQ-C total score (defined as a 4 point or greater reduction from

Objectives	Endpoints
	baseline) • Change from baseline in COPD assessment test (CAT) • Percentage of responders according to CAT (defined as a ≥2 unit improvement in score from baseline)
Other	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on other COPD efficacy measures	• Rate of mild, moderate or severe exacerbations • Time to first mild, moderate or severe exacerbation • Rate of moderate or severe exacerbation • Time to moderate or severe exacerbation • Time to severe exacerbations • Time to clinically important deterioration (CID) composite endpoint • Time to clinically important deterioration composite endpoint excluding FEV_1 • Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the electronic diary (eDiary) over 24 weeks • Inspiratory capacity (IC) • Full Vital capacity (FVC) • Change from baseline in trough FEV_1 • Change from baseline in global impression of disease severity

Objectives	Endpoints
Safety	
• To evaluate safety and tolerability of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5mcg once daily) and salmeterol 50mcg twice daily)	• Incidence of adverse events
Exploratory	
• To compare albuterol/salbutamol use captured in the eDiary with the electronic metered dose inhaler (eMDI) device	• Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the eMDI device over 24 weeks as data allow
• To explore the effect of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on physical activity	• Change from baseline in physical activity
• To investigate the CID composite endpoint ability to predict short term outcomes	• To compare physical activity levels, ER-S, rescue medication use, exacerbations and mortality in subjects with and without a CID

Overall Design

This is a multi-centre, randomized, double blind, double dummy, 3-arm parallel group study. Eligible subjects will be randomized in a ratio of 1:1:1 to UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA® dry powder inhaler (DPI), or UMEC (62.5 mcg once daily) administered via the ELLIPTA DPI or salmeterol (50 mcg twice daily (BID)) administered via the DISKUS® DPI.

Eligible subjects at Screening will enter a run-in period for 4 weeks during which they continue taking their inhaled COPD medications (excluding ICS and any exclusionary medications). In addition, subjects will be provided with short acting albuterol/salbutamol to be used on as needed basis (rescue medication) throughout the study.

Subjects who experience a moderate or severe COPD exacerbation during the run-in period will be deemed run-in failures. Subjects experiencing a mild exacerbation, defined as worsening of symptoms that requires **no** treatment with antibiotics or steroids and is self managed by the patient by an increase of inhaled rescue medication, will be allowed to continue in the study.

At the randomization Visit 2 (Day 1) those subjects who successfully complete the run-in period as well as meet the other pre-defined eligibility and randomization criteria will discontinue their inhaled COPD medications and will be randomized to one of the 3 treatment arms for 24 weeks.

All subjects will be given an eDiary for use during the run-in, and treatment period to complete PRO questionnaires and record medical problems experienced during the study. Subjects will be performing slow and forced spirometry at specific visits.

In addition, a subset of subjects up to 150 per treatment arm will undergo assessment of their physical activity measured through a physical activity monitor (Actigraph GT9X) worn for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3, and for 7 days prior to last clinic Visit (Visit 5).

There will be a total of 5 clinic visits and one follow-up phone call (Visit 6). The total duration of subject participation in the study will be approximately 29 to 31 weeks consisting of 2 weeks pre-screening if necessary, 4 weeks run-in, 24 week treatment and one week Follow-Up.

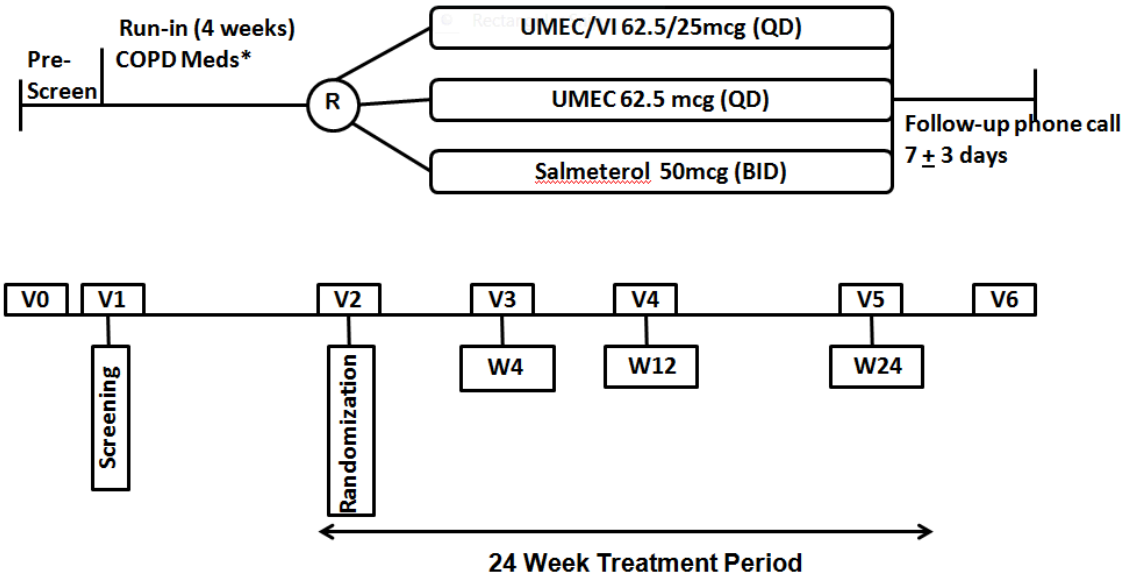
Subjects will be considered to have completed the study upon completion of the Follow–Up contact by telephone.

Treatment Arms and Duration

Subjects will be stratified based on long-acting bronchodilator usage during the run-in (none, one or 2 long-acting bronchodilators per day) and randomized in a ratio of 1:1:1 to either

- UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA DPI) or
- UMEC (62.5 mcg once daily) administered via the ELLIPTA DPI or
- Salmeterol (50 mcg BID) administered via DISKUS

Study schematic



*Inhaled COPD medications including LABAs, LAMAs or LABA/LAMA combination products are allowed in run-in. ICS alone or in combination with a bronchodilator or any exclusionary medications are not allowed.

Type and Number of Subjects

Approximately 3232 subjects will be screened, such that 2424 subjects will be randomized and approximately 2181 evaluable subjects complete the study.

Analysis

The primary purpose of this study is to demonstrate improvements in lung function for subjects treated with UMEC/VI compared with UMEC for 24 weeks.

The primary endpoint is change from baseline in trough FEV_1 at Week 24.

The null hypothesis is no difference between treatment groups (H0: $\mu T - \mu S = 0$), with the alternative hypothesis that there is a difference between treatment groups (H1: $\mu T - \mu S \neq 0$), where μT is the mean change from baseline for UMEC/VI and μS is the mean change from baseline for UMEC.

The primary endpoint of mean change from baseline in trough FEV_1 at the end of Week 24 will be analysed using Mixed Models repeated Measures (MMRM) analysis. The MMRM analysis will include measurements at Treatment Weeks 4, 12 and 24. Treatment group (a categorical variable) will be fitted as the explanatory variable with appropriate pre-defined variables, stratum (number of bronchodilators per day during run-in) and baseline values, fitted as covariates. Visit (nominal) will be fitted as a categorical variable and visit-by-baseline and visit-by-treatment interaction terms will be included to allow treatment effects to be estimated at each visit separately. The variance covariance matrix

will be assumed to be unstructured (based on previous experience no issues are expected with fitting models with this matrix structure).

The estimated treatment differences between UMEC/VI versus UMEC for each endpoint will be presented with the 95% confidence intervals for the difference and the p-value.

2. INTRODUCTION

2.1. Study Rationale

Chronic obstructive pulmonary disease (COPD) is associated with poor health-related quality of life (HRQoL). Pharmacologic therapy is used to improve lung function, reduce symptoms, frequency and severity of exacerbations, and improve patients HRQoL [GOLD, 2015]. Umeclidinium/Vilanterol (UMEC/VI 62.5/25 mcg) is indicated for the maintenance treatment of COPD that contain long-acting muscarinic antagonist (LAMA) and long-acting beta$_2$-agonist (LABA) bronchodilators. Umeclidinium (UMEC) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Salmeterol has long been used for symptoms management of COPD. However, a direct comparison of these maintenance therapies has not been conducted with respect to HRQoL.

The primary purpose of this study is to demonstrate improvements in lung function for subjects treated with UMEC/VI compared with UMEC for 24 weeks. The effect of UMC/VI, UMEC, and salmeterol with respect to patient HRQoL measured through patient reported outcomes (PROs) questionnaires, symptoms and lung function will also be evaluated.

2.2. Brief Background

COPD is characterized by an airflow limitation which is not fully reversible, usually progressive and accompanied by a chronic cough, sputum production and dyspnea which can be a major cause of disability and anxiety associated with the disease [Maleki-Yazdi, 2014]

Furthermore, acute exacerbations contribute to the overall severity of disease as these episodes are accompanied by worsened symptoms and are associated with increased decline in lung function and mortality [Wedzicha, 2013; Schmidt, 2014].

Pharmacologic therapy is used to improve lung function, reduce symptoms, reduce the frequency and severity of exacerbations, and also to improve health status and exercise tolerance. Maintenance treatment is recommended primarily through the use of LABAs or LAMAs. COPD treatment guidelines recommend an incremental approach to pharmacological treatment as the disease state worsens, involving the use of combinations of drug classes with different or complementary mechanisms [GOLD, 2015].

UMEC/VI inhalation powder is a combination of UMEC (umeclidinium bromide), a LAMA, and VI (Vilanterol), a LABA, delivered via the ELLIPTA dry powder inhaler

(DPI). UMEC/VI at a dose of 62.5/25mcg once-daily is marketed in the United States (US) and Europe under the trade name ANORO® ELLIPTA.
UMEC (62.5 mcg) inhalation powder is marketed in the United States (US) and Europe under the trade name INCRUSE® ELLIPTA. UMEC (62.5mcg) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. UMEC (62.5 mcg) improves forced expiratory volume in one second (FEV_1), dyspnea and HRQoL whether used as monotherapy [Trivedi, 2014; Feldman, 2016] or as an add on to fluticasone propionate and vilanterol (FF/VI) [Siler, 2015]. Salmetrol (50 mcg) DISKUS is a long-acting broncholdilator that has long been used for the maintenance treatment of COPD [Tashkin, 2010].

Clinically important deterioration (CID) is a novel, exploratory composite endpoint which assesses individual deteriorations in lung function and in patient PROs defined by the accepted minimal clinically important difference (MCID), as well as the incidence of moderate to severe exacerbations [Singh, 2016], (Section 7.3.5). CID will be analysed to determine whether UMEC/VI (62.5/25mcg) therapy provides greater clinical stability as compared with UMEC and salmeterol monotherapies.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To compare the effect of UMEC/VI (62.5/25 mcg once daily) with UMEC (62.5 mcg once daily) on lung function	• Change from baseline in trough Forced Expiratory Volume in One Second (FEV_1) at week 24
Secondary	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on patient reported outcomes (PROs)	• Change from baseline in self administered computerised (SAC) transient dyspnea index (TDI) • Percentage of TDI responders according to SAC TDI score. A responder is defined as a ≥1 unit improvement in SAC TDI score • Assessment of respiratory daily symptoms over 24 weeks using Evaluating Respiratory Symptoms-COPD (E-RS) and its subscales (breathlessness, cough and sputum and chest symptoms) • Percentage of E-RS responders according to E-RS score (defined as reduction in E-RS score of ≥2 or ≥3.35 units) from baseline

Objectives	Endpoints
	• Change from baseline in St George's Respiratory Questionnaire (SGRQ-C) • Percentage of responders according to SGRQ-C total score (defined as a 4 point or greater reduction from baseline) • Change from baseline in COPD assessment test (CAT) • Percentage of responders according to CAT (defined as a ≥2 unit improvement in score from baseline)
Other	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on other COPD efficacy measures	• Rate of mild, moderate or severe exacerbations • Time to first mild, moderate or severe exacerbation • Rate of moderate or severe exacerbation • Time to moderate or severe exacerbation • Time to severe exacerbations • Time to clinically important deterioration (CID) composite endpoint • Time to clinically important deterioration composite endpoint excluding FEV_1 • Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the electronic diary (eDiary) over 24 weeks • Inspiratory capacity (IC) • Full Vital capacity (FVC)

Objectives	Endpoints
	• Change from baseline in trough FEV_1 • Change from baseline in global impression of disease severity
Safety	
• To evaluate safety and tolerability of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5mcg once daily) and salmeterol (50mcg twice daily)	• Incidence of adverse events
Exploratory	
• To compare albuterol/salbutamol use captured in the eDiary with the electronic metered dose inhaler (eMDI) device	• Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the eMDI device over 24 weeks as data allow
• To explore the effect of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on physical activity	• Change from baseline in physical activity
• To investigate the CID composite endpoint ability to predict short term outcomes	• To compare physical activity levels, ER-S, rescue medication use, exacerbations and mortality in subjects with and without a CID

4. STUDY DESIGN

4.1. Overall Design

This is a multi-centre, randomized, double blind, double-dummy, 3-arm parallel group study. Eligible subjects will be stratified based on long-acting bronchodilator usage during the run-in (none, one or 2 long-acting bronchodilators per day) and randomized in a ratio of 1:1:1 to UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA inhaler, or UMEC (62.5 mcg once daily) administered via the ELLIPTA or salmeterol (50 mcg BID) administered via the DISKUS.

There will be a total of 5 clinic visits and one follow-up phone call (Visit 6). The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) if subject does not take or has not taken any excluded protocol medications, but must be completed prior to initiating any Visit 1 procedures.

Subjects, who meet all the eligibility criteria at Screening, will enter a run-in period for 4 weeks in order to continue to assess the subject's eligibility for the study. During the run-in period subjects will continue with their inhaled COPD medications (excluding ICS and

any exclusionary medications). In addition, subjects will be provided with short acting albuterol/salbutamol to be used on as needed basis for relief of COPD symptoms (rescue medication) throughout the study.

Subjects who experience a moderate or severe COPD exacerbation during the run-in period will be deemed run-in failures. Subjects who experience a mild COPD exacerbation, defined as worsening of symptoms that requires **no** treatment with antibiotics or steroids and is self managed by the patient by an increase of inhaled rescue medication, (Appendix 5), will be able to continue in the study based on the judgment of the investigator and agreement of the sponsor's medical monitor.

At the randomization Visit 2 (Day 1) those subjects who successfully complete the run-in period as well as meet the other pre-defined eligibility and randomization criteria will discontinue their inhaled COPD medications and will be randomized to one of the 3 treatment arms for 24 weeks.

During the run-in and treatment period, subjects will be completing PRO questionnaires in the eDiary and performing slow and forced spirometry at specific clinic visits.

In addition, a subset of subjects up to 150 per treatment arm will undergo assessment of their physical activity measured through a physical activity monitor (Actigraph GT9X) worn for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3, and for 7 days prior to last clinic Visit (Visit 5).

Concurrent use of COPD maintenance medications including LAMAs, LABAs, oral beta-agonists, theophyllines, inhaled corticosteroids, inhaled corticosteroids and LABA combination and phosphodiesterase 4 inhibitors will not be allowed during the study (Section 6.11.2) .

The occurrence of adverse events (AEs) will be evaluated throughout the study beginning at Visit 2 (Day 1) and until the follow-up contact (Visit 6). Serious adverse events (SAEs) will be collected over the same time period as AEs. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact (Appendix 4).

All subjects will be given an electronic diary (eDiary) for use during the run-in, and the treatment period to complete PRO questionnaires, record COPD daily symptoms, any medical problems experienced during the study and the time they take their COPD medications. Daily rescue medication usage (number of inhalations taken in the last 24h) will also be captured in the eDiary. In addition, and in some countries, rescue medication use will also be captured by the use of electronic metered dose inhaler (eMDI).

At Screening Visit 1, all subjects must be trained on the proper use of their existing COPD medications inhalation devices and instructed to strictly adhere to and record the time they take their COPD medications in the eDiary.

At the randomization Visit 2, all subjects must be trained on the proper use of the ELLIPTA and DISKUS inhalation devices and instructed to strictly adhere to and record the time they take their study medications in the eDiary.

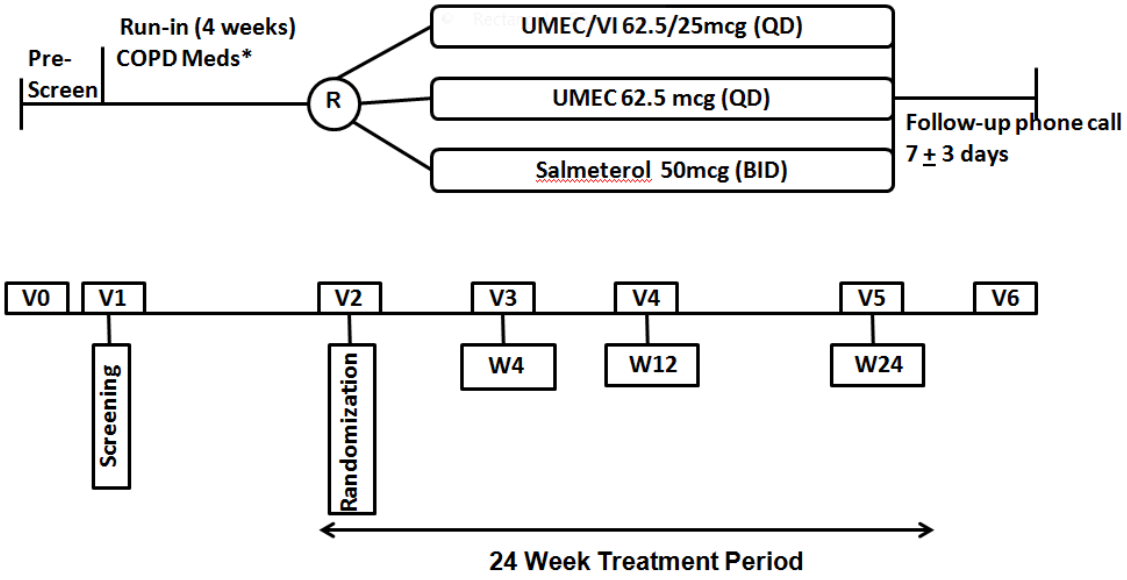
All subjects must be trained on the correct use of the eDiary and instructed to complete the eDiary during the run-in and treatment period.

Subjects will be considered to have completed the study upon completion of the follow – up contact by telephone.

There are no plans to routinely provide any of the study treatments for compassionate use following study completion as the study treatment are commercially available.

The study design schematic is illustrated in Figure 1

Figure 1 Study Schematic



*Inhaled COPD medications including LABAs, LAMAs or LABA/LAMA combination products are allowed in run-in. ICS alone or in combination with a bronchodilator or any exclusionary medications are not allowed.

4.2. Treatment Arms and Duration

Subjects will be stratified based on long-acting bronchodilator usage during the run-in (none, one or 2 long-acting bronchodilators per day) and randomized in a ratio of 1:1:1 to either

- UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA DPI) or
- UMEC (62.5 mcg once daily) administered via the ELLIPTA DPI or
- Salmeterol (50 mcg BID) administered via DISKUS

The total duration of subject participation in the study will be approximately 29 to 31 weeks consisting of 2 weeks pre-screening if necessary, 4 weeks run-in, 24 week treatment and one week follow-up.

4.3. Type and Number of Subjects

Approximately 3232 will be screened globally in approximately 205 sites such that approximately 2424 subjects will be randomized and approximately 2181 evaluable subjects complete the study.

4.4. Design Justification

A randomized, double blinded, parallel group study is a standard, well-established design to evaluate the efficacy and safety of an investigational drug. A salmeterol arm is included to allow a comparison to be made between UMEC/VI, UMEC with salmeterol, a standard practice treatment.

The double-dummy design is appropriate when drugs are of different appearance or different administration regimen which is appropriate in this study where the inhalers used have a different appearance and used once daily and twice daily.

The European Medicines Agency (EMA) COPD Guidelines suggest that duration of 12 to 24 weeks is considered adequate for assessment of response of COPD symptoms to treatment intervention with bronchodilators (EMA COPD guidelines, 2012).

The primary endpoint is trough FEV_1 at week 24. This endpoint is generally considered to be a robust, well established and an objective means to show the efficacy of a bronchodilator [Dahl, 2010; Feldman, 2010].

Other endpoints such SAC TDI, E-RS, SGRQ-C, CAT, Subject Global Rating of Change in global impression of disease severity are captured to allow responder analyses and to provide comparative data on PROs between the treatment groups.

4.5. Dose Justification

This study is intended to evaluate the efficacy of marketed doses of UMEC/VI (62.5/25mcg once daily), UMEC (62.5 mcg once daily) and salmeterol (50mcg twice daily) that are approved for the maintenance treatment of COPD, with respect to PRO measures.

4.6. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with UMEC/VI and UMEC can be found in the investigator's brochures (IB) [GlaxoSmithKline Document Number RM2009/00437/07] and [GlaxoSmithKline Document Number RM2006/00835/09] and in the label information sheets. The current safety profile for UMEC (62.5mcg) and the UMEC/VI (62.5/25mcg) based on data available to date, is comparable with other LABAs and LAMAs. Summary safety data can also be found in the information sheet for salmeterol [Serevent product information, 2003].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
Investigational Product (IP) [UMEC/VI]		
Severe milk protein allergy	Anoro contains Lactose monohydrate (which contains milk protein) as an excipient.	Exclusion criteria have been set for subjects with milk protein allergy.
Cardiovascular effects such as cardiac arrhythmias *e.g.* supraventricular tachycardia and extrasystoles.	Class effects associated with LABAs and LAMA containing therapy. The clinical significance of these arrhythmias is unknown. Clinical experience with UMEC/VI to date in completed studies did not show any association with major cardiovascular events. Data available in the product label for UMEC/VI	Exclusion criteria have been set for subjects with uncontrolled or severe cardiovascular disease according to the principal investigation's (PI) opinion where the potential risk may outweigh the benefit. The PI should also determine the clinical significance of abnormal ECG findings at screening and exclude subjects who would be at undue risk by participating in the trial. Patients with the following abnormalities will be excluded from participation: atrial fibrillation with rapid ventricular rate >120bpm, sustained or nonsustained ventricular tachycardia, or second degree heart block Mobitz type II or third degree heart block (unless pacemaker or defibrillator had been inserted).
Beta agonists and risk of asthma-related death	Long-acting beta agonists such as vilanterol when used alone may increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including vilanterol. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.	Subjects with a current diagnosis of asthma are excluded from participation in the study.
Paradoxical bronchospasm	As with other inhaled medicines, UMEC/VI can produce paradoxical bronchospasm which may be life threatening.	If paradoxical bronchospasm occurs following dosing with UMEC/VI, this treatment should be discontinued immediately and alternative therapy should be instituted.
Use in patients with narrow-angle glaucoma or urinary retention	No association has been found to date, in completed studies with UMEC/VI or UMEC monotherapy, on glaucoma or urinary retention. However, glaucoma or urinary retention	Exclusion criterion states that subjects with medical conditions such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction should only be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	have been observed with other antimuscarinic agents, and could potentially be due to the pharmacology.	included if, in the opinion of the principal investigator, the benefit outweighs the risk.
Use of beta blockers	Beta-adrenergic blockers may weaken or antagonize the effect of $beta_2$-agonists such as vilanterol.	The study permitted medications and non drug therapies section states that concomitant administration with beta-blockers is only permitted if, in the Investigator's opinion, the likely benefit outweighs the potential risk.
Pregnancy	There is no experience to date of pregnancy during the use of UMEC/VI.	The study inclusion criteria ensures that female subjects of child bearing potential must have a negative pregnancy test at screening, and agree to a reliable contraceptive method, used consistently and correctly (i.e. in accordance with the approved product label and the instructions of the physician for the duration of the study). Exclusion criteria include **Pregnancy:** Women who are pregnant or lactating or are planning on becoming pregnant during the study.
Severe hepatic impairment	UMEC/VI has not been studied in severe hepatic impairment.	Exclusion criterion states that subjects severe hepatic impairment should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Investigational product (IP) [UMEC]		
Cardiovascular effects such as cardiac arrhythmia, e.g. atrial fibrillation and tachycardia	A potential class effect associated with anti-muscarinic therapies. Data available to date in the IB for UMEC [GlaxoSmithKline Document Number RM2006/00835/09	Screening electrocardiogram (ECG) criteria to exclude subjects potentially at risk
Narrow-angle glaucoma, urinary retention	A class effect associated with anti-muscarinic therapies. Data available in the IB for UMEC [GlaxoSmithKline Document Number RM2006/00835/09	Exclusion criterion states that subjects with medical conditions such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Paradoxical bronchospasm that may be life threatening	Known effect associated with inhalation therapy	A short-acting inhaled bronchodilator (albuterol/salbutamol) will be provided for use as needed throughout the study. The investigators will be instructed to assess subject's condition to determine their eligibility to

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		continue in the study and the need for alternative therapy.
Severe hepatic impairment	UMEC has not been studied in severe hepatic impairment.	Exclusion criterion states that subjects with severe hepatic impairment should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Pregnancy/Lactation	There is no experience to date of pregnancy during the use of UMEC.	The study inclusion criteria ensure that female subjects enrolled, who are of Child bearing potential, have a negative pregnancy test at screening, and agree to a reliable contraceptive method, used consistently and correctly (i.e. in accordance with the approved product label and the instructions of the physician for the duration of the study). Exclusion criteria states - Pregnancy: Women who are pregnant or lactating or are planning on becoming pregnant during the study.
Study Procedures		
Spirometry procedures	This may cause difficulty breathing, changes in pulse rate and blood pressure, coughing, wheezing, chest tightness or fainting.	Subjects will be monitored during the procedure for these effects and spirometry will be discontinued should these occur.
ECG lead placement	This may cause skin irritation.	It may be necessary to have small patches (about a centimetre in diameter) of hair on the chest shaved to properly attach electrodes to the chest.
Blood sampling procedure (optional pharmacogenetic blood sample)	Giving blood may make subjects feel faint, or experience mild pain, bruising, irritation or redness at the site. In rare cases, they may get an infection	Subjects will be monitored during the blood draw for these effects and should call their study doctor if any of these effects do not resolve
Other		
Side effects of rescue albuterol/salbutamol. Adverse events seen in clinical studies to date are however consistent for the beta$_2$-adrenergic class of compounds	Class effects associated with short acting beta-agonists (SABAs)	Subjects should call their study doctor if they experience any of these symptoms

4.6.2. Benefit Assessment

Subjects will receive single or combination of long-acting bronchodilator therapies approved for maintenance treatment of COPD. Participating subjects in this study will contribute to the process of further characterizing the benefit of these long-acting bronchodilators with respect to PROs and symptoms in the treatment of COPD.

Specific benefits associated with the study design and procedures include the following:

- Subjects will receive treatments approved for the treatment of COPD that have been shown to be effective in the population under study
- All subjects will receive albuterol/salbutamol for use "as needed" for relief of COPD symptoms
- The combination of study procedures of spirometry, CAT, SGRQ, TDI, E-RS will provide the study subjects with a comprehensive evaluation of their symptoms, health status and COPD disease severity. Subjects will also be monitored throughout the study for any worsening of COPD symptoms or decline in general health. Finally smoking cessation counselling will also be provided.

4.6.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with UMEC/VI, UMEC, salmeterol and with study procedures are justified by the anticipated benefits from active treatments that may be afforded to patients with COPD.

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 IBs, [GlaxoSmithKline Document Number RM2006/00835/09], [GlaxoSmithKline Document Number RM2009/00437/07] and product labels.

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

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. **40 years or older** at date of signing informed consent at Screening Visit 1

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. **Outpatient with a diagnosis of COPD** in accordance with the definition of the American Thoracic Society/European Respiratory Society (ATS/ERS) [Celli, 2004]. 3. **FEV_1**: Persistent airflow limitations as indicated by: A pre and post-albuterol/salbutamol FEV_1/FVC ratio of <0.70 and a post-albuterol/salbutamol FEV_1 of ≥30% to ≤80% predicted normal values at Screening Visit 1. Predicted values will be based upon the ERS Global Lung Function Initiative [Quanjer, 2012]. 4. **CAT score**: A CAT score of ≥10 at Screening Visit 1

Smoking History
5. **Current or former cigarette smokers** with a history of cigarette smoking of ≥ 10 pack-years [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 both equal 10 pack-years)]. Former smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Pipe and/or cigar use cannot be used to calculate pack-year history.

SEX
6. **Male and female** subjects are eligible to participate in the study 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 must be tested. 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) (Appendix 7) from 30 days prior to the first dose of study medication and until [at least five terminal half-lives OR until any continuing pharmacologic effect has ended, whichever is longer] after the last dose of study medication and completion of the follow-up visit.

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

INFORMED CONSENT
7. **Capable of giving signed informed consent** prior to study participation, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION
1. **Asthma**: 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).
2. **Alpha-antitrypsin deficiency:** Subjects with known α1-antitrypsin deficiency as the underlying cause of COPD
3. **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.
4. **Unstable liver disease:** 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). • 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 or within 3 months prior to first dose of study treatment) are acceptable if subject otherwise meets entry criteria
5. **Unstable or life threatening cardiac disease:** Investigational Product should be used with caution in subjects with severe cardiovascular disease. In the opinion of the investigator, use should only be considered if the benefit is likely to

outweigh the risk in conditions such as:

- 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

6. **12 Lead ECG:** 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. Subjects with the following abnormalities are excluded from participation in the study:

- Atrial fibrillation with rapid ventricular rate >120 bpm
- Sustained or non-sustained ventricular tachycardia
- Second degree heart block Mobitz type II or third degree heart block (unless pacemaker or defibrillator had been inserted)

7. **Antimuscarinic effects:** Subjects with medical conditions such as narrow-angle glaucoma, urinary retention, prostatic hypertrophy, or bladder neck obstruction should be excluded unless, in the opinion of the study physician, the benefit outweighs the risk.

8. **Other disease abnormalities:** Any subject who is considered unlikely to survive the duration of the study period or has any rapidly progressing disease or immediate life-threatening illness (e.g. cancer). In addition, any subject who has any other condition (e.g. neurological condition) that is likely to affect respiratory function should not be included in the study.

9. **Hospitalization:** Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1. **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).

10. **Inhaled corticosteroids (ICS):** Had received ICS or ICS/LABA for the treatment of COPD in the 6 weeks prior to Screening Visit1

11. **Exacerbation:** Had >1 moderate exacerbation in the 12 months prior Screening Visit1, or one severe exacerbation requiring hospitalisation in the 12 months prior Screening Visit 1.

12. **Other respiratory tract infections** that have not resolved at least 7 days prior to Screening V1.

13. **Lung Resection:** Subjects with lung volume reduction surgery (including procedures such as endobronchial valves) within the 12 months prior to Screening V1.

14. **Oxygen:** Use of long-term oxygen therapy (LTOT) described as resting oxygen therapy >3L/min at screening required to maintain adequate oxygenation (*e.g.* S_aO_2 >90%). (Oxygen use ≤3L/min flow is not exclusionary, and patients may adjust oxygen levels up or down as needed during the study.)

CONCOMITANT MEDICATIONS

1. **Medications prior to Screening:** Use of the following medications according to the following defined time intervals prior to Screening (Visit 1):

Medication	No use within the following time intervals prior to Screening
Inhaled corticosteroids (ICS)	6 weeks
Depot corticosteroids	12 weeks
Systemic, oral or parenteral corticosteroids[a]	6 weeks
Antibiotics (for lower respiratory tract infection)	6 weeks
Phosphodiesterase 4 (PDE_4) Inhibitor (*e.g* roflumilast)	14 days
LABA/Inhaled Corticosteroid (ICS) combination products	6 weeks
Theophyllines	48 hours
Oral $beta_2$-agonists Long-acting Short-acting	 48 hours 12 hours
Inhaled short acting $beta_2$-agonists[b]	4 hours
Inhaled short-acting anticholinergics	4 hours
Inhaled short-acting anticholinergic/short-acting $beta_2$-agonist combination products	4 hours
Any other investigational medication	30 days or within 5 drug half-lives (whichever is longer)

a- Localized corticosteroid injections (e.g., intra-articular and epidural) are permitted.

b- Use of study provided albuterol/salbutamol is permitted during the study, except in the 4-hour period prior to spirometry testing

2. **Medication prior to spirometry:** Unable to withhold albuterol/salbutamol for the 4 hour period required prior to spirometry testing at each study visit.
3. **Maintenance use of short-acting bronchodilators**: Regular use (prescribed for daily/ regular use, not for as-needed use) of short-acting bronchodilators (*e.g*. albuterol/salbutamol).

RELEVANT HABITS

1. **Drug or alcohol abuse:** A known or suspected history of alcohol or drug abuse within 2 years prior to Screening Visit 1 that in the opinion of the investigator would prevent the subject from completing the study procedures.

CONTRAINDICATIONS

1. **Any history of allergy or hypersensitivity** to any anticholinergic/muscarinic receptor antagonist, sympathomimetic, lactose/milk protein or magnesium stearate.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
1. **Pulmonary Rehabilitation program:** Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Screening Visit 1. Subjects who are in the maintenance phase of a pulmonary rehabilitation program are not excluded.
2. **Affiliation with investigator sites:** Is an investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member of the aforementioned that is involved in this study
3. **Inability to read:** In the opinion of the investigator, any subject who is unable to read and/or would not be able to complete questionnaires on the electronic diary.

Subjects who fail to meet inclusion and exclusion criteria at the **Screening Visit 1** will be considered screen failures and cannot be **re-screened.**

5.3. Randomization Criteria

In order to be randomized to one of the 3 treatment arms at Visit 2, subjects must have completed the run-in period and must have fulfilled all inclusion and exclusion criteria described in Section 5.1 and Section 5.2. In addition to the following:

REQUIRED CRITERIA FOR RANDOMIZATION AND TREATMENT
1. **COPD Exacerbation**: Subjects must **not** have experienced a moderate or severe COPD exacerbation or a lower respiratory tract infection during run-in or at Day 1 (Visit 2) inclusive. A moderate exacerbation is defined as worsening of symptoms of COPD requiring the use of antibiotics or systemic corticosteroids. A severe exacerbation is defined as worsening symptoms of COPD requiring hospitalization.
2. **CAT score**: A CAT score of ≥10 at Visit 2
3. **Prohibited Medications:** No use of any prohibited medications during the run-in period or at Visit 2, including any ICS or ICS/LABA combination
4. **Any change to COPD medications:** Including dosage and regimen during the run-in
5. **Completion of electronic diary:** Must have completed the electronic diary for at least 80% of days during the run-in period

Subjects who do not meet the required criteria for randomization at Visit 2 will not be randomized.

5.4. Screening/Baseline/Run-in Failures

Pre-screen, screen and run-in failures are defined as follows:

- Pre-screening failures: A subject, who is assigned a subject number at the Pre-screening Visit 0 but does not have any Screening Visit 1 procedures, will be considered a pre-screen failure.

- Screening failures: Those subjects that complete at least one Screening Visit 1 procedure but do not enter the run-in period.
- Run-in failures: Those subjects that enter the run-in period but are not randomized to any of the study treatment arms.

Subjects who are pre-screen, screen and run-in failure will be recorded in the eCRF. 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 to be recorded in eCRF including demography, screen failure details, eligibility criteria, and serious adverse events (Section 7.4.1).

5.5. Withdrawal/Stopping Criteria

5.5.1. Withdrawal from the Study

Subjects may be withdrawn from the study at any time by the Investigator if it is considered to be detrimental for them to continue in the study. Reasons for withdrawal from study treatment can include: an AE, clinically significant abnormality, lack of efficacy, sponsor terminated study, pregnancy, or for any other reason.

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.

A reason for the withdrawal from the study must be captured in the electronic case report form (eCRF).

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

- **Liver Chemistry:** Meets any of the Liver chemistry stopping criteria (See Section 5.5.3)

  Note: clinical laboratory assessments are not required for this study. However, laboratory samples may be taken for liver event analysis, if clinically indicated by the study investigator.

- **Pregnancy:** Positive pregnancy test (see Appendix 7)

Subjects withdrawn from study treatment will not be replaced.

Note: Withdrawal from study treatment requires withdrawal from the study.

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".

5.5.2. Reason for Study Withdrawal

The primary reason for study withdrawal will be recorded in the eCRF. When a subject withdraws consent, the investigator must document the reason (if specified by the subject) in the eCRF.

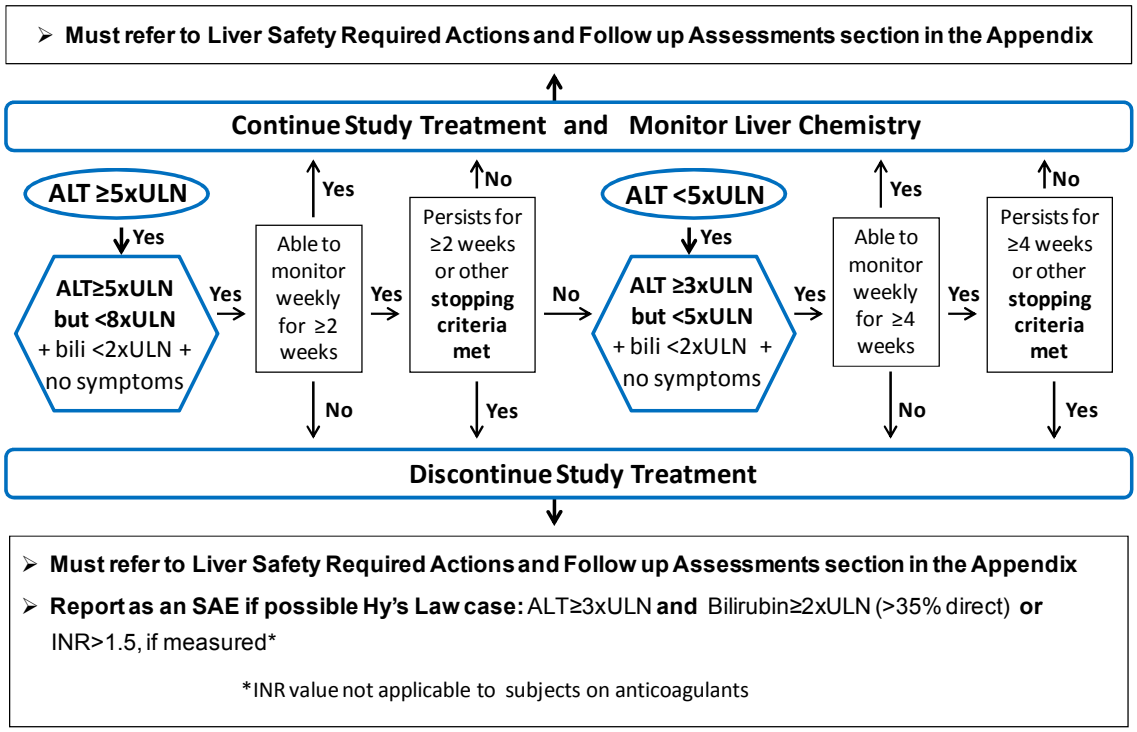
The primary reason for study withdrawal may include:

- Adverse event
- Lost to follow-up
- Withdrew consent
  - subject relocated
  - frequency of visits
  - burden of procedures
  - other (specify)
- Protocol deviation
- Lack of efficacy
- COPD exacerbation
- Study closed/terminated
- Subject reached protocol-defined stopping criteria
  - Liver event
- Pregnancy
- Investigator discretion

5.5.3. 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

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.

5.5.3.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.6. Follow-up contact

A safety follow-up contact (Visit 6) should be conducted 7±2 days following the completion of Visit 5 or the Early Withdrawal Visit, if applicable.

The following procedures will be performed:

- AE/SAE assessment
- COPD exacerbation assessment
- Concomitant medication assessment limited to any medications used to treat a COPD exacerbation or SAE (if applicable)
- Pregnancy information (if applicable)

Subjects who have successfully completed all on-treatment randomized visits will be discharged from the study upon completion of the safety follow-up contact.

5.7. Subject and Study Completion

A subject will be considered to have completed the study if he/she receives study treatment at Visit 5 (Week 24) and completes the follow-up contact Visit 6.

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.

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

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

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 authorised site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

GlaxoSmithKline (GSK) will provide the study treatments for use in this study.

The following study medications will be used in this study:

- UMEC/VI 62.5/ 25mcg administered via ELLIPTA
- UMEC 62.5 mcg administered via ELLIPTA
- Salmeterol 50 mcg administered via DISKUS
- Placebo via ELLIPTA
- Placebo via DISKUS

Subjects will be instructed to take one dose of medication each morning from the ELLIPTA (one inhalation equals one dose), and one dose in the morning and one in the evening from the DISKUS). Subject instructions and details on how to use the ELLIPTA and DISKUS are provided in the study reference manual (SRM).

A description of the UMEC/VI investigational product administered via the ELLIPTAis provided below in Table 1. The ELLIPTA will contain two, double-foil, laminate, blister strips. The ELLIPTA will provide a total of 30 doses (60 blisters) and will deliver, when actuated, the contents of a single blister simultaneously from each of the two blister strips.

The DISKUS will provide a total of 60 doses and will deliver, when actuated, the contents of a single blister.

A description of the UMEC investigational product administered via the ELLIPTA is provided below in Table 2. A description of placebo inhalation powder via ELLIPTA is shown in Table 3. A description of salmeterol 50mcg and placebo via DISKUS are shown in Table 4 and Table 5 respectively.

Table 1 Description of UMEC/VI Inhalation Powder via ELLIPTA

Formulation	**First strip**	**Second strip**
	Umeclidinium bromide blended with lactose monohydrate and magnesium stearate[1]	Vilanterol trifenatate blended with lactose monohydrate and magnesium stearate[2]
Dosage Form	ELLIPTA Inhaler with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	62.5 mcg	25 mcg
Physical description	White powder	White powder
Route of Administration	Inhaled	

1. Magnesium stearate 0.6% w/w of total drug product
2. Magnesium stearate 1.0% w/w of total drug product

Table 2 Description of UMEC Inhalation Powder via ELLIPTA

Formulation	**First strip**
	Umeclidinium bromide blended with lactose monohydrate and magnesium stearate[1]
Dosage Form	ELLIPTA Inhaler with 30 doses (1 strip with 30 blisters)
Unit Dose Strengths	62.5mcg
Physical description	Dry white powder
Route of Administration	Inhaled

1. Magnesium stearate 0.6% w/w of total drug product

Table 3 Description of Placebo inhalation powder via ELLIPTA

Formulation	**First strip**	**Second strip**
	Lactose monohydrate blended with magnesium stearate[1]	Lactose monohydrate blended with magnesium stearate[2]
Dosage Form	ELLIPTA Inhaler with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	Not applicable	Not applicable
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	

1. Magnesium stearate 0.6% w/w of total drug product
2. Magnesium stearate 1% w/w of total drug product

Table 4 Description of salmeterol Inhalation powder via DISKUS

Formulation	**First strip**
	Salmeterol Xinafoate blended with lactose monohydrate
Dosage Form	Diskus Inhaler with 60 doses (1 strip with 60 blisters per strip)
Unit Dose Strengths	50 mcg
Physical description	White powder
Route of Administration	Inhaled

Table 5 Description of Placebo inhalation powder via DISKUS

Formulation	Lactose monohydrate
Dosage Form	Diskus Inhaler with 60 doses (1 strip with 60 blisters per strip)
Unit Dose Strengths	Not Applicable
Physical description	White powder
Route of Administration	Inhaled

Albuterol/salbutamol via metered-dose-inhaler (MDI) will be issued for reversibility testing at Visit 1. Albuterol/salbutamol MDI for as needed (prn) use will be issued throughout the study. Albuterol/salbutamol will be sourced from local commercial stock if appropriate.

6.2. Medical Devices

The eMDI devices are provided by GSK and are used in this study to electronically record rescue medication usage. They have US FDA 510(K) clearance to market (Class II device) and EU CE marking (Class I device). Description of the eMDI and its use will be provided in the **SRM.**

6.3. Treatment Assignment

Subjects who meet the randomization criteria will be assigned to one of the 3 study treatments in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Once a randomization number is assigned to a subject, it cannot be reassigned to any other subject in the study.

This study will utilize RAMOS NG, which will provide a means for central 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 RAMOS NG to randomize subjects is provided in the SRM.

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. On the other days during the treatment period (i.e. "non-clinic days"), subjects will be instructed to self-administer their study treatment in the morning and evening. Subjects should enter the time they take their study treatment in the eDiary.

Subjects will be randomly assigned to one of the blinded study treatment regimens in equal proportion (ratio of 1:1:1):

- UMEC/VI 62.5/25 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- UMEC 62.5 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- Salmeterol 50 mcg twice daily via DISKUS + placebo once daily via ELLIPTA

The randomisation will be stratified based on **long-acting bronchodilator** usage during the run-in (none, one or 2 **long-acting bronchodilators** per day).

Study treatment/investigational product will be dispensed at Visits 2, 3 and 4.

In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2, 60 and 90 days from V3 and V4 respectively (see Time and event table Section 7.1).

Used study drug and rescue medication will be collected at Visits 3, 4 and 5 or at the Early Withdrawal Visit.

6.4. Planned Dose Adjustments

No dose adjustment is allowed for this study

6.5. Blinding

This will be a double-blind double dummy study 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. 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.

6.6. Packaging and Labeling

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

6.7. Preparation/Handling/Storage/Accountability

No special preparation of the study treatment is required.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer 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 SRM.

All ELLIPTA DPI study treatment should be stored up to 25°C (77°F). Each All ELLIPTA DPI 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 investigational product.

Salmeterol DISKUS should be stored up to 25 °C.

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.

6.7.1. Study Treatment Return

All used and unused ELLIPTA and DISKUS inhalers 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 SRM.

Study treatment will be collected at Visit 3, 4 and 5 or at the Early Withdrawal Visit, if applicable.

For any ELLIPTA or DISKUS inhaler that fails to function properly, the subject should return to the clinic as soon as possible to obtain a new inhaler. The site will contact the RAMOS NG 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 RAMOS NG

In addition, any ELLIPTA that fails to function properly must be identified and returned to GSK for testing.

6.8. Compliance with Study Treatment Administration

When subjects self-administer study treatment(s) at home, compliance with study treatment(s) will be assessed through querying the subject during the site visits and through study drug compliance assessed at Visits 2, 3, 4 and 5 documented in the source documents and eCRF. A record of the number of ELLIPTA and DISKUS dispensed and the number of doses inhaled by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays if any will also be recorded in the eCRF.

Compliance with the ELLIPTA inhaler will be determined by reviewing the dose counter on the ELLIPTA. Compliance with the study DISKUS will be determined by reviewing the dose counter on the DISKUS. Subjects should be ≥80% to ≤120% compliant on taking study medication between each pair of on-treatment visits. Subjects who fall outside this range should be re-educated on treatment compliance by their site. This re-education should be documented in the subject's source document. If medication compliance repeatedly falls outside of acceptable ranges, the study sponsor/site monitor must be contacted to discuss subject eligibility for continued participation in the study.

6.9. Treatment of Study Treatment Overdose

An overdose is defined as a dose greater than the total doses described in Section 6.1 and Section 6.8 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 medication, the investigator should use clinical judgment in treating the overdose and contact the study 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 may not be limited to, the approved product label for salmeterol albuterol, UMEC and UMEC/VI or equivalent document provided by GSK.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.10. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study, since the study treatments are commercially available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, post-study treatment.

6.11. Concomitant Medications and Non-Drug Therapies

All COPD medications used within 30 days prior to Pre-Screening (Visit 0) and onwards should be recorded in the eCRF including any changes in medications. Beginning at Visit 1 and throughout the rest of the study, all medications should be recorded in the eCRF including any changes. Study provided albuterol/salbutamol and double-blinded study drug should **not** be recorded in the eCRF. The minimum requirement includes but is not limited to drug name, dose, route and the dates of administration. Medications initiated after completion of Visit 5 or the Early Withdrawal Visit will not be recorded in the eCRF, with the exception of those used to treat a COPD exacerbation or SAE that occurs between Visit 5 (or the Early Withdrawal Visit) and the follow-up contact atVisit 6.

6.11.1. Permitted Medications and Non-Drug Therapies

The following relevant medications are permitted during this study:

- Study-provided albuterol/salbutamol for use as relief medication throughout the run-in and treatment periods
- Mucolytics such as acetylcysteine
- Medications for rhinitis (e.g. intranasal corticosteroids, antihistamines, cromolyn, nedocromil, nasal decongestants)
- Influenza vaccine
- pneumococcal vaccine
- Antibiotics for short term treatment (≤14 days) of acute infections including COPD exacerbations
- Systemic corticosteroids for short term (≤14 consecutive days) treatment of COPD exacerbations

- As-needed supplemental oxygen use provided it is ≤3L/min flow at rest at screening. Patients may adjust oxygen levels as needed during the study.
- Pulmonary rehabilitation program in maintenance phase
- Smoking cessation treatment, including a stable regimen of nicotine replacement
- Use of positive airway pressure/non-invasive ventilation for sleep apnea/sleep disordered breathing (*e.g*. CPAP, BiPAP)
- Localized corticosteroid injections (e.g., intra-articular and epidural)
- 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)
- Immunotherapy injections
- Topical or ophthalmic corticosteroids
- Over-the counter (OTC) cough suppressants
- Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). Administer with caution as they may potentiate the effect of beta-agonists on the vascular system
- Diuretics. Caution is advised in the co-administration of beta agonists with non-potassium sparing diuretics
- Allergy vaccination
- All medications for other disorders as long as the dose remains constant whenever possible and their use would not be expected to affect lung function

6.11.2. Prohibited Medications and Non-Drug Therapies

Use of the medications listed in Table 6 is not permitted during the study

Table 6 Prohibited Medications and Non-Drug Therapies

Medication
Depot corticosteroids
Systemic, oral or parenteral corticosteroids[1]
Inhaled corticosteroids (ICS)[2]
Antibiotics >14 days
LABA/ICS combination products
PDE4 inhibitor (e.g. roflumilast)
Inhaled long acting $beta_2$-agonists (LABA, e.g. salmeterol, formoterol, indacaterol, vilanterol)
Long-acting muscarinic antagonists (LAMA, e.g. tiotropium, aclidinium, glycopyrronium, umeclidinium[3])
LAMA/LABA combination products except for study drugs
Theophyllines
Oral $beta_2$-agonists
Inhaled short acting $beta_2$-agonists[4]
Inhaled short-acting anticholinergics
Inhaled short-acting anticholinergic/short-acting $beta_2$-agonist combination products
Any other investigational medication

1 Except for the treatment of COPD exacerbations during the study. Localized corticosteroid injections (e.g., intra-articular and epidural) are permitted.
2 Except if during the study use of ICS is deemed necessary for the treatment of subjects' exacerbation.
3 Expect for study drug
4 Use of study provided albuterol/salbutamol is permitted during the study, except in the 4-hour period prior to spirometry testing.

The following medications or treatments are also **not** allowed during the study:

- Use of long-term oxygen therapy (LTOT) described as resting oxygen therapy >3L/min only at screening. Oxygen may be titrated to any level deemed necessary during the study.
- Regular (prescribed for daily/regular use, not for as-needed use) therapy with albuterol/salbutamol.
- Initiation of pulmonary rehabilitation during the study.

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 Section 7.1, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

7.1. Time and Events Table

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 -7/+2 days prior Visit 1**	**28 -7/+2 days prior Visit 2**	**1 -7/+2 days**	**28 -7/+2 days**	**84 -7/+2 days**	**168 -7/+2 days**		**7±3 days after V5 or EW Visit**
Screen/Baseline								
Written informed consent	X							
Demography	X							
Medical/COPD history		X						
Smoking history/status		X						
Smoking cessation counselling		X						
Concomitant medication assessment	X	X	X	X	X	X	X	X
Height and weight		X						
Cardiovascular History/family history of premature CV disease])		X						
Screening spirometry (including post bronchodilator testing)[3]		X						
CAT questionnaire		X	X					
Verify Inclusion/Exclusion Criteria		X						
Training on use of inhalers		X	X					
Training on use of eDiary and eMDI		X	X					
Verify randomization Criteria			X					
Register Visit in InForm	X	X	X	X	X	X	X	X
Register Visit in RAMOS NG	X	X	X	X	X	X	X	X

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 -7/+2 days prior Visit 1**	**28 -7/+2 days prior Visit 2**	**1 -7/+2 days**	**28 -7/+2 days**	**84 -7/+2 days**	**168 -7/+2 days**		**7±3 days after V5 or EW Visit**
Efficacy/HRQoL assessments								
Spirometry, including pre-dose FEV_1, trough FEV_1 and inspiratory capacity			X	X	X	X		
SAC BDI questionnaire [4]			X					
SAC TDI questionnaire [4]				X	X	X		
SGRQ-C questionnaire [4]			X	X	X	X		
CAT questionnaire [4]		X	X	X	X	X		
EXACT/ER-S: COPD [5]		→	→	→	→	→		
Patient Global Rating of COPD severity			X	X	X	X		
Patient Global Rating of Change in COPD				X	X	X		
Safety assessments								
Adverse events/Serious adverse events [6]	X	X	X	X	X	X	X	X
COPD exacerbation assessment	X	X	X	X	X	X	X	X
12-Lead ECG		X						
Urine pregnancy test [7]		X	X			X	X	
Pharmacogenetic sample[8]			←	X	→			
Medication/Supplies								
Dispense rescue albuterol/slabutamol. Dispense MDI[9]		X	X	X	X	X		
Assess COPD medication compliance[10] during run-in			X					
Dispense eDiary		X						
Assess compliance with eDiary during run-in			X					
Collect rescue albuterol/slabutamol.			X	X	X	X	X	
Collect eDiary						X	X	
Dispense study treatment[11]			X	X	X			
Collect study treatment				X	X	X	X	

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 -7/+2 days prior Visit 1**	**28 -7/+2 days prior Visit 2**	**1 -7/+2 days**	**28 -7/+2 days**	**84 -7/+2 days**	**168 -7/+2 days**		**7±3 days after V5 or EW Visit**
Assess study treatment compliance during treatment[10]				X	X	X	X	
Study sub-set								
Physical activity monitor[12]		X	X	X		X		
Collect Physical activity monitor						X	X	

1. Pre-screen Visit 0 must be completed prior to Screening Visit1. It can be completed 2 weeks prior or on the same day of V1, if no wash out of exclusionary medications is required.
2. Early Withdrawal Visit: Subjects that withdraw should return to the clinic as soon as possible to complete the Early Withdrawal Visit procedures.
3. Spirometry at screening should be performed as described in (Section 7.2.2.1).
4. SAC BDI, SAC TDI, SGRQ-C, CAT questionnaires will be completed at clinic visits and in the eDiary
5. EXACT/ER-S: COPD is completed daily in the eDiary approximately 2 hours before bed-time, starting on Day 1 of the run-in period.
6. For the start date of collecting AEs and SAEs see (Appendix 4)
7. Pregnancy test: for females for child bearing potential only.
8. Pharmacogenetic sample may be drawn at visit 2 or any visit after.
9. Rescue medication use to be recorded in the eDiary daily **and** in some sites in the eDiary and the eMDI
10. Sites are requested to call subjects every 2 weeks to remind them to take study treatment regularly and to record the time of the morning and evening dose in the eDiary.
11. In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2 and within 60 days from V3 respectively.
12. The Actigraph GT9X should be worn for 7 days from Visit 1, for 7 days from Visit 2, for 7 days from Visit 3 and for 7 days prior to Visit 5.

7.2. Screening and Critical Baseline Assessments

7.2.1. Pre-screening Visit

During the Pre-screening Visit, the study designated personnel must provide informed consent to the study participant. Subjects can perform the Pre-screening Visit (Visit 0) up to 2 weeks prior to or on the same day as the Screening Visit (Visit 1) if subject does not take or has not taken any protocol excluded medications.

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. A subject number will be assigned at the time the informed consent form (ICF) is signed. **No study related procedures may be performed until the informed consent form document has been signed by the subject.**

Once the informed consent is signed and if required, changes can be made to the subject's current medication regimen. The investigator should exercise clinical judgment, and is discouraged from changing medications only for the purpose of the clinical study.

During the pre-screening Visit 0, the following information is collected:

- Demographic parameters: year of birth, gender, race and ethnicity
- Concomitant medications review
- COPD exacerbation assessment

From the pre-screening visit onwards concomitant medications, exacerbations and SAEs (considered as related to study participation) must be reported

7.2.2. Critical procedures performed at Screening (Visit 1)

The following critical assessments will be conducted at Visit 1:

- Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening
- Medical history including COPD (including date of diagnosis and COPD type (emphysema and/or chronic bronchitis), smoking history, COPD exacerbation history, smoking status and previous and/or current medical conditions)
- Concomitant medication review (COPD and non COPD medications in the 3 months prior to Screening).
- Height and weight
- 12-Lead ECG. (Note: ECG is performed at screening Visit 1 to test for eligibility only. See Section 7.4.4).

- Urine pregnancy test if applicable
- Train subject on the use of eDiary
- COPD assessment test (CAT) and patient global rating of COPD severity in eDiary
- Pre- and post-albuterol/salbutamol spirometry (reversibility, see Section 7.2.2.1)
- Inclusion/Exclusion criteria assessment
- Review exacerbations, AEs, (SAEs if related to study participation)
- Train subject on the proper use of their COPD medication inhalation devices
- Instruct subject to take their COPD medications as instructed and to enter the time they take their medication in the eDiary
- Dispense rescue medication

Medical history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.1 and Section 5.2.

Assessment of subject's health status will be made at screening using CAT. PRO questionnaires should be completed by subjects before any other assessments at a clinic visit, in the order specified in Section 7.3.1

7.2.2.1. Albuterol/Salbutamol Reversibility Assessment

At Visit 1, both pre- and post-albuterol/salbutamol spirometry will be obtained to determine subject eligibility. Reversibility assessment should be performed as follows:

- Perform pre-bronchodilator spirometry and record FEV_1 and FVC
- Subject to self-administer 4 Inhalations (4X100µg) of albuterol/salbutamol MDI
- Perform post-bronchodilator spirometry and record FEV_1 and FVC approximately 10 to 30 minutes after albuterol/salbutamol administration

  The results of the spirometry must meet the ATS/ERS criteria [Miller, 2005] for the subject to continue in the study.

7.2.3. Critical procedures performed at first treatment Visit (Baseline V2)

- Review and assess compliance with subject's COPD medications during the run-in period
- Review and assess compliance with completing the eDiary during the run-in period
- Review AEs, SAEs and exacerbations

- Urine pregnancy test, if applicable
- Baseline dyspnea Index, BDI, patient global rating of COPD severity, patient global rating of change in COPD, SGRQ-C and CAT questionnaires in eDiary
- Review randomization criteria (Section 5.3)
- Register and randomize subject in RAMOS NG
- Pre-dose spirometry; IC and FEV_1
- Train subject on the proper use of ELLIPTA and DISKUS inhalers
- Dispense study medication
- Dispense rescue medication
- Optional pharmacogentic sample can be collected at V2 or any visit after.

7.3. Efficacy Assessments

7.3.1. HRQoL assessments: Completion of PRO questionnaires in the Electronic Diary

All subjects will be completing PRO questionnaires in the eDiary.

It is requested that questionnaires are completed before any procedures are performed on the subject.

All questionnaires will be completed using the eDiary at clinic and at home. Adequate time should be allowed to complete all items of the questionnaires and the questionnaires must be reviewed by the investigator or designated study staff for completeness and, if necessary, the subject must be encouraged to complete any missing items. Where more than one questionnaire is to be completed at a visit the order should be as follows:

1. Baseline dyspnea index (Visit 2) then Transient dyspnea index at subsequent visits
2. Patient global rating of COPD severity and global rating of change in COPD
3. St George's respiratory questionnaire
4. COPD Assessment Test

Instructions for completing the questionnaires can be found in the **SRM.**

7.3.1.1. Self Administered Computerised Baseline Dyspnea Index/Transitional Dyspnea Index (SAC BDI/TDI)

The BDI is used to measure the severity of dyspnea in patients at baseline. The TDI measures changes in the patient's dyspnea from baseline. The self-administered computerized version of the BDI/TDI (SAC BDI/TDI)[Mahler, 2004] is used to measure severity of dyspnea in patients at baseline (SAC BDI) on Day 1 (Visit 2) of treatment and change from the baseline (SAC TDI) at Week 4, 12 and 24 (Visits 3, 4 and 5). The

scores in both indexes depend on ratings for three different categories: functional impairment; magnitude of task, and magnitude of effort. SAC BDI/TDI should be completed before performing spirometry.

The SAC BDI/TDI was developed to address issues of potential bias in the interviewer administered (original) BDI/TDI [Mahler, 1984]. The SAC BDI/TDI provides a standardized approach to the measurement of dyspnea, equivalent to the original BDI/TDI with advantages over the interviewer method for grading dyspnea in patients with COPD by standardizing the process for each patient and eliminating individual judgment required by the interviewers when completing the original BDI/TDI. This also removes the need for the same investigator to conduct all interviews with a subject based on the patient's responses. SAC TDI provides a continuous measure of change in dyspnea using a visual analogue scale to record responses.

Details for the completion of the SAC BDI/TDI are provided in the SRM.

7.3.1.2. SGRQ-C

The St George's Respiratory Questionnaire-Chronic Obstructive Pulmonary Disease specific (SGRQ-C) will be completed by subjects at Randomisation (V2, Day 1), at Week 4, 12 and 24 or at the Early Withdrawal Visit (where applicable).

The SGRQ-C [Meguro, 2007] is a well established, disease-specific questionnaire. It was 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 scores equivalent to the SGRQ instrument [Meguro, 2007].

7.3.1.3. COPD Assessment Test (CAT)

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.

The CAT will be completed in the eDiary by subjects at Screening Visit 1 and Randomisation Visit 2 to assess their eligibility to enter the study. CAT is also completed at Weeks 4, 12 and 24. Additional instructions for completion of the CAT are provided in the **SRM.**

7.3.1.4. EXACT and the Evaluating Respiratory Symptoms- COPD (E-RS: COPD)

EXACT-PRO is a 14 item patient reported outcome instrument designed to capture information on the occurrence, frequency, severity, and duration of exacerbations of disease in patients with COPD [Leidy, 2011]. EXACT captures information on the severity of the respiratory and systemic manifestations of a COPD exacerbation as reported by the patient. The instrument is to be completed daily (typically 2 hrs before bedtime) using the electronic diary. The daily recording of information allows an assessment of the underlying day to day variability of a patient's symptoms and facilitates the detection of symptom worsening indicative of a COPD exacerbation. The total score for EXACT ranges from 0-100. The entire instrument is intended to be completed in about 3 minutes or less (typically the time required for completion decreases as the patient becomes more familiar with the tool and the electronic diary).

The E-RS: COPD consists of 11 items from the 14 item EXACT instrument [Leidy, 2014]. E-RS: COPD is intended to capture information related to the respiratory symptoms of COPD, i.e. breathlessness, cough, sputum production, chest congestion and chest tightness. The E-RS: COPD has a scoring range of 0-40 higher scores indicate more severe symptoms.

Three subscales of the E-RS are used to describe different symptoms; dyspnea, cough and sputum and chest symptoms.

The EXACT questionnaire will be completed by subjects in the eDiary, at home every night throughout the entire study, starting from Screening V1

7.3.1.5. Subject Global Rating of COPD Severity and Global Rating of Change in COPD

Subjects will complete the Global Rating of COPD Severity at Randomization Visit 2 and visits 3, 4 and 5 or Early Withdrawal Visit. This single global question will ask subjects to rate their severity of COPD on a four point scale (mild, moderate, severe, and very severe).

This question should be used immediately before the patient completes other visit specific questionnaires but after completion of SAC TDI questionnaire.

Subjects will also complete a Global Rating of Change in COPD (overall disease) question at Visits 3, 4 and 5 or Early Withdrawal Visit. Response options will be on a 7 point Likert scale ranging from much better to much worse. Completing the question at each Visit allows for early detection of response as well as continued response.

7.3.2. 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 standardized spirometry equipment provided by an external vendor.

All subjects will have spirometry performed at Screening to assess eligibility (see Section 7.2.2.1) and at Visits 2, 3, 4 and 5 during the treatment period.

For FEV_1 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 (i.e. a plateau in the volume time curve) and be free from artifacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons [Miller, 2005].

The largest FEV_1 and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort.

Spirometry for FEV_1 and FVC assessments that is not obtained as follows will be considered a protocol deviation:

- Started between 6:00AM and 11:00AM.
- After withholding albuterol/salbutamol (all visits) for ≥4 hours
- At Screening Visit 1, after wash out of medications as specified in the exclusion criteria in Section 5.2 (Concomitant Medications).
- At Screening Visit 1, before the morning dose of usual COPD medications
- At Visit 2 after discontinuing inhaled COPD medications and prior the first dose of study treatment
- At Visit 3, 4 and 5 after withholding the morning dose of study treatment.
- Pre dose assessment performed prior dosing.

Subjects should refrain from smoking for 1 hour prior to each pulmonary function test.

Trough FEV_1 measurements for UMC/VI or UMEC on Weeks 4, 12 and 24 (Visits 3, 4 and 5) should be performed 23 hours and 24 hours after the previous day's dose of study medication recorded in the eDiary. This will also provide trough FEV_1 measurements for the evening dose of salmeterol.

7.3.3. Inspiratory capacity (IC)

Inspiratory capacity (IC) is the volume of gas that can be taken into the lungs in a normal and full inhalation. Starting from the resting inspiratory position it is equal to the tidal volume plus the inspiratory reserve volume. IC has been widely used to assess static and dynamic hyperinflation in patients with COPD.

IC will be measured by spirometry **prior** to forced manoeuvres pre-dose at Visits 2 (30 and 5 min prior to dosing) and at trough at Visits 3, 4, and 5 (23 and 24 hrs post dosing on the previous day). For IC determination the average of at least three acceptable manoeuvres should be recorded. Subjects should be tested while sitting, relaxed and wearing a nose clip. They should be asked to breathe regularly for several breaths until the end-expiratory lung volume is stable (this usually requires at least three tidal manoeuvres) then urged to take a deep breath to Total Lung Capacity (TLC) with no hesitation.

Spirometry for IC determination done in conjunction with FEV_1 and FVC assessments that is not obtained as follows will be considered a protocol deviation:

- Started between 6:00AM and 11:00AM.
- After withholding albuterol/salbutamol (all visits) ≥4 hours
- At Visit 2 after discontinuation of run-in medication
- At Visit 3, 4 and 5 after withholding the morning dose of study drug

7.3.4. COPD Exacerbation

A mild exacerbation is defined as worsening of symptoms that require no treatment with antibiotics or steroids, and is self managed by the patient by an increase of inhaled rescue medications. A moderate COPD exacerbation is defined as worsening symptoms of COPD that require treatment with oral/systemic corticosteroids and/or antibiotics. A severe exacerbation is defined as worsening symptoms of COPD that require in-patient hospitalization or emergency room for longer than 24 hrs.

If a subject experiences a mild, moderate or severe COPD exacerbation, the COPD exacerbation page of the eCRF should be completed. COPD exacerbations should not be recorded as an AE, unless they meet the definition of a SAE. Details of COPD exacerbation identification, categorization and treatment guidelines are described in Appendix 5.

Subjects who experience a mild exacerbation during the run-in period will not be withdrawn from the study. However, Subjects who experience moderate or severe exacerbation during the run-in period will be withdrawn from the study and will not be allowed to be re-screened.

Subjects who experience a mild, moderate or severe exacerbation during the treatment period, will **not** be withdrawn from the study unless the investigator or GSK medical monitor think it is best for the patient to withdraw from the study.

Signs and symptoms of COPD included on the electronic diary cards will not be considered AEs and will not be recorded in the eCRF.

The time period for collection of COPD exacerbations will be from the Pre-Screening (Visit 0) until completion of the follow-up contact. If a subject experiences a COPD exacerbation from the time the ICF is signed until randomization, summary information (yes/no status question) will be collected in the eCRF. COPD exacerbations after randomization through follow-up will be recorded on the COPD exacerbation page of the eCRF.

7.3.5. Clinically important deterioration (CID)

Clinically important deterioration (CID) is a composite endpoint defined as:

- A decrease of ≥ 100 mL from baseline in trough FEV_1

- A deterioration in HRQoL defined as ≥ 4 units increase from baseline in SGRQ
- The occurrence of an on-treatment moderate/severe COPD exacerbation

In addition, this study will explore CAT and TDI PROs as part of the composite endpoint.

7.3.6. Rescue albuterl/salbutamol use

Subjects will record the number of daily albuterol/salbutemol puffs they use in the eDiary. In addition, in some countries and selected sites the number of puffs will be collected through the eMDI device (Section 6.2)

7.3.7. Physical activity monitor (study subset)

Physical activity limitation is a common feature of COPD and its measures are highly related to the degree of disease severity [Watz, 2009].

Reduced physical activity levels in COPD is associated with increased morbidity and mortality, sustained disability, depression, and social and physical isolation [Shu-Yi, 2014; Gimeno, 2014]

Improved activity has been identified as an important factor that may modify morbidity and mortality in COPD [Moy, 2012].

The Actigraph GT9X physical activity monitor will be used to measure levels of activity. The activity monitor will be worn by up to approximately 150 subjects per treatment arm for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3 (Week 4) and for 7 days prior to Week 24 (Visit 5).

There will be 4 assessment periods, including a screening assessment in order to provide a reliable estimate of habitual physical activity. Each subject will be given an activity monitor and instruction leaflet at the start of each assessment period. Further details of distribution, operation and retrieval of the monitors will be provided in the **SRM**.

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1)

Safety endpoint includes:

- Incidence of adverse events

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

The definitions of an AE or SAE can be found in Appendix 4.

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

7.4.1.1. 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 7.4.1.3), at the timepoints 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 CRF.
- 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 12.4.4 to Section 12.4.6)

7.4.1.2. 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?

7.4.1.3. 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).

7.4.1.4. Pneumonia Events

Investigators will be required to fill out a pneumonia event specific eCRF within one week of when the pneumonia AE/SAE(s) is first reported.

7.4.1.5. Cardiovascular and Death Events

For any cardiovascular events detailed in (Section 12.4.3) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs 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 CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF 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.

7.4.1.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following disease related events (DREs) are common in subjects with COPD and can be serious/life threatening:

- COPD exacerbation

COPD exacerbations are associated with the disease to be studied and will not be recorded as AEs unless the exacerbation meets the definition of a 'serious' AE. Exacerbations that meet the definition of 'serious' AEs will be recorded on the appropriate eCRF section and should be reported to GSK for all subjects regardless of whether or not they are randomized to study medication. Signs and symptoms of COPD included on the electronic diary will not be considered AEs and will not be recorded in the eCRF

7.4.1.7. 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.

7.4.2. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of Screening and until the follow-up contact.
- 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 7.

7.4.3. Medical Device Incidents (Including Malfunctions)

Procedures for documenting medical device incidents are provided in Appendix 6.

7.4.4. Electrocardiogram (ECG)

A Single 12-lead ECG will be obtained at Screening using an ECG machine provided by the investigational site that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

The 12-lead ECG measurement and rhythm strip (10 seconds) will be obtained before spirometry testing. ECG measurement should be obtained after subjects have rested for approximately 5 minutes then the subjects should be placed in the supine position for the ECG measurements. An ECG is only required at Screening Visit 1 for eligibility assessment only.

The investigator, a designated sub-investigator, or other appropriately trained site personnel will be responsible for performing and interpreting the 12-lead ECG at Screening Visit 1. The investigator must provide his/her dated signature on the original paper tracing, attesting to the authenticity of the ECG machine interpretation.

7.5. Genetics

Information regarding genetic research is included in Appendix 3

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, 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.
- CRFs (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 purpose of this study is to demonstrate improvements in lung function for subjects treated with UMEC/VI compared with UMEC for 24 weeks.

The primary endpoint is change from baseline in trough FEV_1 at Week 24.
The null hypothesis is no difference between treatment groups (H0: $\mu T - \mu S = 0$), with the alternative hypothesis that there is a difference between treatment groups (H1: $\mu T - \mu S \neq 0$), where μT is the mean change from baseline for UMEC/VI and μS is the mean change from baseline for UMEC.

9.2. Sample Size Considerations

The primary endpoint is change from baseline in trough FEV_1 at Week 24. As an important aim of the study is to compare UMEC/VI, UMEC and salmeterol with respect to HRQoL the sample size has been calculated to provide sufficient power for the comparison of the primary and secondary endpoint TDI, at Week 24.

The sample size calculations use a two-sided 5% significance level and an estimate of between subject standard deviation for TDI of 2.94 units. The estimate of SD is based on DB2113373 [Donohue, 2013], a study which consisted of treatment arms of UMEC/VI 62.5/25, UMEC 62.5 VI (Vilanterol) 25mcg and placebo and is the value at Day 168 in a subgroup of subjects who were ICS free at screening. Based on these data, 727 evaluable subjects per treatment arm will be required to provide 90% power to detect a statistically significant difference if the true difference is 0.5 units, ½ the MCID, between UMEC/VI and UMEC. The smallest observed effect predicted to result in a statistically significant difference between treatment groups is 0.31 units.

With this number of evaluable subjects per arm, the study will have >99% power assuming a true treatment difference of 80mL between UMEC/VI and UMEC for trough FEV1 at 24 weeks at the two-sided 5% significance level. This calculation uses a SD for trough FEV1 of 240mL, based on prior results for trials comparing dual bronchodilators versus single bronchodilators (Donohue, 2013; Bateman, 2013). The smallest observed effect predicted to result in a statistically significant difference between treatment groups is 25mL.

In order to account a for a 10% withdrawal rate**,** approximately 808 subjects per treatment arm will be randomised.

9.2.1. Sample Size Assumptions

9.2.2. Sample Size Sensitivity

The assumption of a SD of 2.94 units for the TDI total score is based on estimates from previous studies. The following table presents the power achieved with the proposed sample size of 727 randomised subjects per arm, should the assumption around the SD of the data change.

The actual assumptions used in the sample size calculation are shaded.

Endpoint	Between subject SD	Treatment Difference	Power
TDI	2.54	0.5	96%
	2.74	0.5	94%
	2.94	0.5	90%
	3.14	0.5	86%
	3.34	0.5	81%

9.2.3. Sample Size Re-estimation or Adjustment

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

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	• 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.	• Subject Disposition • Reasons for withdrawal prior to randomisation • Inclusion, exclusion and randomisation criteria deviations • SAEs for non-randomised

Population	Definition / Criteria	Analyses Evaluated
		subjects
Intent-to-treat (ITT)	• All randomized subjects, excluding those who were randomized in error and received at least one dose of study medication. 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 randomization number will be considered to have been randomized. • Displays will be based on the treatment to which the subject was randomized.	• Study Population • Efficacy • Safety
Intent-to-treat ICS free (ITT ICS free)	• All subjects in the ITT Population who have not received ICS.	• Study Population • Efficacy • Safety

9.3.2. Interim Analysis

No interim analysis is planned for the study.

9.4. Key Elements of Analysis Plan

Treatment Comparisons

The primary treatment comparison of UMEC/VI with UMEC will be performed on the ITT population.

The other treatment comparisons of UMEC/VI and UMEC with Salmeterol will be performed on the ITT population and ITT ICS free population.

9.4.1. Primary Analyses

The treatment comparison of primary interest will be UMEC/VI versus UMEC for the primary endpoint of change from baseline in trough FEV_1 at Week 24. The primary analyses will be performed using a mixed model repeated measures (MMRM) analysis and will be based on a two-sided hypothesis testing approach on the ITT Population.

In order to account for multiplicity across treatment comparisons and endpoints, a step-down closed testing procedure will be applied whereby inference for secondary and other endpoints or treatment comparisons are dependent upon statistical significance having been achieved for the primary comparison. If the primary comparison is significant i.e. the associated p-value for UMEC/VI versus UMEC for change from baseline in trough FEV1 at Week 24 is below 0.05, this will allow inference of treatment comparisons (UMEC/VI versus UMEC on all other endpoints, and UMEC/VI versus Salmeterol and UMEC versus Salmeterol on all endpoints including the primary endpoint), which will be declared statistically significant if the associated p-value is below 0.05.

There will be 2 analyses one for one for the German Federal Joint Committee (G-BA) and one for the rest of the world (ROW).

The step-down closed testing procedure only applies to the ROW. For the G-BA statistical inference for secondary and other endpoints or treatment comparisons will not be conditional on achieving statistical significance of the primary comparison.

The primary endpoint of mean change from baseline in trough FEV1 at the end of Week 24 and secondary endpoint change from baseline in TDI score at Week 24 will both be analysed using MMRM analysis. The MMRM analysis for change from baseline in trough FEV1 and TDI will include measurements at Treatment Weeks 4, 12 and 24. Treatment group (a categorical variable) will be fitted as the explanatory variable with appropriate pre-defined variables, stratum (number of bronchodilators per day during run-in) and baseline values, fitted as covariates. Visit (nominal) will be fitted as a categorical variable and visit-by-baseline and visit-by-treatment interaction terms will be included to allow treatment effects to be estimated at each visit separately. The variance covariance matrix will be assumed to be unstructured (based on previous experience no issues are expected with fitting models with this matrix structure).

While missing data are not explicitly imputed in the primary MMRM analyses, there is an underlying assumption that the data are missing at random.

The estimated treatment differences between UMEC/VI versus UMEC for each endpoint will be presented with the 95% confidence intervals for the difference and the p-value.

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

9.4.2. Other Analyses

The MMRM analysis will be repeated for the ITT ICS free population. Estimated differences between UMEC/VI or UMEC and Salmeterol will be presented together with 95% confidence intervals (CIs) for the difference and p-values.

Secondary and other efficacy endpoints and treatment comparisons will be adjusted for multiplicity as per Section 9.4.1.

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

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 eCRF 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 randomization 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
CAT	COPD Assessment Test
CI	Confidence Intervals
CID	Clinically important deterioration
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine phosphokinase
CRF	Case Report Form
CV	Cardiovascular
DPI	Dry Powder Inhaler
DRE	Disease Related Event
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
eMDI	Electronic Metered Dose Inhaler
E-RS	Evaluating Respiratory Symptoms- COPD Tool
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
IB	Investigator Brochure
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IP	Investigational product
INR	International normalized ratio
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

mcg	Microgram
MCID	Minimal Clinically Important Difference
MDI	Metered Dose Inhaler
mL	Milliliter
mMRC	Modified Medical Research Council
MMRM	Mixed Models Repeated Measures
MSDS	Material Safety Data Sheet
NYHA	New York Heart Association
OTC	Over the Counter
PGx	Pharmacogenetic
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PP	Per Protocol
prn	As required
QTc	QT interval corrected for heart rate
RAP	Reporting and Analysis Plan
SABA	Short Acting Beta-Agonist
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SRT	Safety Review Team
TDI	Transition Dyspnea Index
RAMOS NG	Randomization and medication ordering system new generation
ULN	Upper Limit of Normal
UMEC	Umeclidinium (GSK573719)
UMEC/VI	Umeclidinium & Vilanterol as a fixed dose combination
VI	Vilanterol Trifenate

Trademark Information

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

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

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 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**
• 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 SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve , stabilize, or return to within normal ranges. baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment. Permanently discontinue stud**y treatment and may continu**e subject in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained within a week after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or

Liver Chemistry Stopping Criteria - Liver Stopping Event	
MONITORING: **<u>For bilirubin or INR criteria:</u>** • 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 normal ranges. • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • 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 normal ranges.	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 **<u>For bilirubin or INR criteria:</u>** • 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.

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 ≥ 3xULN **and** bilirubin ≥ 2xULN. 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 ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **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 SRM.

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 etiology 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 any concomitant medicines;
- COPD susceptibility, severity, and progression of 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.

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 the baseline visit, after the subject has been randomized and 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 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.

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 <u>meeting</u> 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 <u>NOT</u> 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., hospitalization 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 hospitalization or prolongation of existing hospitalization

NOTE:

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

d. Results in disability/incapacity

NOTE:

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

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

e. Is a congenital anomaly/birth defect

f. Other situations:

- 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 hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** 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.

12.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial 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
- 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 by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: COPD Exacerbation Identification, Categorization and Treatment Guidelines

12.5.1. 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 usage in their daily eDiary
- 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

12.5.2. COPD Exacerbation Severity

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

> **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 hospitalization or 24 hrs in the emergency room.

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.

12.5.3. 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 outlined 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 IP as these additional medications may increase the risk of overdose. If necessary the PI or other health care personnel may stop the subject's IP temporarily in order to treat the COPD exacerbation.

12.5.4. 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 ≤ 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

12.5.5. 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 not exceed 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

12.5.6. 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 12.5.1.

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.

12.5.7. 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.

12.5.8. 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.

12.6. Appendix 6: Definition of and Procedures for Documenting Medical Device Incidents

12.6.1. Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.2 for the list of GSK medical devices).

Medical Device Incident Definition:

- Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other persons or to a serious deterioration in their state of health.
- Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- an **incident** associated with a device happened and
- the **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.
- A serious deterioration in state of health can include:
- life-threatening illness
- permanent impairment of body function or permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent one of the above
- fetal distress, fetal death or any congenital abnormality or birth defects

Examples of incidents

- a patient, user, care giver or professional is injured as a result of a medical device failure or its misuse
- a patient's treatment is interrupted or compromised by a medical device failure
- misdiagnosis due to medical device failure leads to inappropriate treatment
- a patient's health deteriorates due to medical device failure

12.6.2. Documenting Medical Device Incidents

Medical Device Incident Documenting:
• Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 4. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK. • It is very important that the investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the design to prevent recurrence.

12.7. Appendix 7: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

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

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization 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, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.7.2. 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 fetal 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. 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 be withdrawn from the study

12.8. Appendix 8: Country Specific Requirements

No country-specific requirements exist.

12.9. Appendix 9: protocol changes

Scope:

This amendment applies to all sites

Protocol Changes for Amendment No.1 are summarised below.

Strike through text refers to deleted text and underlined refers to added text.

Protocol Changes:

Title
Rationale for change: Correct a typographical error in the title: Umeclidi~~m~~ium to Umeclidinium

Regulatory Agency Identifying Number(s):
Rationale for change: To correct a typographical error of the EudraCT no. and add an IND no.
Revised text:-EudraCT no ~~2016-002513-226,~~ 2016-002513-22 , IND no. 104479

Section 1
Overall Design
Rationale for change: To Correct a typographical error in the last paragraph.
Revised text: ~~Salmeterol~~, salbutamol
"This is a multi-centre, randomized, double blind, double-dummy, 3-arm parallel group study. Eligible subjects will be stratified based on long-acting bronchodilator usage during the run-in (none, one or 2 long-acting bronchodilators per day) and randomized in a ratio of 1:1:1 to UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA inhaler, or UMEC (62.5 mcg once daily) administered via the ELLIPTA or salmeterol (50 mcg BID) administered via the DISKUS.

There will be a total of 5 clinic visits and one follow-up phone call (Visit 6). The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) if subject does not take or has not taken any excluded protocol medications, but must be completed prior to initiating any Visit 1 procedures.

Subjects, who meet all the eligibility criteria at Screening, will enter a run-in period for 4 weeks in order to continue to assess the subject's eligibility for the study. During the run-in period subjects will continue with their inhaled COPD medications (excluding ICS and any exclusionary medications). In addition, subjects will be provided with short acting albuterol/~~salmeterol~~ salbutamol to be used on as needed basis for relief of COPD symptoms (rescue medication) throughout the study".

Section 4.4 Design justification: To be consistent with Section 7.3.1.5 and Section 7.1 the wording has been updated.
Rationale for change: Ensure consistency with Section 7.3.1.5 and Section 7.1 the wording has been changed in paragraph 5.
Revised text: "Other endpoints such SAC TDI, E-RS, SGRQ-C, CAT, Subject Global Rating of COPD Severity and ~~Change in~~ Global Rating ~~impression~~ of Change in COPD ~~disease severity~~ are captured to allow responder analyses and to provide comparative data on PROs between the treatment groups".

Section 7.1 Time and Event table
Rationale for change; to:
Correct an un-intentional deletion of the ("x") in some cells and confirm that concomitant medications should be reviewed at every clinic visit.
Increase the visit window from ~~± 2~~ days to -7/+2
Ensure consistency of wording between Section 7.2 and table 7.1. "~~Written~~" was deleted
Include height and weight at Screening and correct errors in foot note no.11
"In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2 and within 60 ~~and 90~~ days from V3 ~~and V4~~ respectively"

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 ~~±2~~ -7/+2 days prior Visit 1**	**28 ~~± 2~~ -7/+2 days prior Visit 2**	**1~~± 2~~ -7/+2 days**	**28 ~~±2~~ -7/+2 days**	**84 ± 2 days**	**168 ~~±2~~ -7/+2 days**		**7~~± 2~~ 3 days after V5 or EW Visit**
Screen/Baseline								
~~Written~~ Informed consent	X							
Demography	X							
Medical/COPD history		X						
Smoking history/status		X						
Smoking cessation counselling		X						
Concomitant medication assessment	X	X	X	X	X	X	X	X
Height and weight		X						
Cardiovascular History/family history of premature CV disease])		X						
Screening spirometry (including post bronchodilator testing)[3]		X						
CAT questionnaire		X	X					
Verify Inclusion/Exclusion Criteria		X						
Training on use of inhalers		X	X					
Training on use of eDiary and eMDI		X	X					
Verify randomization Criteria			X					
Register Visit in InForm	X	X	X	X	X	X	X	X
Register Visit in RAMOS NG	X	X	X	X	X	X	X	X

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 ±2 -7/+2 days prior Visit 1**	**28 ± 2 -7/+2 days prior Visit 2**	**1± 2 -7/+2 days**	**28 ±2 -7/+2 days**	**84 ± 2 days**	**168 ±2 -7/+2 days**		**7± 2 3 days after V5 or EW Visit**
Efficacy/HRQoL assessments								
Spirometry, including pre-dose FEV_1, trough FEV_1 and inspiratory capacity			X	X	X	X		
SAC BDI questionnaire [4]			X					
SAC TDI questionnaire [4]				X	X	X		
SGRQ-C questionnaire [4]			X	X	X	X		
CAT questionnaire [4]		X	X	X	X	X		
EXACT/ER-S: COPD [5]		→	→	→	→	→		
Patient Global Rating of COPD severity			X	X	X	X		
Patient Global Rating of Change in COPD				X	X	X		
Safety assessments								
Adverse events/Serious adverse events [6]	X	X	X	X	X	X	X	X
COPD exacerbation assessment	X	X	X	X	X	X	X	X
12-Lead ECG		X						
Urine pregnancy test [7]		X	X			X	X	
Pharmacogenetic sample[8]			←	X	→			
Medication/Supplies								
Dispense rescue albuterol/slabutamol. Dispense MDI[9]		X	X	X	X	X		
Assess COPD medication compliance[10] during run-in			X					
Dispense eDiary		X						
Assess compliance with eDiary during run-in			X					
Collect rescue albuterol/slabutamol.			X	X	X	X	X	
Collect eDiary						X	X	
Dispense study treatment[11]			X	X	X			

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 ~~±2~~ -7/+2 days prior Visit 1**	**28 ~~± 2~~ -7/+2 days prior Visit 2**	**1~~± 2~~ -7/+2 days**	**28 ~~±2~~ -7/+2 days**	**84 ± 2 days**	**168 ~~±2~~ -7/+2 days**		**7~~± 2~~ 3 days after V5 or EW Visit**
Collect study treatment				X	X	X	X	
Assess study treatment compliance during treatment[10]				X	X	X	X	
Study sub-set								
Physical activity monitor[12]		X	X	X		X		
Collect Physical activity monitor						X	X	

1. Pre-screen Visit 0 must be completed prior to Screening Visit1. It can be completed 2 weeks prior or on the same day of V1, if no wash out of exclusionary medications is required.
2. Early Withdrawal Visit: Subjects that withdraw should return to the clinic as soon as possible to complete the Early Withdrawal Visit procedures.
3. Spirometry at screening should be performed as described in (Section 7.2.2.1).
4. SAC BDI, SAC TDI, SGRQ-C, CAT questionnaires will be completed at clinic visits and in the eDiary
5. EXACT/ER-S: COPD is completed daily in the eDiary approximately 2 hours before bed-time, starting on Day 1 of the run-in period.
6. For the start date of collecting AEs and SAEs see (Appendix 4)
7. Pregnancy test: for females for child bearing potential only.
8. Pharmacogenetic sample may be drawn at visit 2 or any visit after.
9. Rescue medication use to be recorded in the eDiary daily **and** in some sites in the eDiary and the eMDI
10. Sites are requested to call subjects every 2 weeks to remind them to take study treatment regularly and to record the time of the morning and evening dose in the eDiary.
11. In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2 and within 60 ~~and 90~~ days from V3 ~~and V4~~ respectively.
12. The Actigraph GT9X should be worn for 7 days from Visit 1, for 7 days from Visit 2, for 7 days from Visit 3 and for 7 days prior to Visit 5.

Section 7.2.2 Critical procedures performed at Screening (Visit 1)
Rationale for change: To clarify that height and weight are collected at V1
Revised text: "Height and weight"

Section 7.3.2 Spirometry
Rationale for change: To further clarify that spirometry at Screening Visit 1 should be performed before subject inhales their usual morning COPD medication(s) a bullet point was added. "At Screening Visit 1, before the morning dose of usual COPD medications"
Revised text:
"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 standardized spirometry equipment provided by an external vendor.

All subjects will have spirometry performed at Screening to assess eligibility (see Section 7.2.2.1) and at Visits 2, 3, 4 and 5 during the treatment period.

For FEV_1 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 (i.e. a plateau in the volume time curve) and be free from artifacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons [Miller, 2005].

The largest FEV_1 and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort.

Spirometry for FEV_1 and FVC assessments that is not obtained as follows will be considered a protocol deviation:

- Started between 6:00AM and 11:00AM.
- After withholding albuterol/salbutamol (all visits) for ≥4 hours
- At Screening Visit 1, after wash out of medications as specified in the exclusion criteria in Section 5.2 (Concomitant Medications).
- At Screening Visit 1, before the morning dose of usual COPD medications
- At Visit 2 after discontinuing inhaled COPD medications and prior the first dose of study treatment
- At Visit 3, 4 and 5 after withholding the morning dose of study treatment.
- Pre dose assessment performed prior dosing.

Subjects should refrain from smoking for 1 hour prior to each pulmonary function test.

Trough FEV_1 measurements for UMC/VI or UMEC on Weeks 4, 12 and 24 (Visits 3, 4 and 5) should be performed 23 hours and 24 hours after the previous day's dose of study

medication recorded in the eDiary. This will also provide trough FEV_1 measurements for the evening dose of salmeterol".

7.3.7 Physical activity monitor (study subset)

Rationale for changes: Ensure consistency of the wording between Section 1 and Section 4.1 "overall design" and Section 7.3.7.
per treatment arm added to paragraph 4.
Revised Text:
Physical activity monitor (study subset)
"Physical activity limitation is a common feature of COPD and its measures are highly related to the degree of disease severity [Watz, 2009].
Reduced physical activity levels in COPD is associated with increased morbidity and mortality, sustained disability, depression, and social and physical isolation [Shu-Yi, 2014; Gimeno, 2014]

Improved activity has been identified as an important factor that may modify morbidity and mortality in COPD [Moy, 2012].

The Actigraph GT9X physical activity monitor will be used to measure levels of activity. The activity monitor will be worn by up to approximately 150 subjects per treatment arm for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3 (Week 4) and for 7 days prior to Week 24 (Visit 5).

There will be 4 assessment periods, including a screening assessment in order to provide a reliable estimate of habitual physical activity. Each subject will be given an activity monitor and instruction leaflet at the start of each assessment period. Further details of distribution, operation and retrieval of the monitors will be provided in the **SRM"**.

TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	A 24-week treatment, multi-center, randomized, double-blind, double-dummy, parallel group study to compare Umeclidinium/Vilanterol, Umeclidimium, and Salmeterol in subjects with chronic obstructive pulmonary disease (COPD)

Compound Number: GSK2592356

Development Phase IV

Effective Date: 13-SEP-2016

Author(s): PPD

SPONSOR SIGNATORY:

PPD

13 Sept. 2016

David Lipson, MD — Date

GSK

PPD

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD	Telephone: PPD PPD	Cell: PPD	Fax: PPD	GlaxoSmithKline Stockley Park West, 1-3 Ironbridge Road, Heathrow, Uxbridge, Middlesex, UB11 1BT, United Kingdom
Secondary Medical Monitor		PPD MD Telphone: PPD PPD	Cell:	Fax:	GlaxoSmithKline Stockley Park West, 1-3 Ironbridge Road, Heathrow, Uxbridge, Middlesex, UB11 1BT, United Kingdom
SAE contact information		Telephone: PPD PPD	Cell: PPD	Fax: PPD	GlaxoSmithKline Stockley Park West, 1-3 Ironbridge Road, Heathrow, Uxbridge, Middlesex, UB11 1BT, United Kingdom

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact

person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): IND no. 106616 and EudraCT no. 2016-002513-226

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described 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 201749

Rationale

The primary purpose of this study is to demonstrate improvements in lung function in subjects treated with Umeclidinium/Vilanterol (UMEC/VI) compared with Umeclidinium (UMEC) for 24 weeks. A further important aspect of the study is to evaluate the effect of UMC/VI, UMEC, and salmeterol with respect to health-related quality of life (HRQoL), measured through patient reported outcomes (PROs) questionnaires, and lung function. Additional assessments to further evaluate other measures of chronic obstructive pulmonary disease (COPD) efficacy and symptoms control will be performed.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To compare the effect of UMEC/VI (62.5/25 mcg once daily) with UMEC (62.5 mcg once daily) on lung function	• Change from baseline in trough Forced Expiratory Volume in One Second (FEV_1) at week 24
Secondary	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on patient reported outcomes (PROs)	• Change from baseline in self administered computerised (SAC) transient dyspnea index (TDI) • Percentage of TDI responders according to SAC TDI score. A responder is defined as a ≥1 unit improvement in SAC TDI score • Assessment of respiratory daily symptoms over 24 weeks using Evaluating Respiratory Symptoms-COPD (E-RS) and its subscales (breathlessness, cough and sputum and chest symptoms) • Percentage of E-RS responders according to E-RS score (defined as reduction in E-RS score of ≥2 or ≥3.35 units) from baseline • Change from baseline in St George's Respiratory Questionnaire (SGRQ-C) • Percentage of responders according to SGRQ-C total score (defined as a 4 point or greater reduction from

Objectives	Endpoints
	baseline) • Change from baseline in COPD assessment test (CAT) • Percentage of responders according to CAT (defined as a ≥2 unit improvement in score from baseline)
Other	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on other COPD efficacy measures	• Rate of mild, moderate or severe exacerbations • Time to first mild, moderate or severe exacerbation • Rate of moderate or severe exacerbation • Time to moderate or severe exacerbation • Time to severe exacerbations • Time to clinically important deterioration (CID) composite endpoint • Time to clinically important deterioration composite endpoint excluding FEV_1 • Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the electronic diary (eDiary) over 24 weeks • Inspiratory capacity (IC) • Full Vital capacity (FVC) • Change from baseline in trough FEV_1 • Change from baseline in global impression of disease severity

Objectives	Endpoints
Safety	
• To evaluate safety and tolerability of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5mcg once daily) and salmeterol 50mcg twice daily)	• Incidence of adverse events
Exploratory	
• To compare albuterol/salbutamol use captured in the eDiary with the electronic metered dose inhaler (eMDI) device	• Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the eMDI device over 24 weeks as data allow
• To explore the effect of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on physical activity	• Change from baseline in physical activity
• To investigate the CID composite endpoint ability to predict short term outcomes	• To compare physical activity levels, ER-S, rescue medication use, exacerbations and mortality in subjects with and without a CID

Overall Design

This is a multi-centre, randomized, double blind, double dummy, 3-arm parallel group study. Eligible subjects will be randomized in a ratio of 1:1:1 to UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA® dry powder inhaler (DPI), or UMEC (62.5 mcg once daily) administered via the ELLIPTA DPI or salmeterol (50 mcg twice daily (BID)) administered via the DISKUS® DPI.

Eligible subjects at Screening will enter a run-in period for 4 weeks during which they continue taking their inhaled COPD medications (excluding ICS and any exclusionary medications). In addition, subjects will be provided with short acting albuterol/salmeterol to be used on as needed basis (rescue medication) throughout the study.

Subjects who experience a moderate or severe COPD exacerbation during the run-in period will be deemed run-in failures. Subjects experiencing a mild exacerbation, defined as worsening of symptoms that requires **no** treatment with antibiotics or steroids and is self managed by the patient by an increase of inhaled rescue medication, will be allowed to continue in the study.

At the randomization Visit 2 (Day 1) those subjects who successfully complete the run-in period as well as meet the other pre-defined eligibility and randomization criteria will discontinue their inhaled COPD medications and will be randomized to one of the 3 treatment arms for 24 weeks.

All subjects will be given an eDiary for use during the run-in, and treatment period to complete PRO questionnaires and record medical problems experienced during the study. Subjects will be performing slow and forced spirometry at specific visits.

In addition, a subset of subjects up to 150 per treatment arm will undergo assessment of their physical activity measured through a physical activity monitor (Actigraph GT9X) worn for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3, and for 7 days prior to last clinic Visit (Visit 5).

There will be a total of 5 clinic visits and one follow-up phone call (Visit 6). The total duration of subject participation in the study will be approximately 29 to 31 weeks consisting of 2 weeks pre-screening if necessary, 4 weeks run-in, 24 week treatment and one week Follow-Up.

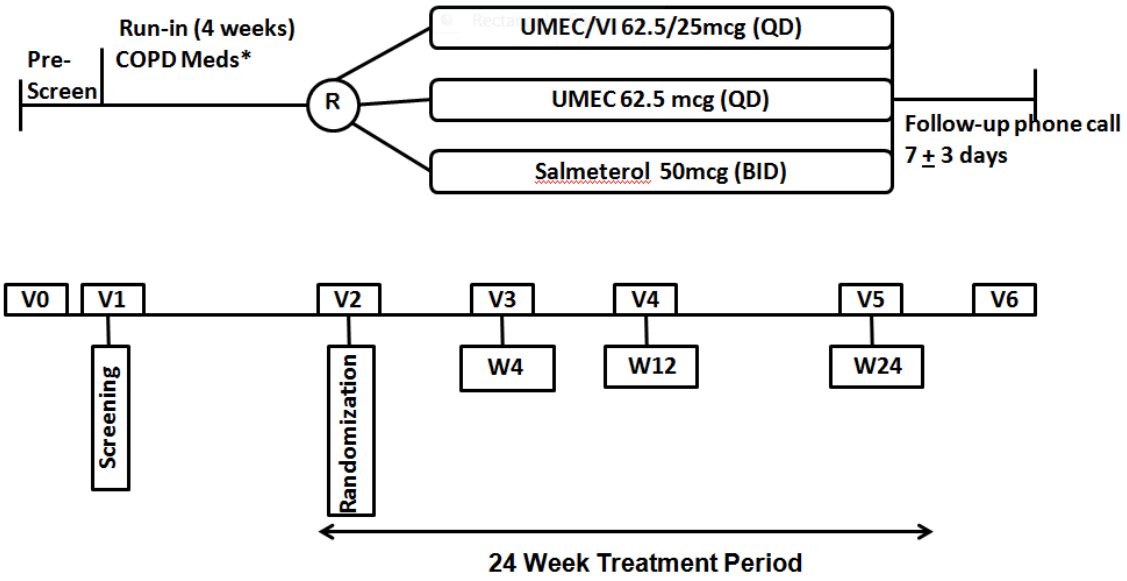
Subjects will be considered to have completed the study upon completion of the Follow–Up contact by telephone.

Treatment Arms and Duration

Subjects will be stratified based on long-acting bronchodilator usage during the run-in (none, one or 2 long-acting bronchodilators per day) and randomized in a ratio of 1:1:1 to either

- UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA DPI) or
- UMEC (62.5 mcg once daily) administered via the ELLIPTA DPI or
- Salmeterol (50 mcg BID) administered via DISKUS

Study schematic



*Inhaled COPD medications including LABAs, LAMAs or LABA/LAMA combination products are allowed in run-in. ICS alone or in combination with a bronchodilator or any exclusionary medications are not allowed.

Type and Number of Subjects

Approximately 3232 subjects will be screened, such that 2424 subjects will be randomized and approximately 2181 evaluable subjects complete the study.

Analysis

The primary purpose of this study is to demonstrate improvements in lung function for subjects treated with UMEC/VI compared with UMEC for 24 weeks.

The primary endpoint is change from baseline in trough FEV_1 at Week 24.

The null hypothesis is no difference between treatment groups (H0: $\mu T - \mu S = 0$), with the alternative hypothesis that there is a difference between treatment groups (H1: $\mu T - \mu S \neq 0$), where μT is the mean change from baseline for UMEC/VI and μS is the mean change from baseline for UMEC.

The primary endpoint of mean change from baseline in trough FEV_1 at the end of Week 24 will be analysed using Mixed Models repeated Measures (MMRM) analysis. The MMRM analysis will include measurements at Treatment Weeks 4, 12 and 24. Treatment group (a categorical variable) will be fitted as the explanatory variable with appropriate pre-defined variables, stratum (number of bronchodilators per day during run-in) and baseline values, fitted as covariates. Visit (nominal) will be fitted as a categorical variable and visit-by-baseline and visit-by-treatment interaction terms will be included to allow treatment effects to be estimated at each visit separately. The variance covariance matrix

will be assumed to be unstructured (based on previous experience no issues are expected with fitting models with this matrix structure).

The estimated treatment differences between UMEC/VI versus UMEC for each endpoint will be presented with the 95% confidence intervals for the difference and the p-value.

2. INTRODUCTION

2.1. Study Rationale

Chronic obstructive pulmonary disease (COPD) is associated with poor health-related quality of life (HRQoL). Pharmacologic therapy is used to improve lung function, reduce symptoms, frequency and severity of exacerbations, and improve patients HRQoL [GOLD, 2015]. Umeclidinium/Vilanterol (UMEC/VI 62.5/25 mcg) is indicated for the maintenance treatment of COPD that contain long-acting muscarinic antagonist (LAMA) and long-acting beta$_2$-agonist (LABA) bronchodilators. Umeclidinium (UMEC) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Salmeterol has long been used for symptoms management of COPD. However, a direct comparison of these maintenance therapies has not been conducted with respect to HRQoL.

The primary purpose of this study is to demonstrate improvements in lung function for subjects treated with UMEC/VI compared with UMEC for 24 weeks. The effect of UMC/VI, UMEC, and salmeterol with respect to patient HRQoL measured through patient reported outcomes (PROs) questionnaires, symptoms and lung function will also be evaluated.

2.2. Brief Background

COPD is characterized by an airflow limitation which is not fully reversible, usually progressive and accompanied by a chronic cough, sputum production and dyspnea which can be a major cause of disability and anxiety associated with the disease [Maleki-Yazdi, 2014]

Furthermore, acute exacerbations contribute to the overall severity of disease as these episodes are accompanied by worsened symptoms and are associated with increased decline in lung function and mortality [Wedzicha, 2013; Schmidt, 2014].

Pharmacologic therapy is used to improve lung function, reduce symptoms, reduce the frequency and severity of exacerbations, and also to improve health status and exercise tolerance. Maintenance treatment is recommended primarily through the use of LABAs or LAMAs. COPD treatment guidelines recommend an incremental approach to pharmacological treatment as the disease state worsens, involving the use of combinations of drug classes with different or complementary mechanisms [GOLD, 2015].

UMEC/VI inhalation powder is a combination of UMEC (umeclidinium bromide), a LAMA, and VI (Vilanterol), a LABA, delivered via the ELLIPTA® dry powder inhaler (DPI). UMEC/VI at a dose of 62.5/25mcg once-daily is marketed in the United States (US) and Europe under the trade name ANORO® ELLIPTA®.
UMEC (62.5 mcg) inhalation powder is marketed in the United States (US) and Europe under the trade name INCRUSE® ELLIPTA®. UMEC (62.5mcg) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. UMEC (62.5 mcg) improves forced expiratory volume in one second (FEV_1), dyspnea

and HRQoL whether used as monotherapy [Trivedi, 2014; Feldman, 2016] or as an add on to fluticasone propionate and vilanterol (FF/VI) [Siler, 2015]. Salmetrol (50 mcg) DISKUS® is a long-acting broncholdilator that has long been used for the maintenance treatment of COPD [Tashkin, 2010].

Clinically important deterioration (CID) is a novel, exploratory composite endpoint which assesses individual deteriorations in lung function and in patient PROs defined by the accepted minimal clinically important difference (MCID), as well as the incidence of moderate to severe exacerbations [Singh, 2016], (Section 7.3.5). CID will be analysed to determine whether UMEC/VI (62.5/25mcg) therapy provides greater clinical stability as compared with UMEC and salmeterol monotherapies.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To compare the effect of UMEC/VI (62.5/25 mcg once daily) with UMEC (62.5 mcg once daily) on lung function	• Change from baseline in trough Forced Expiratory Volume in One Second (FEV_1) at week 24
Secondary	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on patient reported outcomes (PROs)	• Change from baseline in self administered computerised (SAC) transient dyspnea index (TDI) • Percentage of TDI responders according to SAC TDI score. A responder is defined as a ≥1 unit improvement in SAC TDI score • Assessment of respiratory daily symptoms over 24 weeks using Evaluating Respiratory Symptoms-COPD (E-RS) and its subscales (breathlessness, cough and sputum and chest symptoms) • Percentage of E-RS responders according to E-RS score (defined as reduction in E-RS score of ≥2 or ≥3.35 units) from baseline • Change from baseline in St George's Respiratory Questionnaire (SGRQ-C) • Percentage of responders according to SGRQ-C total score (defined as a 4 point or greater reduction from

Objectives	Endpoints
	baseline) • Change from baseline in COPD assessment test (CAT) • Percentage of responders according to CAT (defined as a ≥2 unit improvement in score from baseline)
Other	
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on other COPD efficacy measures	• Rate of mild, moderate or severe exacerbations • Time to first mild, moderate or severe exacerbation • Rate of moderate or severe exacerbation • Time to moderate or severe exacerbation • Time to severe exacerbations • Time to clinically important deterioration (CID) composite endpoint • Time to clinically important deterioration composite endpoint excluding FEV_1 • Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the electronic diary (eDiary) over 24 weeks • Inspiratory capacity (IC) • Full Vital capacity (FVC) • Change from baseline in trough FEV_1 • Change from baseline in global impression of disease severity

Objectives	Endpoints
Safety	
• To evaluate safety and tolerability of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5mcg once daily) and salmeterol (50mcg twice daily)	• Incidence of adverse events
Exploratory	
• To compare albuterol/salbutamol use captured in the eDiary with the electronic metered dose inhaler (eMDI) device	• Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the eMDI device over 24 weeks as data allow
• To explore the effect of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on physical activity	• Change from baseline in physical activity
• To investigate the CID composite endpoint ability to predict short term outcomes	• To compare physical activity levels, ER-S, rescue medication use, exacerbations and mortality in subjects with and without a CID

4. STUDY DESIGN

4.1. Overall Design

This is a multi-centre, randomized, double blind, double-dummy, 3-arm parallel group study. Eligible subjects will be stratified based on long-acting bronchodilator usage during the run-in (none, one or 2 long-acting bronchodilators per day) and randomized in a ratio of 1:1:1 to UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA inhaler, or UMEC (62.5 mcg once daily) administered via the ELLIPTA or salmeterol (50 mcg BID) administered via the DISKUS.

There will be a total of 5 clinic visits and one follow-up phone call (Visit 6). The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) if subject does not take or has not taken any excluded protocol medications, but must be completed prior to initiating any Visit 1 procedures.

Subjects, who meet all the eligibility criteria at Screening, will enter a run-in period for 4 weeks in order to continue to assess the subject's eligibility for the study. During the run-in period subjects will continue with their inhaled COPD medications (excluding ICS and any exclusionary medications). In addition, subjects will be provided with short acting albuterol/salmeterol to be used on as needed basis for relief of COPD symptoms (rescue medication) throughout the study.

Subjects who experience a moderate or severe COPD exacerbation during the run-in period will be deemed run-in failures. Subjects who experience a mild COPD exacerbation, defined as worsening of symptoms that requires **no** treatment with antibiotics or steroids and is self managed by the patient by an increase of inhaled rescue medication, (Appendix 5), will be able to continue in the study based on the judgment of the investigator and agreement of the sponsor's medical monitor.

At the randomization Visit 2 (Day 1) those subjects who successfully complete the run-in period as well as meet the other pre-defined eligibility and randomization criteria will discontinue their inhaled COPD medications and will be randomized to one of the 3 treatment arms for 24 weeks.

During the run-in and treatment period, subjects will be completing PRO questionnaires in the eDiary and performing slow and forced spirometry at specific clinic visits.

In addition, a subset of subjects up to 150 per treatment arm will undergo assessment of their physical activity measured through a physical activity monitor (Actigraph GT9X) worn for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3, and for 7 days prior to last clinic Visit (Visit 5).

Concurrent use of COPD maintenance medications including LAMAs, LABAs, oral beta-agonists, theophyllines, inhaled corticosteroids, inhaled corticosteroids and LABA combination and phosphodiesterase 4 inhibitors will not be allowed during the study (Section 6.11.2) .

The occurrence of adverse events (AEs) will be evaluated throughout the study beginning at Visit 2 (Day 1) and until the follow-up contact (Visit 6). Serious adverse events (SAEs) will be collected over the same time period as AEs. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact (Appendix 4).

All subjects will be given an electronic diary (eDiary) for use during the run-in, and the treatment period to complete PRO questionnaires, record COPD daily symptoms, any medical problems experienced during the study and the time they take their COPD medications. Daily rescue medication usage (number of inhalations taken in the last 24h) will also be captured in the eDiary. In addition, and in some countries, rescue medication use will also be captured by the use of electronic metered dose inhaler (eMDI).

At Screening Visit 1, all subjects must be trained on the proper use of their existing COPD medications inhalation devices and instructed to strictly adhere to and record the time they take their COPD medications in the eDiary.

At the randomization Visit 2, all subjects must be trained on the proper use of the ELLIPTA and DISKUS inhalation devices and instructed to strictly adhere to and record the time they take their study medications in the eDiary.

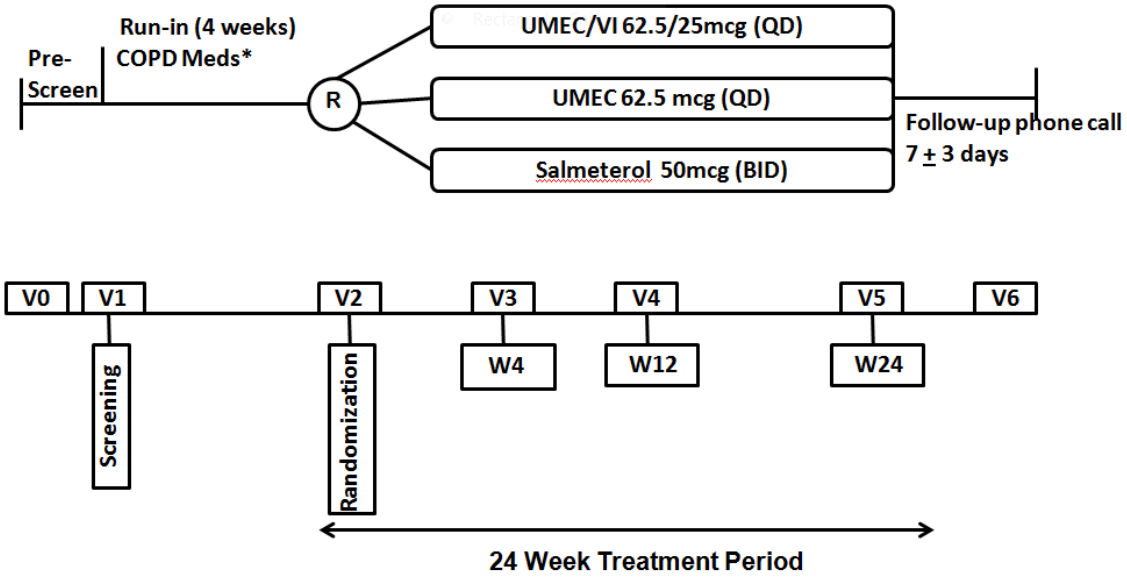
All subjects must be trained on the correct use of the eDiary and instructed to complete the eDiary during the run-in and treatment period.

Subjects will be considered to have completed the study upon completion of the follow – up contact by telephone.

There are no plans to routinely provide any of the study treatments for compassionate use following study completion as the study treatment are commercially available.

The study design schematic is illustrated in Figure 1

Figure 1 Study Schematic



*Inhaled COPD medications including LABAs, LAMAs or LABA/LAMA combination products are allowed in run-in. ICS alone or in combination with a bronchodilator or any exclusionary medications are not allowed.

4.2. Treatment Arms and Duration

Subjects will be stratified based on long-acting bronchodilator usage during the run-in (none, one or 2 long-acting bronchodilators per day) and randomized in a ratio of 1:1:1 to either

- UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA DPI) or
- UMEC (62.5 mcg once daily) administered via the ELLIPTA DPI or
- Salmeterol (50 mcg BID) administered via DISKUS

  The total duration of subject participation in the study will be approximately 29 to 31 weeks consisting of 2 weeks pre-screening if necessary, 4 weeks run-in, 24 week treatment and one week follow-up.

4.3. Type and Number of Subjects

Approximately 3232 will be screened globally in approximately 205 sites such that approximately 2424 subjects will be randomized and approximately 2181 evaluable subjects complete the study.

4.4. Design Justification

A randomized, double blinded, parallel group study is a standard, well-established design to evaluate the efficacy and safety of an investigational drug. A salmeterol arm is included to allow a comparison to be made between UMEC/VI, UMEC with salmeterol, a standard practice treatment.

The double-dummy design is appropriate when drugs are of different appearance or different administration regimen which is appropriate in this study where the inhalers used have a different appearance and used once daily and twice daily.

The European Medicines Agency (EMA) COPD Guidelines suggest that duration of 12 to 24 weeks is considered adequate for assessment of response of COPD symptoms to treatment intervention with bronchodilators (EMA COPD guidelines, 2012).

The primary endpoint is trough FEV_1 at week 24. This endpoint is generally considered to be a robust, well established and an objective means to show the efficacy of a bronchodilator [Dahl, 2010; Feldman, 2010].

Other endpoints such SAC TDI, E-RS, SGRQ-C, CAT, Subject Global Rating of Change in global impression of disease severity are captured to allow responder analyses and to provide comparative data on PROs between the treatment groups.

4.5. Dose Justification

This study is intended to evaluate the efficacy of marketed doses of UMEC/VI (62.5/25mcg once daily), UMEC (62.5 mcg once daily) and salmeterol (50mcg twice daily) that are approved for the maintenance treatment of COPD, with respect to PRO measures.

4.6. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with UMEC/VI and UMEC can be found in the investigator's brochures (IB) [GlaxoSmithKline Document Number RM2009/00437/07] and [GlaxoSmithKline Document Number RM2006/00835/09] and in the label information sheets. The current safety profile for UMEC (62.5mcg) and the UMEC/VI (62.5/25mcg) based on data available to date, is comparable with other LABAs and LAMAs. Summary safety data can also be found in the information sheet for salmeterol [Serevent product information 2003].The following section outlines the risk assessment and mitigation strategy for this protocol: 6

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [UMEC/VI]		
Severe milk protein allergy	Anoro contains Lactose monohydrate (which contains milk protein) as an excipient.	Exclusion criteria have been set for subjects with milk protein allergy.
Cardiovascular effects such as cardiac arrhythmias *e.g.* supraventricular tachycardia and extrasystoles.	Class effects associated with LABAs and LAMA containing therapy. The clinical significance of these arrhythmias is unknown. Clinical experience with UMEC/VI to date in completed studies did not show any association with major cardiovascular events. Data available in the product label for UMEC/VI	Exclusion criteria have been set for subjects with uncontrolled or severe cardiovascular disease according to the principal investigation's (PI) opinion where the potential risk may outweigh the benefit. The PI should also determine the clinical significance of abnormal ECG findings at screening and exclude subjects who would be at undue risk by participating in the trial. Patients with the following abnormalities will be excluded from participation: atrial fibrillation with rapid ventricular rate >120bpm, sustained or nonsustained ventricular tachycardia, or second degree heart block Mobitz type II or third degree heart block (unless pacemaker or defibrillator had been inserted).
Beta agonists and risk of asthma-related death	Long-acting beta agonists such as vilanterol when used alone may increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABAs, including vilanterol. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.	Subjects with a current diagnosis of asthma are excluded from participation in the study.
Paradoxical bronchospasm	As with other inhaled medicines, UMEC/VI can produce paradoxical bronchospasm which may be life threatening.	If paradoxical bronchospasm occurs following dosing with UMEC/VI, this treatment should be discontinued immediately and alternative therapy should be instituted.
Use in patients with narrow-angle glaucoma or urinary retention	No association has been found to date, in completed studies with UMEC/VI or UMEC monotherapy, on glaucoma or urinary retention. However, glaucoma or urinary retention	Exclusion criterion states that subjects with medical conditions such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction should only be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	have been observed with other antimuscarinic agents, and could potentially be due to the pharmacology.	included if, in the opinion of the principal investigator, the benefit outweighs the risk.
Use of beta blockers	Beta-adrenergic blockers may weaken or antagonize the effect of $beta_2$-agonists such as vilanterol.	The study permitted medications and non drug therapies section states that concomitant administration with beta-blockers is only permitted if, in the Investigator's opinion, the likely benefit outweighs the potential risk.
Pregnancy	There is no experience to date of pregnancy during the use of UMEC/VI.	The study inclusion criteria ensures that female subjects of child bearing potential must have a negative pregnancy test at screening, and agree to a reliable contraceptive method, used consistently and correctly (i.e. in accordance with the approved product label and the instructions of the physician for the duration of the study). Exclusion criteria include **Pregnancy:** Women who are pregnant or lactating or are planning on becoming pregnant during the study.
Severe hepatic impairment	UMEC/VI has not been studied in severe hepatic impairment.	Exclusion criterion states that subjects severe hepatic impairment should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Investigational product (IP) [UMEC]		
Cardiovascular effects such as cardiac arrhythmia, e.g. atrial fibrillation and tachycardia	A potential class effect associated with anti-muscarinic therapies. Data available to date in the IB for UMEC [GlaxoSmithKline Document Number RM2006/00835/09	Screening electrocardiogram (ECG) criteria to exclude subjects potentially at risk
Narrow-angle glaucoma, urinary retention	A class effect associated with anti-muscarinic therapies. Data available in the IB for UMEC [GlaxoSmithKline Document Number RM2006/00835/09	Exclusion criterion states that subjects with medical conditions such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Paradoxical bronchospasm that may be life threatening	Known effect associated with inhalation therapy	A short-acting inhaled bronchodilator (albuterol/salbutamol) will be provided for use as needed throughout the study. The investigators will be instructed to assess subject's condition to determine their eligibility to

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		continue in the study and the need for alternative therapy.
Severe hepatic impairment	UMEC has not been studied in severe hepatic impairment.	Exclusion criterion states that subjects with severe hepatic impairment should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Pregnancy/Lactation	There is no experience to date of pregnancy during the use of UMEC.	The study inclusion criteria ensure that female subjects enrolled, who are of Child bearing potential, have a negative pregnancy test at screening, and agree to a reliable contraceptive method, used consistently and correctly (i.e. in accordance with the approved product label and the instructions of the physician for the duration of the study). Exclusion criteria states - Pregnancy: Women who are pregnant or lactating or are planning on becoming pregnant during the study.
Study Procedures		
Spirometry procedures	This may cause difficulty breathing, changes in pulse rate and blood pressure, coughing, wheezing, chest tightness or fainting.	Subjects will be monitored during the procedure for these effects and spirometry will be discontinued should these occur.
ECG lead placement	This may cause skin irritation.	It may be necessary to have small patches (about a centimetre in diameter) of hair on the chest shaved to properly attach electrodes to the chest.
Blood sampling procedure (optional pharmacogenetic blood sample)	Giving blood may make subjects feel faint, or experience mild pain, bruising, irritation or redness at the site. In rare cases, they may get an infection	Subjects will be monitored during the blood draw for these effects and should call their study doctor if any of these effects do not resolve
Other		
Side effects of rescue albuterol/salbutamol. Adverse events seen in clinical studies to date are however consistent for the beta$_2$-adrenergic class of compounds	Class effects associated with short acting beta-agonists (SABAs)	Subjects should call their study doctor if they experience any of these symptoms

4.6.2. Benefit Assessment

Subjects will receive single or combination of long-acting bronchodilator therapies approved for maintenance treatment of COPD. Participating subjects in this study will contribute to the process of further characterizing the benefit of these long-acting bronchodilators with respect to PROs and symptoms in the treatment of COPD.

Specific benefits associated with the study design and procedures include the following:

- Subjects will receive treatments approved for the treatment of COPD that have been shown to be effective in the population under study
- All subjects will receive albuterol/salbutamol for use "as needed" for relief of COPD symptoms
- The combination of study procedures of spirometry, CAT, SGRQ, TDI, E-RS will provide the study subjects with a comprehensive evaluation of their symptoms, health status and COPD disease severity. Subjects will also be monitored throughout the study for any worsening of COPD symptoms or decline in general health. Finally smoking cessation counselling will also be provided.

4.6.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with UMEC/VI, UMEC, salmeterol and with study procedures are justified by the anticipated benefits from active treatments that may be afforded to patients with COPD.

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 IBs, [GlaxoSmithKline Document Number RM2006/00835/09], [GlaxoSmithKline Document Number RM2009/00437/07] and product labels.

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

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. **40 years or older** at date of signing informed consent at Screening Visit 1

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. **Outpatient with a diagnosis of COPD** in accordance with the definition of the American Thoracic Society/European Respiratory Society (ATS/ERS) [Celli, 2004]. 3. **FEV_1**: Persistent airflow limitations as indicated by: A pre and post-albuterol/salbutamol FEV_1/FVC ratio of <0.70 and a post-albuterol/salbutamol FEV_1 of ≥30% to ≤80% predicted normal values at Screening Visit 1. Predicted values will be based upon the ERS Global Lung Function Initiative [Quanjer, 2012]. 4. **CAT score**: A CAT score of ≥10 at Screening Visit 1

Smoking History
5. **Current or former cigarette smokers** with a history of cigarette smoking of ≥ 10 pack-years [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 both equal 10 pack-years)]. Former smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. Pipe and/or cigar use cannot be used to calculate pack-year history.

SEX
6. **Male and female** subjects are eligible to participate in the study 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 must be tested. 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) (Appendix 7) from 30 days prior to the first dose of study medication and until [at least five terminal half-lives OR until any continuing pharmacologic effect has ended, whichever is longer] after the last dose of study medication and completion of the follow-up visit. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
7. **Capable of giving signed informed consent** prior to study participation, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION
1. **Asthma**: 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). 2. **Alpha-antitrypsin deficiency:** Subjects with known α1-antitrypsin deficiency as the underlying cause of COPD 3. **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. 4. **Unstable liver disease:** 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). • 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 or within 3 months prior to first dose of study treatment) are acceptable if subject otherwise meets entry criteria 5. **Unstable or life threatening cardiac disease:** Investigational Product should be used with caution in subjects with severe cardiovascular disease. In the opinion of the investigator, use should only be considered if the benefit is likely to

outweigh the risk in conditions such as:

- 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

6. **12 Lead ECG:** 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. Subjects with the following abnormalities are excluded from participation in the study:

- Atrial fibrillation with rapid ventricular rate >120 bpm
- Sustained or non-sustained ventricular tachycardia
- Second degree heart block Mobitz type II or third degree heart block (unless pacemaker or defibrillator had been inserted)

7. **Antimuscarinic effects:** Subjects with medical conditions such as narrow-angle glaucoma, urinary retention, prostatic hypertrophy, or bladder neck obstruction should be excluded unless, in the opinion of the study physician, the benefit outweighs the risk.

8. **Other disease abnormalities:** Any subject who is considered unlikely to survive the duration of the study period or has any rapidly progressing disease or immediate life-threatening illness (e.g. cancer). In addition, any subject who has any other condition (e.g. neurological condition) that is likely to affect respiratory function should not be included in the study.

9. **Hospitalization:** Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1. **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).

10. **Inhaled corticosteroids (ICS):** Had received ICS or ICS/LABA for the treatment of COPD in the 6 weeks prior to Screening Visit1

11. **Exacerbation:** Had >1 moderate exacerbation in the 12 months prior Screening Visit1, or one severe exacerbation requiring hospitalisation in the 12 months prior Screening Visit 1.

12. **Other respiratory tract infections** that have not resolved at least 7 days prior to Screening V1.

13. **Lung Resection:** Subjects with lung volume reduction surgery (including procedures such as endobronchial valves) within the 12 months prior to Screening V1.

14. **Oxygen:** Use of long-term oxygen therapy (LTOT) described as resting oxygen therapy >3L/min at screening required to maintain adequate oxygenation (*e.g.* S_aO_2 >90%). (Oxygen use ≤3L/min flow is not exclusionary, and patients may adjust oxygen levels up or down as needed during the study.)

CONCOMITANT MEDICATIONS

1. **Medications prior to Screening:** Use of the following medications according to the following defined time intervals prior to Screening (Visit 1):

Medication	No use within the following time intervals prior to Screening
Inhaled corticosteroids (ICS)	6 weeks
Depot corticosteroids	12 weeks
Systemic, oral or parenteral corticosteroids[a]	6 weeks
Antibiotics (for lower respiratory tract infection)	6 weeks
Phosphodiesterase 4 (PDE_4) Inhibitor (*e.g* roflumilast)	14 days
LABA/Inhaled Corticosteroid (ICS) combination products	6 weeks
Theophyllines	48 hours
Oral $beta_2$-agonists Long-acting Short-acting	 48 hours 12 hours
Inhaled short acting $beta_2$-agonists[b]	4 hours
Inhaled short-acting anticholinergics	4 hours
Inhaled short-acting anticholinergic/short-acting $beta_2$-agonist combination products	4 hours
Any other investigational medication	30 days or within 5 drug half-lives (whichever is longer)

a- Localized corticosteroid injections (e.g., intra-articular and epidural) are permitted.

b- Use of study provided albuterol/salbutamol is permitted during the study, except in the 4-hour period prior to spirometry testing

2. **Medication prior to spirometry:** Unable to withhold albuterol/salbutamol for the 4 hour period required prior to spirometry testing at each study visit.
3. **Maintenance use of short-acting bronchodilators**: Regular use (prescribed for daily/ regular use, not for as-needed use) of short-acting bronchodilators (*e.g*. albuterol/salbutamol).

RELEVANT HABITS

1. **Drug or alcohol abuse:** A known or suspected history of alcohol or drug abuse within 2 years prior to Screening Visit 1 that in the opinion of the investigator would prevent the subject from completing the study procedures.

CONTRAINDICATIONS

1. **Any history of allergy or hypersensitivity** to any anticholinergic/muscarinic receptor antagonist, sympathomimetic, lactose/milk protein or magnesium stearate.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
1. **Pulmonary Rehabilitation program:** Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Screening Visit 1. Subjects who are in the maintenance phase of a pulmonary rehabilitation program are not excluded.
2. **Affiliation with investigator sites:** Is an investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member of the aforementioned that is involved in this study
3. **Inability to read:** In the opinion of the investigator, any subject who is unable to read and/or would not be able to complete questionnaires on the electronic diary.

Subjects who fail to meet inclusion and exclusion criteria at the **Screening Visit 1** will be considered screen failures and cannot be **re-screened.**

5.3. Randomization Criteria

In order to be randomized to one of the 3 treatment arms at Visit 2, subjects must have completed the run-in period and must have fulfilled all inclusion and exclusion criteria described in Section 5.1 and Section 5.2. In addition to the following:

REQUIRED CRITERIA FOR RANDOMIZATION AND TREATMENT
1. **COPD Exacerbation**: Subjects must **not** have experienced a moderate or severe COPD exacerbation or a lower respiratory tract infection during run-in or at Day 1 (Visit 2) inclusive. A moderate exacerbation is defined as worsening of symptoms of COPD requiring the use of antibiotics or systemic corticosteroids. A severe exacerbation is defined as worsening symptoms of COPD requiring hospitalization.
2. **CAT score**: A CAT score of ≥10 at Visit 2
3. **Prohibited Medications:** No use of any prohibited medications during the run-in period or at Visit 2, including any ICS or ICS/LABA combination
4. **Any change to COPD medications:** Including dosage and regimen during the run-in
5. **Completion of electronic diary:** Must have completed the electronic diary for at least 80% of days during the run-in period

Subjects who do not meet the required criteria for randomization at Visit 2 will not be randomized.

5.4. Screening/Baseline/Run-in Failures

Pre-screen, screen and run-in failures are defined as follows:

- Pre-screening failures: A subject, who is assigned a subject number at the Pre-screening Visit 0 but does not have any Screening Visit 1 procedures, will be considered a pre-screen failure.

- Screening failures: Those subjects that complete at least one Screening Visit 1 procedure but do not enter the run-in period.
- Run-in failures: Those subjects that enter the run-in period but are not randomized to any of the study treatment arms.

Subjects who are pre-screen, screen and run-in failure will be recorded in the eCRF. 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 to be recorded in eCRF including demography, screen failure details, eligibility criteria, and serious adverse events (Section 7.4.1).

5.5. Withdrawal/Stopping Criteria

5.5.1. Withdrawal from the Study

Subjects may be withdrawn from the study at any time by the Investigator if it is considered to be detrimental for them to continue in the study. Reasons for withdrawal from study treatment can include: an AE, clinically significant abnormality, lack of efficacy, sponsor terminated study, pregnancy, or for any other reason.

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.

A reason for the withdrawal from the study must be captured in the electronic case report form (eCRF).

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

- **Liver Chemistry:** Meets any of the Liver chemistry stopping criteria (See Section 5.5.3)

  Note: clinical laboratory assessments are not required for this study. However, laboratory samples may be taken for liver event analysis, if clinically indicated by the study investigator.

- **Pregnancy:** Positive pregnancy test (see Appendix 7)

Subjects withdrawn from study treatment will not be replaced.

Note: Withdrawal from study treatment requires withdrawal from the study.

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".

5.5.2. Reason for Study Withdrawal

The primary reason for study withdrawal will be recorded in the eCRF. When a subject withdraws consent, the investigator must document the reason (if specified by the subject) in the eCRF.

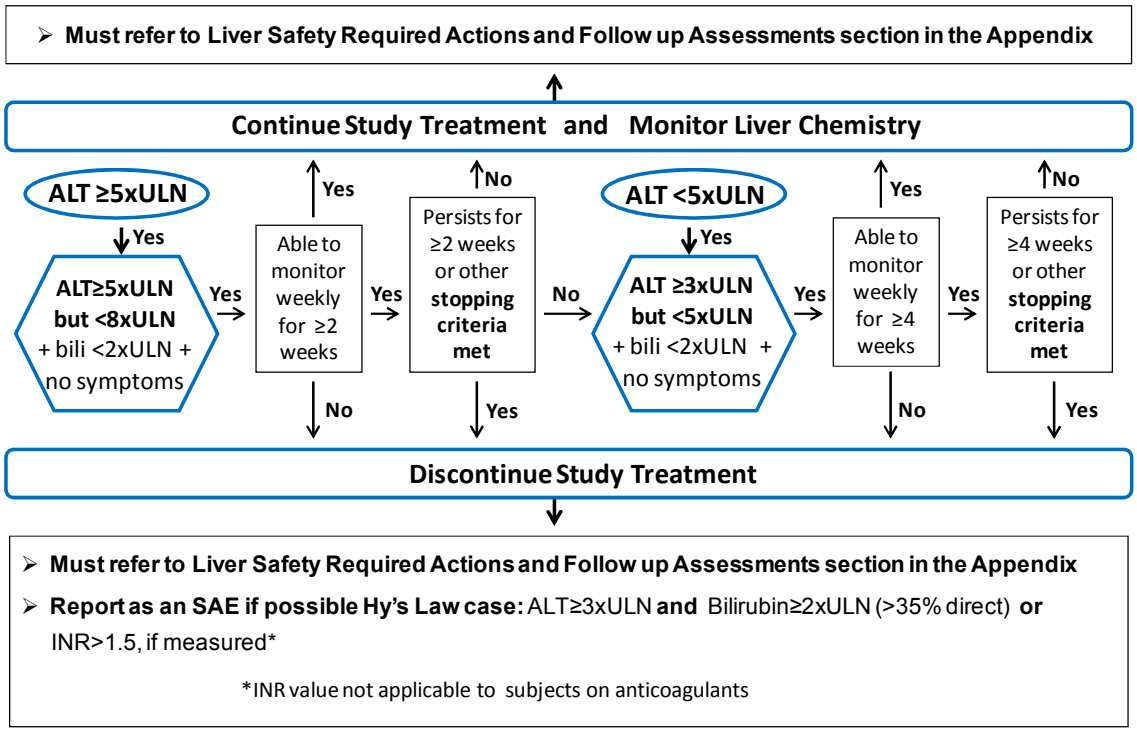
The primary reason for study withdrawal may include:

- Adverse event
- Lost to follow-up
- Withdrew consent
  - subject relocated
  - frequency of visits
  - burden of procedures
  - other (specify)
- Protocol deviation
- Lack of efficacy
- COPD exacerbation
- Study closed/terminated
- Subject reached protocol-defined stopping criteria
  - Liver event
  - Pregnancy
- Investigator discretion

5.5.3. 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

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.

5.5.3.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.6. Follow-up contact

A safety follow-up contact (Visit 6) should be conducted 7±2 days following the completion of Visit 5 or the Early Withdrawal Visit, if applicable.

The following procedures will be performed:

- AE/SAE assessment
- COPD exacerbation assessment
- Concomitant medication assessment limited to any medications used to treat a COPD exacerbation or SAE (if applicable)
- Pregnancy information (if applicable)

Subjects who have successfully completed all on-treatment randomized visits will be discharged from the study upon completion of the safety follow-up contact.

5.7. Subject and Study Completion

A subject will be considered to have completed the study if he/she receives study treatment at Visit 5 (Week 24) and completes the follow-up contact Visit 6.

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.

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

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

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 authorised site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

GlaxoSmithKline (GSK) will provide the study treatments for use in this study.

The following study medications will be used in this study:

- UMEC/VI 62.5/ 25mcg administered via ELLIPTA
- UMEC 62.5 mcg administered via ELLIPTA
- Salmeterol 50 mcg administered via DISKUS
- Placebo via ELLIPTA
- Placebo via DISKUS

Subjects will be instructed to take one dose of medication each morning from the ELLIPTA (one inhalation equals one dose), and one dose in the morning and one in the evening from the DISKUS). Subject instructions and details on how to use the ELLIPTA and DISKUS are provided in the study reference manual (SRM).

A description of the UMEC/VI investigational product administered via the ELLIPTAis provided below in Table 1. The ELLIPTA will contain two, double-foil, laminate, blister strips. The ELLIPTA will provide a total of 30 doses (60 blisters) and will deliver, when actuated, the contents of a single blister simultaneously from each of the two blister strips.

The DISKUS will provide a total of 60 doses and will deliver, when actuated, the contents of a single blister.

A description of the UMEC investigational product administered via the ELLIPTA is provided below in Table 2. A description of placebo inhalation powder via ELLIPTA is shown in Table 3. A description of salmeterol 50mcg and placebo via DISKUS are shown in Table 4 and Table 5 respectively.

Table 1 Description of UMEC/VI Inhalation Powder via ELLIPTA

Formulation	**First strip**	**Second strip**
	Umeclidinium bromide blended with lactose monohydrate and magnesium stearate[1]	Vilanterol trifenatate blended with lactose monohydrate and magnesium stearate[2]
Dosage Form	ELLIPTA Inhaler with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	62.5 mcg	25 mcg
Physical description	White powder	White powder
Route of Administration	Inhaled	

1. Magnesium stearate 0.6% w/w of total drug product
2. Magnesium stearate 1.0% w/w of total drug product

Table 2 Description of UMEC Inhalation Powder via ELLIPTA

Formulation	**First strip**
	Umeclidinium bromide blended with lactose monohydrate and magnesium stearate[1]
Dosage Form	ELLIPTA Inhaler with 30 doses (1 strip with 30 blisters)
Unit Dose Strengths	62.5mcg
Physical description	Dry white powder
Route of Administration	Inhaled

1. Magnesium stearate 0.6% w/w of total drug product

Table 3 Description of Placebo inhalation powder via ELLIPTA

Formulation	**First strip**	**Second strip**
	Lactose monohydrate blended with magnesium stearate[1]	Lactose monohydrate blended with magnesium stearate[2]
Dosage Form	ELLIPTA Inhaler with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	Not applicable	Not applicable
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	

1. Magnesium stearate 0.6% w/w of total drug product
2. Magnesium stearate 1% w/w of total drug product

Table 4 Description of salmeterol Inhalation powder via DISKUS

Formulation	First strip
	Salmeterol Xinafoate blended with lactose monohydrate
Dosage Form	Diskus Inhaler with 60 doses (1 strip with 60 blisters per strip)
Unit Dose Strengths	50 mcg
Physical description	White powder
Route of Administration	Inhaled

Table 5 Description of Placebo inhalation powder via DISKUS

Formulation	Lactose monohydrate
Dosage Form	Diskus Inhaler with 60 doses (1 strip with 60 blisters per strip)
Unit Dose Strengths	Not Applicable
Physical description	White powder
Route of Administration	Inhaled

Albuterol/salbutamol via metered-dose-inhaler (MDI) will be issued for reversibility testing at Visit 1. Albuterol/salbutamol MDI for as needed (prn) use will be issued throughout the study. Albuterol/salbutamol will be sourced from local commercial stock if appropriate.

6.2. Medical Devices

The eMDI devices are provided by GSK and are used in this study to electronically record rescue medication usage. They have US FDA 510(K) clearance to market (Class II device) and EU CE marking (Class I device). Description of the eMDI and its use will be provided in the **SRM.**

6.3. Treatment Assignment

Subjects who meet the randomization criteria will be assigned to one of the 3 study treatments in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Once a randomization number is assigned to a subject, it cannot be reassigned to any other subject in the study.

This study will utilize RAMOS NG, which will provide a means for central 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 RAMOS NG to randomize subjects is provided in the SRM.

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. On the other days during the treatment period (i.e. "non-clinic days"), subjects will be instructed to self-administer their study treatment in the morning and evening. Subjects should enter the time they take their study treatment in the eDiary.

Subjects will be randomly assigned to one of the blinded study treatment regimens in equal proportion (ratio of 1:1:1):

- UMEC/VI 62.5/25 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- UMEC 62.5 mcg once daily via ELLIPTA + placebo twice daily via DISKUS
- Salmeterol 50 mcg twice daily via DISKUS + placebo once daily via ELLIPTA

The randomisation will be stratified based on **long-acting bronchodilator** usage during the run-in (none, one or 2 **long-acting bronchodilators** per day).

Study treatment/investigational product will be dispensed at Visits 2, 3 and 4.

In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2, 60 and 90 days from V3 and V4 respectively (see Time and event table Section 7.1).

Used study drug and rescue medication will be collected at Visits 3, 4 and 5 or at the Early Withdrawal Visit.

6.4. Planned Dose Adjustments

No dose adjustment is allowed for this study

6.5. Blinding

This will be a double-blind double dummy study 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. 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.

6.6. Packaging and Labeling

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

6.7. Preparation/Handling/Storage/Accountability

No special preparation of the study treatment is required.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer 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 SRM.

All ELLIPTA DPI study treatment should be stored up to 25°C (77°F). Each All ELLIPTA DPI 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 investigational product.

Salmeterol DISKUS should be stored up to 25 °C.

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.

6.7.1. Study Treatment Return

All used and unused ELLIPTA and DISKUS inhalers 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 SRM.

Study treatment will be collected at Visit 3, 4 and 5 or at the Early Withdrawal Visit, if applicable.

For any ELLIPTA or DISKUS inhaler that fails to function properly, the subject should return to the clinic as soon as possible to obtain a new inhaler. The site will contact the RAMOS NG 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 RAMOS NG

In addition, any ELLIPTA that fails to function properly must be identified and returned to GSK for testing.

6.8. Compliance with Study Treatment Administration

When subjects self-administer study treatment(s) at home, compliance with study treatment(s) will be assessed through querying the subject during the site visits and through study drug compliance assessed at Visits 2, 3, 4 and 5 documented in the source documents and eCRF. A record of the number of ELLIPTA and DISKUS dispensed and the number of doses inhaled by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays if any will also be recorded in the eCRF.

Compliance with the ELLIPTA inhaler will be determined by reviewing the dose counter on the ELLIPTA. Compliance with the study DISKUS will be determined by reviewing the dose counter on the DISKUS. Subjects should be ≥80% to ≤120% compliant on taking study medication between each pair of on-treatment visits. Subjects who fall outside this range should be re-educated on treatment compliance by their site. This re-education should be documented in the subject's source document. If medication compliance repeatedly falls outside of acceptable ranges, the study sponsor/site monitor must be contacted to discuss subject eligibility for continued participation in the study.

6.9. Treatment of Study Treatment Overdose

An overdose is defined as a dose greater than the total doses described in Section 6.1 and Section 6.8 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 medication, the investigator should use clinical judgment in treating the overdose and contact the study 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 may not be limited to, the approved product label for salmeterol albuterol, UMEC and UMEC/VI or equivalent document provided by GSK.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.10. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study, since the study treatments are commercially available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, post-study treatment.

6.11. Concomitant Medications and Non-Drug Therapies

All COPD medications used within 30 days prior to Pre-Screening (Visit 0) and onwards should be recorded in the eCRF including any changes in medications. Beginning at Visit 1 and throughout the rest of the study, all medications should be recorded in the eCRF including any changes. Study provided albuterol/salbutamol and double-blinded study drug should **not** be recorded in the eCRF. The minimum requirement includes but is not limited to drug name, dose, route and the dates of administration. Medications initiated after completion of Visit 5 or the Early Withdrawal Visit will not be recorded in the eCRF, with the exception of those used to treat a COPD exacerbation or SAE that occurs between Visit 5 (or the Early Withdrawal Visit) and the follow-up contact atVisit 6.

6.11.1. Permitted Medications and Non-Drug Therapies

The following relevant medications are permitted during this study:

- Study-provided albuterol/salbutamol for use as relief medication throughout the run-in and treatment periods
- Mucolytics such as acetylcysteine
- Medications for rhinitis (e.g. intranasal corticosteroids, antihistamines, cromolyn, nedocromil, nasal decongestants)
- Influenza vaccine
- pneumococcal vaccine
- Antibiotics for short term treatment (≤14 days) of acute infections including COPD exacerbations
- Systemic corticosteroids for short term (≤14 consecutive days) treatment of COPD exacerbations

- As-needed supplemental oxygen use provided it is ≤3L/min flow at rest at screening. Patients may adjust oxygen levels as needed during the study.
- Pulmonary rehabilitation program in maintenance phase
- Smoking cessation treatment, including a stable regimen of nicotine replacement
- Use of positive airway pressure/non-invasive ventilation for sleep apnea/sleep disordered breathing (*e.g*. CPAP, BiPAP)
- Localized corticosteroid injections (e.g., intra-articular and epidural)
- 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)
- Immunotherapy injections
- Topical or ophthalmic corticosteroids
- Over-the counter (OTC) cough suppressants
- Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). Administer with caution as they may potentiate the effect of beta-agonists on the vascular system
- Diuretics. Caution is advised in the co-administration of beta agonists with non-potassium sparing diuretics
- Allergy vaccination
- All medications for other disorders as long as the dose remains constant whenever possible and their use would not be expected to affect lung function

6.11.2. Prohibited Medications and Non-Drug Therapies

Use of the medications listed in Table 6 is not permitted during the study

Table 6 Prohibited Medications and Non-Drug Therapies

Medication
Depot corticosteroids
Systemic, oral or parenteral corticosteroids[1]
Inhaled corticosteroids (ICS)[2]
Antibiotics >14 days
LABA/ICS combination products
PDE4 inhibitor (e.g. roflumilast)
Inhaled long acting beta$_2$-agonists (LABA, e.g. salmeterol, formoterol, indacaterol, vilanterol)
Long-acting muscarinic antagonists (LAMA, e.g. tiotropium, aclidinium, glycopyrronium, umeclidinium[3])
LAMA/LABA combination products except for study drugs
Theophyllines
Oral beta$_2$-agonists
Inhaled short acting beta$_2$-agonists[4]
Inhaled short-acting anticholinergics
Inhaled short-acting anticholinergic/short-acting beta$_2$-agonist combination products
Any other investigational medication

1 Except for the treatment of COPD exacerbations during the study. Localized corticosteroid injections (e.g., intra-articular and epidural) are permitted.
2 Except if during the study use of ICS is deemed necessary for the treatment of subjects' exacerbation.
3 Expect for study drug
4 Use of study provided albuterol/salbutamol is permitted during the study, except in the 4-hour period prior to spirometry testing.

The following medications or treatments are also **not** allowed during the study:

- Use of long-term oxygen therapy (LTOT) described as resting oxygen therapy >3L/min only at screening. Oxygen may be titrated to any level deemed necessary during the study.
- Regular (prescribed for daily/regular use, not for as-needed use) therapy with albuterol/salbutamol.
- Initiation of pulmonary rehabilitation during the study.

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 Section 7.1, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

7.1. Time and Events Table

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 ±2 days prior Visit 1**	**28 ± 2 days prior Visit 2**	**1± 2 days**	**28 ±2 days**	**84 ± 2 days**	**168 ±2 days**		**7± 2 days after V5 or EW Visit**
Screen/Baseline								
Written informed consent	X							
Demography	X							
Medical/COPD history		X						
Smoking history/status		X						
Smoking cessation counselling		X						
Concomitant medication assessment	X	X						
Cardiovascular History/family history of premature CV disease])		X						
Screening spirometry (including post bronchodilator testing)[3]		X						
CAT questionnaire		X	X					
Verify Inclusion/Exclusion Criteria		X						
Training on use of inhalers		X	X					
Training on use of eDiary and eMDI		X	X					
Verify randomization Criteria			X					
Register Visit in InForm	X	X	X	X	X	X	X	X
Register Visit in RAMOS NG	X	X	X	X	X	X	X	X

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 ±2 days prior Visit 1**	**28 ± 2 days prior Visit 2**	**1± 2 days**	**28 ±2 days**	**84 ± 2 days**	**168 ±2 days**		**7± 2 days after V5 or EW Visit**
Efficacy/HRQoL assessments								
Spirometry, including pre-dose FEV_1, trough FEV_1 and inspiratory capacity			X	X	X	X		
SAC BDI questionnaire [4]			X					
SAC TDI questionnaire [4]				X	X	X		
SGRQ-C questionnaire [4]			X	X	X	X		
CAT questionnaire [4]		X	X	X	X	X		
EXACT/ER-S: COPD [5]		→	→	→	→	→		
Patient Global Rating of COPD severity			X	X	X	X		
Patient Global Rating of Change in COPD				X	X	X		
Safety assessments								
Adverse events/Serious adverse events [6]	X	X	X	X	X	X	X	X
COPD exacerbation assessment	X	X	X	X	X	X	X	X
12-Lead ECG		X						
Urine pregnancy test [7]		X	X			X	X	
Pharmacogenetic sample[8]			←	→	X	←	→	
Medication/Supplies								
Dispense rescue albuterol/slabutamol. Dispense MDI[9]		X	X	X	X	X		
Assess COPD medication compliance[10] during run-in			X					
Dispense eDiary		X						
Assess compliance with eDiary during run-in			X					
Collect rescue albuterol/slabutamol.			X	X	X	X	X	
Collect eDiary						X	X	
Dispense study treatment[11]			X	X	X			
Collect study treatment				X	X	X	X	

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mizatio n 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-6 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**42 ±2 days prior Visit 1**	**28 ± 2 days prior Visit 2**	**1± 2 days**	**28 ±2 days**	**84 ± 2 days**	**168 ±2 days**		**7± 2 days after V5 or EW Visit**
Assess study treatment compliance during treatment[10]				X	X	X	X	
Study sub-set								
Physical activity monitor[12]		X	X	X		X		
Collect Physical activity monitor						X	X	

1. Pre-screen Visit 0 must be completed prior to Screening Visit1. It can be completed 2 weeks prior or on the same day of V1, if no wash out of exclusionary medications is required.
2. Early Withdrawal Visit: Subjects that withdraw should return to the clinic as soon as possible to complete the Early Withdrawal Visit procedures.
3. Spirometry at screening should be performed as described in (Section 7.2.2.1).
4. SAC BDI, SAC TDI, SGRQ-C, CAT questionnaires will be completed at clinic visits and in the eDiary
5. EXACT/ER-S: COPD is completed daily in the eDiary approximately 2 hours before bed-time, starting on Day 1 of the run-in period.
6. For the start date of collecting AEs and SAEs see (Appendix 4)
7. Pregnancy test: for females for child bearing potential only.
8. Pharmacogenetic sample may be drawn at visit 2 or any visit after.
9. Rescue medication use to be recorded in the eDiary daily **and** in some sites in the eDiary and the eMDI
10. Sites are requested to call subjects every 2 weeks to remind them to take study treatment regularly and to record the time of the morning and evening dose in the eDiary.
11. In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2 and within 60 and 90 days from V3 and V4 respectively
12. The Actigraph GT9X should be worn for 7 days from Visit 1, for 7 days from Visit 2, for 7 days from Visit 3 and for 7 days prior to Visit 5.

7.2. Screening and Critical Baseline Assessments

7.2.1. Pre-screening Visit

During the Pre-screening Visit, the study designated personnel must provide informed consent to the study participant. Subjects can perform the Pre-screening Visit (Visit 0) up to 2 weeks prior to or on the same day as the Screening Visit (Visit 1) if subject does not take or has not taken any protocol excluded medications.

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. A subject number will be assigned at the time the informed consent form (ICF) is signed. **No study related procedures may be performed until the informed consent form document has been signed by the subject.**

Once the informed consent is signed and if required, changes can be made to the subject's current medication regimen. The investigator should exercise clinical judgment, and is discouraged from changing medications only for the purpose of the clinical study.

During the pre-screening Visit 0, the following information is collected:

- Demographic parameters: year of birth, gender, race and ethnicity
- Concomitant medications review
- COPD exacerbation assessment

From the pre-screening visit onwards concomitant medications, exacerbations and SAEs (considered as related to study participation) must be reported

7.2.2. Critical procedures performed at Screening (Visit 1)

The following critical assessments will be conducted at Visit 1:

- Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening
- Medical history including COPD (including date of diagnosis and COPD type (emphysema and/or chronic bronchitis), smoking history, COPD exacerbation history, smoking status and previous and/or current medical conditions)
- Concomitant medication review (COPD and non COPD medications in the 3 months prior to Screening).
- 12-Lead ECG. (Note: ECG is performed at screening Visit 1 to test for eligibility only. See Section 7.4.4).
- Urine pregnancy test if applicable

- Train subject on the use of eDiary
- COPD assessment test (CAT) and patient global rating of COPD severity in eDiary
- Pre- and post-albuterol/salbutamol spirometry (reversibility, see Section 7.2.2.1)
- Inclusion/Exclusion criteria assessment
- Review exacerbations, AEs, (SAEs if related to study participation)
- Train subject on the proper use of their COPD medication inhalation devices
- Instruct subject to take their COPD medications as instructed and to enter the time they take their medication in the eDiary
- Dispense rescue medication

Medical history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.1 and Section 5.2.

Assessment of subject's health status will be made at screening using CAT. PRO questionnaires should be completed by subjects before any other assessments at a clinic visit, in the order specified in Section 7.3.1

7.2.2.1. Albuterol/Salbutamol Reversibility Assessment

At Visit 1, both pre- and post-albuterol/salbutamol spirometry will be obtained to determine subject eligibility. Reversibility assessment should be performed as follows:

- Perform pre-bronchodilator spirometry and record FEV_1 and FVC
- Subject to self-administer 4 Inhalations (4X100µg) of albuterol/salbutamol MDI
- Perform post-bronchodilator spirometry and record FEV_1 and FVC approximately 10 to 30 minutes after albuterol/salbutamol administration

  The results of the spirometry must meet the ATS/ERS criteria [Miller, 2005] for the subject to continue in the study.

7.2.3. Critical procedures performed at first treatment Visit (Baseline V2)

- Review and assess compliance with subject's COPD medications during the run-in period
- Review and assess compliance with completing the eDiary during the run-in period
- Review AEs, SAEs and exacerbations
- Urine pregnancy test, if applicable

- Baseline dyspnea Index, BDI, patient global rating of COPD severity, patient global rating of change in COPD, SGRQ-C and CAT questionnaires in eDiary
- Review randomization criteria (Section 5.3)
- Register and randomize subject in RAMOS NG
- Pre-dose spirometry; IC and FEV_1
- Train subject on the proper use of ELLIPTA and DISKUS inhalers
- Dispense study medication
- Dispense rescue medication
- Optional pharmacogentic sample can be collected at V2 or any visit after.

7.3. Efficacy Assessments

7.3.1. HRQoL assessments: Completion of PRO questionnaires in the Electronic Diary

All subjects will be completing PRO questionnaires in the eDiary.

It is requested that questionnaires are completed before any procedures are performed on the subject.

All questionnaires will be completed using the eDiary at clinic and at home. Adequate time should be allowed to complete all items of the questionnaires and the questionnaires must be reviewed by the investigator or designated study staff for completeness and, if necessary, the subject must be encouraged to complete any missing items. Where more than one questionnaire is to be completed at a visit the order should be as follows:

1. Baseline dyspnea index (Visit 2) then Transient dyspnea index at subsequent visits
2. Patient global rating of COPD severity and global rating of change in COPD
3. St George's respiratory questionnaire
4. COPD Assessment Test

Instructions for completing the questionnaires can be found in the **SRM.**

7.3.1.1. Self Administered Computerised Baseline Dyspnea Index/Transitional Dyspnea Index (SAC BDI/TDI)

The BDI is used to measure the severity of dyspnea in patients at baseline. The TDI measures changes in the patient's dyspnea from baseline. The self-administered computerized version of the BDI/TDI (SAC BDI/TDI)[Mahler, 2004] is used to measure severity of dyspnea in patients at baseline (SAC BDI) on Day 1 (Visit 2) of treatment and change from the baseline (SAC TDI) at Week 4, 12 and 24 (Visits 3, 4 and 5). The scores in both indexes depend on ratings for three different categories: functional

impairment; magnitude of task, and magnitude of effort. SAC BDI/TDI should be completed before performing spirometry.

The SAC BDI/TDI was developed to address issues of potential bias in the interviewer administered (original) BDI/TDI [Mahler, 1984]. The SAC BDI/TDI provides a standardized approach to the measurement of dyspnea, equivalent to the original BDI/TDI with advantages over the interviewer method for grading dyspnea in patients with COPD by standardizing the process for each patient and eliminating individual judgment required by the interviewers when completing the original BDI/TDI. This also removes the need for the same investigator to conduct all interviews with a subject based on the patient's responses. SAC TDI provides a continuous measure of change in dyspnea using a visual analogue scale to record responses.

Details for the completion of the SAC BDI/TDI are provided in the SRM.

7.3.1.2. SGRQ-C

The St George's Respiratory Questionnaire-Chronic Obstructive Pulmonary Disease specific (SGRQ-C) will be completed by subjects at Randomisation (V2, Day 1), at Week 4, 12 and 24 or at the Early Withdrawal Visit (where applicable).

The SGRQ-C [Meguro, 2007] is a well established, disease-specific questionnaire. It was 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 scores equivalent to the SGRQ instrument [Meguro, 2007].

7.3.1.3. COPD Assessment Test (CAT)

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.

The CAT will be completed in the eDiary by subjects at Screening Visit 1 and Randomisation Visit 2 to assess their eligibility to enter the study. CAT is also completed at Weeks 4, 12 and 24. Additional instructions for completion of the CAT are provided in the **SRM.**

7.3.1.4. EXACT and the Evaluating Respiratory Symptoms- COPD (E-RS: COPD)

EXACT-PRO is a 14 item patient reported outcome instrument designed to capture information on the occurrence, frequency, severity, and duration of exacerbations of

disease in patients with COPD [Leidy, 2011]. EXACT captures information on the severity of the respiratory and systemic manifestations of a COPD exacerbation as reported by the patient. The instrument is to be completed daily (typically 2 hrs before bedtime) using the electronic diary. The daily recording of information allows an assessment of the underlying day to day variability of a patient's symptoms and facilitates the detection of symptom worsening indicative of a COPD exacerbation. The total score for EXACT ranges from 0-100. The entire instrument is intended to be completed in about 3 minutes or less (typically the time required for completion decreases as the patient becomes more familiar with the tool and the electronic diary).

The E-RS: COPD consists of 11 items from the 14 item EXACT instrument [Leidy, 2014]. E-RS: COPD is intended to capture information related to the respiratory symptoms of COPD, i.e. breathlessness, cough, sputum production, chest congestion and chest tightness. The E-RS: COPD has a scoring range of 0-40 higher scores indicate more severe symptoms.

Three subscales of the E-RS are used to describe different symptoms; dyspnea, cough and sputum and chest symptoms.

The EXACT questionnaire will be completed by subjects in the eDiary, at home every night throughout the entire study, starting from Screening V1

7.3.1.5. Subject Global Rating of COPD Severity and Global Rating of Change in COPD

Subjects will complete the Global Rating of COPD Severity at Randomization Visit 2 and visits 3, 4 and 5 or Early Withdrawal Visit. This single global question will ask subjects to rate their severity of COPD on a four point scale (mild, moderate, severe, and very severe).

This question should be used immediately before the patient completes other visit specific questionnaires but after completion of SAC TDI questionnaire.

Subjects will also complete a Global Rating of Change in COPD (overall disease) question at Visits 3, 4 and 5 or Early Withdrawal Visit. Response options will be on a 7 point Likert scale ranging from much better to much worse. Completing the question at each Visit allows for early detection of response as well as continued response.

7.3.2. 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 standardized spirometry equipment provided by an external vendor.

All subjects will have spirometry performed at Screening to assess eligibility (see Section 7.2.2.1) and at Visits 2, 3, 4 and 5 during the treatment period.

For FEV_1 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 (i.e. a plateau in the volume time curve) and be free from artifacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons [Miller, 2005].

The largest FEV_1 and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort.

Spirometry for FEV_1 and FVC assessments that is not obtained as follows will be considered a protocol deviation:

- Started between 6:00AM and 11:00AM.
- After withholding albuterol/salbutamol (all visits) for ≥4 hours
- At Screening Visit 1, after wash out of medications as specified in the exclusion criteria in Section 5.2 (Concomitant Medications).
- At Visit 2 after discontinuing inhaled COPD medications and prior the first dose of study treatment
- At Visit 3, 4 and 5 after withholding the morning dose of study treatment.
- Pre dose assessment performed prior dosing.

Subjects should refrain from smoking for 1 hour prior to each pulmonary function test.

Trough FEV_1 measurements for UMC/VI or UMEC on Weeks 4, 12 and 24 (Visits 3, 4 and 5) should be performed 23 hours and 24 hours after the previous day's dose of study medication recorded in the eDiary. This will also provide trough FEV_1 measurements for the evening dose of salmeterol.

7.3.3. Inspiratory capacity (IC)

Inspiratory capacity (IC) is the volume of gas that can be taken into the lungs in a normal and full inhalation. Starting from the resting inspiratory position it is equal to the tidal volume plus the inspiratory reserve volume. IC has been widely used to assess static and dynamic hyperinflation in patients with COPD.

IC will be measured by spirometry **prior** to forced manoeuvres pre-dose at Visits 2 (30 and 5 min prior to dosing) and at trough at Visits 3, 4, and 5 (23 and 24 hrs post dosing on the previous day). For IC determination the average of at least three acceptable manoeuvres should be recorded. Subjects should be tested while sitting, relaxed and wearing a nose clip. They should be asked to breathe regularly for several breaths until the end-expiratory lung volume is stable (this usually requires at least three tidal manoeuvres) then urged to take a deep breath to Total Lung Capacity (TLC) with no hesitation.

Spirometry for IC determination done in conjunction with FEV_1 and FVC assessments that is not obtained as follows will be considered a protocol deviation:

- Started between 6:00AM and 11:00AM.
- After withholding albuterol/salbutamol (all visits) ≥4 hours

- At Visit 2 after discontinuation of run-in medication
- At Visit 3, 4 and 5 after withholding the morning dose of study drug

7.3.4. COPD Exacerbation

A mild exacerbation is defined as worsening of symptoms that require no treatment with antibiotics or steroids, and is self managed by the patient by an increase of inhaled rescue medications. A moderate COPD exacerbation is defined as worsening symptoms of COPD that require treatment with oral/systemic corticosteroids and/or antibiotics. A severe exacerbation is defined as worsening symptoms of COPD that require in-patient hospitalization or emergency room for longer than 24 hrs.

If a subject experiences a mild, moderate or severe COPD exacerbation, the COPD exacerbation page of the eCRF should be completed. COPD exacerbations should not be recorded as an AE, unless they meet the definition of a SAE. Details of COPD exacerbation identification, categorization and treatment guidelines are described in Appendix 5.

Subjects who experience a mild exacerbation during the run-in period will not be withdrawn from the study. However, Subjects who experience moderate or severe exacerbation during the run-in period will be withdrawn from the study and will not be allowed to be re-screened.

Subjects who experience a mild, moderate or severe exacerbation during the treatment period, will **not** be withdrawn from the study unless the investigator or GSK medical monitor think it is best for the patient to withdraw from the study.

Signs and symptoms of COPD included on the electronic diary cards will not be considered AEs and will not be recorded in the eCRF.

The time period for collection of COPD exacerbations will be from the Pre-Screening (Visit 0) until completion of the follow-up contact. If a subject experiences a COPD exacerbation from the time the ICF is signed until randomization, summary information (yes/no status question) will be collected in the eCRF. COPD exacerbations after randomization through follow-up will be recorded on the COPD exacerbation page of the eCRF.

7.3.5. Clinically important deterioration (CID)

Clinically important deterioration (CID) is a composite endpoint defined as:

- A decrease of $\geq$ 100 mL from baseline in trough FEV_1
- A deterioration in HRQoL defined as $\geq$ 4 units increase from baseline in SGRQ
- The occurrence of an on-treatment moderate/severe COPD exacerbation

In addition, this study will explore CAT and TDI PROs as part of the composite endpoint.

7.3.6. Rescue albuterl/salbutamol use

Subjects will record the number of daily albuterol/salbutemol puffs they use in the eDiary. In addition, in some countries and selected sites the number of puffs will be collected through the eMDI device (Section 6.2)

7.3.7. Physical activity monitor (study subset)

Physical activity limitation is a common feature of COPD and its measures are highly related to the degree of disease severity [Watz, 2009].

Reduced physical activity levels in COPD is associated with increased morbidity and mortality, sustained disability, depression, and social and physical isolation [Shu-Yi, 2014; Gimeno, 2014]

Improved activity has been identified as an important factor that may modify morbidity and mortality in COPD [Moy, 2012].

The Actigraph GT9X physical activity monitor will be used to measure levels of activity. The activity monitor will be worn by up to approximately 150 subjects for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3 (Week 4) and for 7 days prior to Week 24 (Visit 5).

There will be 4 assessment periods, including a screening assessment in order to provide a reliable estimate of habitual physical activity. Each subject will be given an activity monitor and instruction leaflet at the start of each assessment period. Further details of distribution, operation and retrieval of the monitors will be provided in the **SRM**.

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1)

Safety endpoint includes:

- Incidence of adverse events

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

The definitions of an AE or SAE can be found in Appendix 4.

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

7.4.1.1. 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 7.4.1.3), at the timepoints 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 CRF.
- 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 12.4.4 to Section 12.4.6)

7.4.1.2. 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?

7.4.1.3. 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).

7.4.1.4. Pneumonia Events

Investigators will be required to fill out a pneumonia event specific eCRF within one week of when the pneumonia AE/SAE(s) is first reported.

7.4.1.5. Cardiovascular and Death Events

For any cardiovascular events detailed in (Section 12.4.3) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs 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 CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF 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.

7.4.1.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following disease related events (DREs) are common in subjects with COPD and can be serious/life threatening:

- COPD exacerbation

COPD exacerbations are associated with the disease to be studied and will not be recorded as AEs unless the exacerbation meets the definition of a 'serious' AE. Exacerbations that meet the definition of 'serious' AEs will be recorded on the appropriate eCRF section and should be reported to GSK for all subjects regardless of whether or not they are randomized to study medication. Signs and symptoms of COPD included on the electronic diary will not be considered AEs and will not be recorded in the eCRF

7.4.1.7. 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.

7.4.2. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of Screening and until the follow-up contact.
- 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 7.

7.4.3. Medical Device Incidents (Including Malfunctions)

Procedures for documenting medical device incidents are provided in Appendix 6.

7.4.4. Electrocardiogram (ECG)

A Single 12-lead ECG will be obtained at Screening using an ECG machine provided by the investigational site that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

The 12-lead ECG measurement and rhythm strip (10 seconds) will be obtained before spirometry testing. ECG measurement should be obtained after subjects have rested for approximately 5 minutes then the subjects should be placed in the supine position for the ECG measurements. An ECG is only required at Screening Visit 1 for eligibility assessment only.

The investigator, a designated sub-investigator, or other appropriately trained site personnel will be responsible for performing and interpreting the 12-lead ECG at Screening Visit 1. The investigator must provide his/her dated signature on the original paper tracing, attesting to the authenticity of the ECG machine interpretation.

7.5. Genetics

Information regarding genetic research is included in Appendix 3

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, 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.

- CRFs (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 purpose of this study is to demonstrate improvements in lung function for subjects treated with UMEC/VI compared with UMEC for 24 weeks.

The primary endpoint is change from baseline in trough FEV_1 at Week 24.
The null hypothesis is no difference between treatment groups (H0: $\mu T - \mu S = 0$), with the alternative hypothesis that there is a difference between treatment groups (H1: $\mu T - \mu S \neq 0$), where μT is the mean change from baseline for UMEC/VI and μS is the mean change from baseline for UMEC.

9.2. Sample Size Considerations

The primary endpoint is change from baseline in trough FEV_1 at Week 24. As an important aim of the study is to compare UMEC/VI, UMEC and salmeterol with respect to HRQoL the sample size has been calculated to provide sufficient power for the comparison of the primary and secondary endpoint TDI, at Week 24.

The sample size calculations use a two-sided 5% significance level and an estimate of between subject standard deviation for TDI of 2.94 units. The estimate of SD is based on DB2113373 [Donohue, 2013], a study which consisted of treatment arms of UMEC/VI 62.5/25, UMEC 62.5 VI (Vilanterol) 25mcg and placebo and is the value at Day 168 in a subgroup of subjects who were ICS free at screening. Based on these data, 727 evaluable subjects per treatment arm will be required to provide 90% power to detect a statistically significant difference if the true difference is 0.5 units, ½ the MCID, between UMEC/VI and UMEC. The smallest observed effect predicted to result in a statistically significant difference between treatment groups is 0.31 units.

With this number of evaluable subjects per arm, the study will have >99% power assuming a true treatment difference of 80mL between UMEC/VI and UMEC for trough FEV1 at 24 weeks at the two-sided 5% significance level. This calculation uses a SD for trough FEV1 of 240mL, based on prior results for trials comparing dual bronchodilators versus single bronchodilators (Donohue, 2013; Bateman, 2013). The smallest observed effect predicted to result in a statistically significant difference between treatment groups is 25mL.

In order to account a for a 10% withdrawal rate**,** approximately 808 subjects per treatment arm will be randomised.

9.2.1. Sample Size Assumptions

9.2.2. Sample Size Sensitivity

The assumption of a SD of 2.94 units for the TDI total score is based on estimates from previous studies. The following table presents the power achieved with the proposed sample size of 727 randomised subjects per arm, should the assumption around the SD of the data change.

The actual assumptions used in the sample size calculation are shaded.

Endpoint	Between subject SD	Treatment Difference	Power
TDI	2.54	0.5	96%
	2.74	0.5	94%
	2.94	0.5	90%
	3.14	0.5	86%
	3.34	0.5	81%

9.2.3. Sample Size Re-estimation or Adjustment

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

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	• 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.	• Subject Disposition • Reasons for withdrawal prior to randomisation • Inclusion, exclusion and randomisation criteria deviations • SAEs for non-randomised subjects

Population	Definition / Criteria	Analyses Evaluated
Intent-to-treat (ITT)	• All randomized subjects, excluding those who were randomized in error and received at least one dose of study medication. 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 randomization number will be considered to have been randomized. • Displays will be based on the treatment to which the subject was randomized.	• Study Population • Efficacy • Safety
Intent-to-treat ICS free (ITT ICS free)	• All subjects in the ITT Population who have not received ICS.	• Study Population • Efficacy • Safety

9.3.2. Interim Analysis

No interim analysis is planned for the study.

9.4. Key Elements of Analysis Plan

Treatment Comparisons

The primary treatment comparison of UMEC/VI with UMEC will be performed on the ITT population.

The other treatment comparisons of UMEC/VI and UMEC with Salmeterol will be performed on the ITT population and ITT ICS free population.

9.4.1. Primary Analyses

The treatment comparison of primary interest will be UMEC/VI versus UMEC for the primary endpoint of change from baseline in trough FEV_1 at Week 24. The primary analyses will be performed using a mixed model repeated measures (MMRM) analysis and will be based on a two-sided hypothesis testing approach on the ITT Population.

In order to account for multiplicity across treatment comparisons and endpoints, a step-down closed testing procedure will be applied whereby inference for secondary and other endpoints or treatment comparisons are dependent upon statistical significance having been achieved for the primary comparison. If the primary comparison is significant i.e. the associated p-value for UMEC/VI versus UMEC for change from baseline in trough FEV1 at Week 24 is below 0.05, this will allow inference of treatment comparisons (UMEC/VI versus UMEC on all other endpoints, and UMEC/VI versus Salmeterol and UMEC versus Salmeterol on all endpoints including the primary endpoint), which will be declared statistically significant if the associated p-value is below 0.05.

There will be 2 analyses one for one for the German Federal Joint Committee (G-BA) and one for the rest of the world (ROW).

The step-down closed testing procedure only applies to the ROW. For the G-BA statistical inference for secondary and other endpoints or treatment comparisons will not be conditional on achieving statistical significance of the primary comparison.

The primary endpoint of mean change from baseline in trough FEV1 at the end of Week 24 and secondary endpoint change from baseline in TDI score at Week 24 will both be analysed using MMRM analysis. The MMRM analysis for change from baseline in trough FEV1 and TDI will include measurements at Treatment Weeks 4, 12 and 24. Treatment group (a categorical variable) will be fitted as the explanatory variable with appropriate pre-defined variables, stratum (number of bronchodilators per day during run-in) and baseline values, fitted as covariates. Visit (nominal) will be fitted as a categorical variable and visit-by-baseline and visit-by-treatment interaction terms will be included to allow treatment effects to be estimated at each visit separately. The variance covariance matrix will be assumed to be unstructured (based on previous experience no issues are expected with fitting models with this matrix structure).

While missing data are not explicitly imputed in the primary MMRM analyses, there is an underlying assumption that the data are missing at random.

The estimated treatment differences between UMEC/VI versus UMEC for each endpoint will be presented with the 95% confidence intervals for the difference and the p-value.

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

9.4.2. Other Analyses

The MMRM analysis will be repeated for the ITT ICS free population. Estimated differences between UMEC/VI or UMEC and Salmeterol will be presented together with 95% confidence intervals (CIs) for the difference and p-values.

Secondary and other efficacy endpoints and treatment comparisons will be adjusted for multiplicity as per Section 9.4.1.

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

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 eCRF 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 randomization 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
CAT	COPD Assessment Test
CI	Confidence Intervals
CID	Clinically important deterioration
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine phosphokinase
CRF	Case Report Form
CV	Cardiovascular
DPI	Dry Powder Inhaler
DRE	Disease Related Event
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
eMDI	Electronic Metered Dose Inhaler
E-RS	Evaluating Respiratory Symptoms- COPD Tool
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
IB	Investigator Brochure
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IP	Investigational product
INR	International normalized ratio
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

mcg	Microgram
MCID	Minimal Clinically Important Difference
MDI	Metered Dose Inhaler
mL	Milliliter
mMRC	Modified Medical Research Council
MMRM	Mixed Models Repeated Measures
MSDS	Material Safety Data Sheet
NYHA	New York Heart Association
OTC	Over the Counter
PGx	Pharmacogenetic
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PP	Per Protocol
prn	As required
QTc	QT interval corrected for heart rate
RAP	Reporting and Analysis Plan
SABA	Short Acting Beta-Agonist
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SRT	Safety Review Team
TDI	Transition Dyspnea Index
RAMOS NG	Randomization and medication ordering system new generation
ULN	Upper Limit of Normal
UMEC	Umeclidinium (GSK573719)
UMEC/VI	Umeclidinium & Vilanterol as a fixed dose combination
VI	Vilanterol Trifenate

Trademark Information

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

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

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 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**
• 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 SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve , stabilize, or return to within normal ranges. baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment. Permanently discontinue stud**y treatment and may continu**e subject in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained within a week after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or

Liver Chemistry Stopping Criteria - Liver Stopping Event	
MONITORING: **<u>For bilirubin or INR criteria:</u>** • 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 normal ranges. • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • 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 normal ranges.	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 **<u>For bilirubin or INR criteria:</u>** • 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.

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 ≥ 3xULN **and** bilirubin ≥ 2xULN. 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 ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **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 SRM.

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 etiology 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 any concomitant medicines;
- COPD susceptibility, severity, and progression of 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.

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 the baseline visit, after the subject has been randomized and 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 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.

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 <u>meeting</u> 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 <u>NOT</u> 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., hospitalization 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 hospitalization or prolongation of existing hospitalization

NOTE:

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

d. Results in disability/incapacity

NOTE:

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

• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • 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 hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** 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.

12.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial 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
- 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 by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: COPD Exacerbation Identification, Categorization and Treatment Guidelines

12.5.1. 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 usage in their daily eDiary
- 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

12.5.2. COPD Exacerbation Severity

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

> **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 hospitalization or 24 hrs in the emergency room.

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.

12.5.3. 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 outlined 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 IP as these additional medications may increase the risk of overdose. If necessary the PI or other health care personnel may stop the subject's IP temporarily in order to treat the COPD exacerbation.

12.5.4. 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 ≤ 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

12.5.5. 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 not exceed 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

12.5.6. 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 12.5.1.

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.

12.5.7. 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.

12.5.8. 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.

12.6. Appendix 6: Definition of and Procedures for Documenting Medical Device Incidents

12.6.1. Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.2 for the list of GSK medical devices).

Medical Device Incident Definition:

- Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other persons or to a serious deterioration in their state of health.
- Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- an **incident** associated with a device happened and
- the **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.
- A serious deterioration in state of health can include:
- life-threatening illness
- permanent impairment of body function or permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent one of the above
- fetal distress, fetal death or any congenital abnormality or birth defects

Examples of incidents

- a patient, user, care giver or professional is injured as a result of a medical device failure or its misuse
- a patient's treatment is interrupted or compromised by a medical device failure
- misdiagnosis due to medical device failure leads to inappropriate treatment
- a patient's health deteriorates due to medical device failure

12.6.2. Documenting Medical Device Incidents

Medical Device Incident Documenting:
• Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 4. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK. • It is very important that the investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the design to prevent recurrence.

12.7. Appendix 7: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

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

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization 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, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.7.2. 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 fetal 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. 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 be withdrawn from the study

12.8. Appendix 8: Country Specific Requirements

No country-specific requirements exist.