TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	A Randomized, Open-Label, 8-Week Cross-Over Study to Compare Umeclidinium/Vilanterol with Tiotropium/Olodaterol Once-Daily in Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Compound Number: GSK573719+GW642444

Development Phase IV

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Author(s): PPD

SPONSOR SIGNATORY:

PPD

29 MARCH 2016

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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 106616 and EudraCT **2016-000585-36**

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 204990

Rationale

Objective(s)/Endpoint(s)

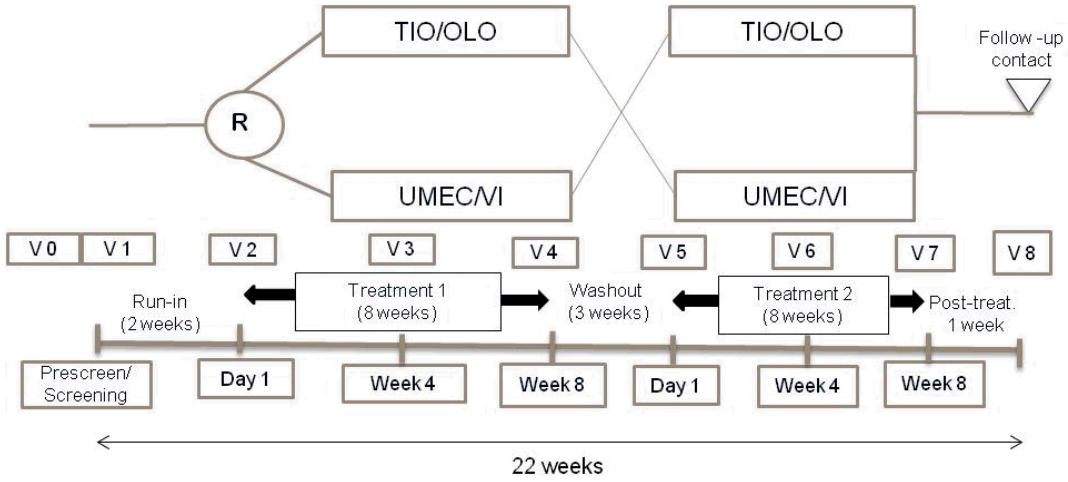
Objectives	Endpoints
Primary	
• To compare the effect of UMEC/VI 62.5/25mcg with TIO/OLO 5/5mcg once daily on lung function in subjects with moderate COPD over 8 weeks of treatment.	• Trough FEV_1 at Week 8
Others	
• To compare the effect of UMEC/VI 62.5/25mcg with TIO/OLO 5 /5mcg on other measures of efficacy and measures of health-related quality of life	• Proportion of responders according to FEV_1 (a responder is defined as a ≥100mL change in Trough FEV_1 from baseline) at Week 8 • Rescue albuterol/salbutamol use (percentage of rescue-free days and mean number of Inhalations/day) captured in e diary • Trough FEV_1, at Week 4 • Trough FVC at Weeks 4 and 8 • Trough IC at Weeks 4 and 8 • COPD Assessment Test (CAT) score at Weeks 4 and 8 • Proportion of responders according to CAT (defined as a ≥1 unit improvement in score from baseline) at Weeks 4 and 8 • Time to clinically important deterioration composite endpoint • Inhaler ease of use • Inhaler errors • Assessment of respiratory daily symptoms over Weeks 1-8 using Evaluating Respiratory Symptoms- COPD (E-RS) and its subscales (breathlessness, cough and sputum and chest symptoms) •
Exploratory	
• To compare the effect of UMEC/VI 62.5/25 mcg with TIO/OLO 5 /5mcg on other measures of efficacy and measures of health-related quality of life	• Rescue albuterol/salbutamol use (percentage of rescue-free days and mean number of Inhalations/day) over Weeks 1-8 using eMDI as data allow
Safety	
To evaluate safety and tolerability of UMEC/VI 62.5/25 mcg and TIO/OLO 5/5mcg	• Incidence of adverse events • Incidence of COPD exacerbations

Overall Design

This is a multicentre, randomized, open label, 2 period crossover complete block design study.

Eligible subjects will be randomised to receive a sequence consisting of umeclidinium/vilanterol (UMEC/VI) inhalation powder [62.5/25mcg once-daily] administered as 1 inhalation once-daily from the Ellipta Inhaler and tiotropium/olodaterol (TIO/OLO) 5/5mcg inhalation spray administered as inhalation of 2 inhalations once-daily from the Respimat inhaler. Each treatment sequence will be 8 weeks.

Study Schematic



R=Randomization

Treatment Arms and Duration

- UMEC/VI 62.5/25mcg (as 1 inhalation from the ELLIPTA inhaler)
- TIO/OLO 5/5mcg (as inhalation of 2 inhalations of 2.5/2.5mcg each from the Respimat inhaler)

All treatments will be administered once-daily in the morning for 8 weeks.

The total duration of subject participation in the study will be approximately 22 weeks consisting of approximately 2 week run-in, two 8 week treatment periods separated by approximately 3 week washout and approximately 1 week follow-up.

Type and Number of Subjects

Approximately 338 subjects with moderate COPD will be screened to achieve 220 randomised and 168 evaluable subjects in the per protocol (PP) population.

Analysis

The null hypothesis is that the difference in trough FEV_1 between treatment groups is less than or equal to a pre-specified non-inferiority margin Δ:

H_0: $T_1 - T_2 \leq \Delta$

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

H_1: $T_1 - T_2 > \Delta$

Where T_1 and T_2 are the treatment means for UMEC/VI 62.5/25mcg and TIO/OLO 5/5mcg, respectively.

The non-inferiority margin has been set at -50mL for trough FEV_1, consistent with previous studies evaluating long-acting bronchodilators for non-inferiority on lung function measures [Ichinose, 2010; Agustí, 2014].

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

If the lower bound of the 95% confidence interval around the (UMEC/VI 62.5/25mcg vs. TIO/OLO 5/5mcg) treatment difference is above 0 then UMEC/VI 62.5/25mcg will be considered superior to TIO/OLO 5/5mcg.

The primary endpoint of trough FEV_1 at Week 8 will be analysed using a repeated measures model including data recorded at each of Week 4 and Week 8 for the PP population. Treatment group (categorical) will be fitted as the explanatory variable, with period baseline, mean baseline, period, and visit fitted as covariates. Visit (nominal) will be fitted as a categorical variable and visit by period baseline, visit by mean baseline and visit by treatment interaction terms will be included. Treatment effects will be estimated at each visit separately. The variance-covariance matrix will be assumed unstructured.

2. INTRODUCTION

2.1. Study Rationale

UMEC/VI and TIO/OLO are both fixed dose combinations indicated for the maintenance treatment chronic obstructive pulmonary disease (COPD) that contain long-acting muscarinic antagonist (LAMA) and long-acting $beta_2$-agonist (LABA) bronchodilators. Both are delivered via unique inhalers. The efficacy and safety of UMEC/VI and TIO/OLO have been well characterized with respect to placebo and their respective component medications. However, a direct comparison of these two combinations has not been conducted to further characterize their relative efficacy and safety profiles.

The purpose of this study is to compare the efficacy and safety of UMEC/VI with TIO/OLO when used in subject with moderate COPD. Additional assessments to evaluate inhaler errors and study-subject rated inhaler ease of use will be conducted.

2.2. Brief Background

COPD is a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. COPD is characterised by symptoms of chronic and progressive breathlessness/ dyspnea, cough and sputum production which can be a major cause of disability and anxiety associated with the disease [Mannino, 2007].

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 long acting bronchodilators with long acting formulations of either $beta_2$-receptor agonists or muscarinic receptor antagonists. 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 of action [Celli, 2004; GOLD, 2015]. As disease progresses from mild to moderate, regular treatment with one or more long-acting bronchodilators is recommended.

UMEC/VI Inhalation Powder is a combination of UMEC, a LAMA, and VI, a LABA, delivered via the ELLIPTA dry powder inhaler. 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®.

TIO/OLO is a combination of TIO, a LAMA, and OLO, a LABA, delivered via the Respimat inhaler. TIO/OLO at a dose of 5/5mcg once-daily is marketed under the trade name Stiolto Respimat.in the United States (US) and Spiolto Respimat in Europe. For ease Stiolto will be used hereafter in this protocol.

Both combinations are indicated for the maintenance treatment of COPD.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To compare the effect of UMEC/VI 62.5/25 mcg with TIO/OLO 5/5mcg once daily on lung function in subjects with moderate COPD over 8 weeks of treatment.	• Clinic visit trough FEV_1 at Week 8
Others	
• To compare the effect of UMEC/VI 62.5/25 mcg with TIO/OLO 5 /5mcg on other measures of efficacy and measures of health-related quality of life	• Proportion of responders according to FEV_1 (a responder is defined as a ≥100mL change in Trough FEV_1 from baseline) at Week 8 • Rescue albuterol/salbutamol use (percentage

Objectives	Endpoints
	of rescue-free days and mean number of Inhalations/day) captured in e diary • Trough FEV_1 at Week 4 • Trough FVC at Weeks 4 and 8 • Trough IC at Weeks 4 and 8 • COPD Assessment Test (CAT) score at Weeks 4 and 8 • Proportion of responders according to CAT (defined as a ≥1 unit improvement in score from baseline) at Weeks 4 and 8 • Time to clinically important deterioration composite endpoint • Inhaler ease of use • Inhaler errors • Assessment of respiratory daily symptoms over Weeks 1-8 using Evaluating Respiratory Symptoms - COPD (E-RS) and its subscales (breathlessness, cough and sputum and chest symptoms)
Exploratory	
• To compare the effect of UMEC/VI 62.5/25 mcg with TIO/OLO 5 /5mcg on other measures of efficacy and measures of health-related quality of life	• Rescue albuterol/salbutamol use (percentage of rescue-free days and mean number of Inhalations/day) over Weeks 1-8 using eMDI as data allow
Safety	
To evaluate safety and tolerability of UMEC/VI 62.5/25 mcg and TIO/OLO 5/5mcg	• Incidence of adverse events (AEs) • Incidence of COPD exacerbations

4. STUDY DESIGN

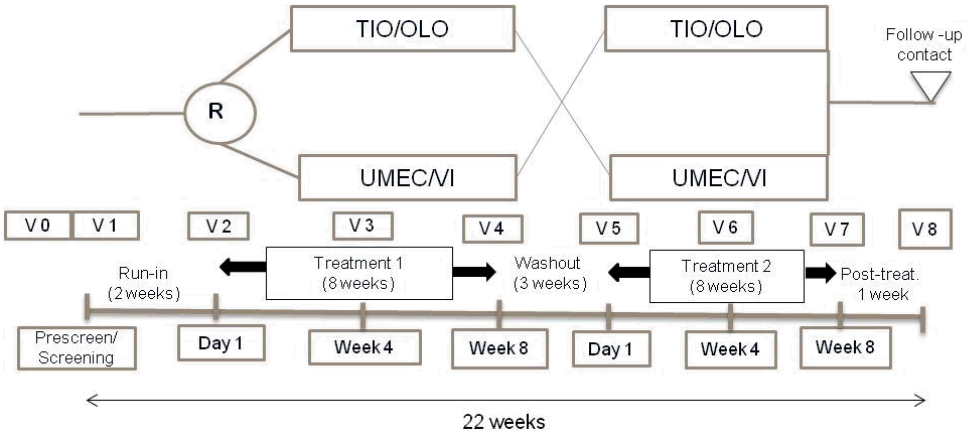
4.1. Overall Design

This is a multicentre, randomized, open label, 2 period cross-over, complete block design study.

Eligible subjects will be randomised to receive a sequence consisting of UMEC/VI 62.5/25 mcg once-daily administered as 1 inhalation once-daily from the Ellipta Inhaler and TIO/OLO 5/5mcg inhalation spray administered as inhalation of 2 inhalations once-daily from the Respimat inhaler. Each treatment sequence will be 8 weeks.

There will be up to 8 clinic visits conducted on an outpatient basis (Figure 1).

Figure 1 Study Schematic



R=Randomization

At Pre-Screen (Visit 0), subjects will provide consent for participation in the study by signing the Informed Consent Form (ICF), prior to undertaking any study procedures, and a review of their demography, medical history, concomitant medications, and a COPD exacerbation assessment will be performed. Once the ICF is signed, subjects will receive a subject identifier. Pre-screening and Screening may occur on the same day, if appropriate. Subjects who meet the eligibility criteria at Screening (Visit 1) will complete a run-in period of approximately 2 weeks followed by two 8-week treatment periods that are separated by a washout of approximate 3 weeks. A follow-up phone call for adverse event and COPD exacerbation assessment will be conducted approximately 1 week after the last clinic visit or early withdrawal.

At Visits 2 and 5, pre-dose (baseline) spirometry for each treatment period will be obtained prior to administration of the first dose of study medication for the treatment period. Trough spirometry will be obtained during each treatment period after 4 weeks (Visits 3 and 6) and 8 weeks (Visits 4 and 7). Health status will be evaluated using the COPD Assessment Test (CAT) at screening (Visit 1), baseline (Visit 2 and 5) and after 4 weeks (Visits 3 and 6) and 8 weeks (Visits 4 and 7) of treatment.

Concurrent use of COPD maintenance medications including LAMAs, LABAs, oral beta-agonists, theophyllines, inhaled corticosteroids, and phosphodiesterase 4 inhibitors will not be allowed during the study and, if applicable, will be washed out prior to study entry.

The occurrence of adverse events will be evaluated throughout the study beginning at Day 1 (Visit 2) and until the follow up contact. Serious adverse events (SAEs) will be collected over the same time period as for adverse events (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. Assessment of COPD exacerbations will be obtained at all study visits.

Albuterol/salbutamol will be provided to subjects to use on an as needed basis for relief of COPD symptoms throughout the run-in, washout and treatment periods

All subjects will be given an electronic diary for use during the run-in, washout and treatment periods to record daily questionnaires, any medical problems experienced during the study and any medication taken for those medical problems.

Daily rescue medication usage (number of inhalations taken in the last 24h) will also be captured in the eDiary and by the use of electronic inhaler (eMDI) as data allows.

For determination of subject disposition, subjects will be considered to have completed the study upon completion of Visit 7. There are no plans to routinely provide any of the study treatments for compassionate use following study completion.

4.2. Treatment Arms and Duration

- UMEC/VI 62.5/ 25mcg (as 1 inhalation from the ELLIPTA inhaler)
- TIO/OLO 5/5mcg (as 2 inhalations of 2.5/2.5mcg each from the Respimat inhaler)

All treatments will be administered once-daily in the morning for 8 weeks.

The total duration of subject participation in the study will be approximately 22 weeks consisting of a approximately 2 week run-in, two 8 week treatment periods separated by approximately 3 week washout and an approximately 1 week follow-up.

4.3. Type and Number of Subjects

Approximately 338 subjects will be screened and, assuming 35% of these will not be eligible for randomization; approximately 220 subjects will be randomized. Based on a dropout rate of 15%, approximately 186 subjects will be included in the ITT population. Approximately 168 subjects will be evaluable in the PP population (based on a 10% protocol deviation rate).

4.4. Design Justification

A randomized, cross-over study is a standard, well-established design to evaluate the efficacy and safety of two active drugs and each patient receives both medicines and acts as their own control. A complete block design will allow for within-subject treatment comparisons which will reduce variability in the response as each subject acts as their own control.

The 3-week washout between the two treatment periods is considered sufficient to enable washout of the effects of UMEC/VI and OLO/TIO on lung function measures. In two exercise studies previously conducted by GSK (DB2114417 and DB2114418), there was no evidence of a treatment by period interaction which suggests no evidence of carry over.

The open label design is appropriate as placebo Respimat from Boehringer Inglehiem (BI) is not available to allow a double-dummy design and the Ellipta and Respimat inhalers differ in appearance. The open-label design will have a negligible effect on the

spirometric data. Pulmonary function testing is an objective physiologic assessment that provides consistent, reproducible results provided adequate measures are used to ensure standardization of testing procedures. Well-qualified research sites with expertise in pulmonary function testing will be used, and a centralized spirometry vendor will provide standardized equipment and site training and provide quality assessment of each spirometry test based on accepted international lung function testing guidelines. Additionally, individuals performing the testing procedures will be blinded to the administered treatment

While the FDA and EMA guidance for trials assessing bronchodilators in patients with COPD recommend 12 weeks of treatment, the wealth of data with Anoro Ellipta and Stiolto Respimat support that treatment duration of 8 weeks is considered adequate for assessing FEV_1 changes in response to the long-acting bronchodilators under study. Treatment response was shown to reach steady-state after 4 weeks in previous large scale parallel-group studies conducted over 6 months [Donohue, 2013; Decramer, 2014; Maleki-Yazdi, 2014] and after 6 weeks in two 12-week cross over studies [Maltais, 2014]. Similar steady state findings were obtained in the primary efficacy studies conducted over 6 months for Stiolto Respimat [Buhl, 2015].

The PP population will be used for the treatment comparison of the primary endpoint of trough FEV_1 at Week 8 for non-inferiority and superiority.

The margin of non-inferiority is -50mL and the true mean treatment difference is assumed to be 0mL. The non-inferiority margin of -50mL has been chosen which is consistent with the non-inferiority margins used for trough FEV_1 or 0 to 24 hour weighted mean FEV_1 in previous studies comparing long-acting bronchodilators or long-acting bronchodilator/ICS combinations [Ichinose, 2010; Agustí, 2014]. Therefore, if the lower confidence interval (2.5% one-sided significance level) of the statistical testing should fall above -50mL then UMEC/VI may be deemed to be statistically non-inferior to OLO/TIO.

If non-inferiority is observed, the testing procedure will continue to examine statistical superiority. Superiority of UMEC/VI over OLO/TIO would be claimed provided the lower bound of the 95% confidence interval is above 0 for the treatment difference and a treatment difference of approximately 50mL is obtained.

4.5. Dose Justification

This study is intended to evaluate doses of UMEC/VI (62.5/25mcg once-daily) and TIO/OLO (5/5mcg once-daily) that are approved for the maintenance treatment of COPD and are therefore most relevant to prescribers and other health care profiles to more fully understanding the comparative efficacy and safety of the medications under study.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with UMEC/VI can be found in the product label, in the Investigator's Brochure and in the label information sheet. Summary safety data can also be found in the labels for TIO/OLO and for albuterol/salbutamol.

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 causal association has been found to date, in completed studies with UMEC/VI or UMEC monotherapy, on glaucoma or urinary	Exclusion criterion states that subjects with medical conditions such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	retention. However, glaucoma or urinary retention have been observed with other antimuscarinic agents, and could potentially be due to the pharmacology.	obstruction should only be 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.
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.
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 have the potential to receive the combination long-acting bronchodilator therapies UMEC/VI and TIO/OLO for COPD which may provide benefit to the subjects to improve airflow obstruction. Subjects who participate in this study will contribute to the process of further characterizing the benefit of these long-acting bronchodilator combinations for 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 for use "as needed" for relief of COPD symptoms
- The combination of study procedures of spirometry, physical examination and COPD Assessment Test (CAT) will provide the study subjects with a comprehensive evaluation of their health and COPD disease severity. Subjects will also be monitored throughout the study to see if their disease and general health worsens. 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 and TIO/OLO 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 products or other study treatment that may impact subject eligibility is provided in the IB, 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:

[1] **Type of subject:**
Outpatient.
[2] **Informed Consent:**
A signed and dated written informed consent prior to study participation

[3] **AGE**

Subjects 40 years of age or older at Visit 1

[4] **Gender**

Male and female subjects are eligible to participate in the study.

At the discretion of the study investigator and in alignment with local country acceptable criteria, a female is eligible to enter and participate in the study 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:

Non-reproductive potential (i.e., physiologically incapable of becoming pregnant, including any female who is post-menopausal or surgically sterile) defined as:

Pre-menopausal females with one of the following:

- Documented tubal ligation
- Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral or tubal occlusion
- Hysterectomy
- Documented Bilateral Oophorectomy

Postmenopausal defined as 12 months of spontaneous amenorrhea in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

OR

Reproductive potential, has a negative pregnancy test at screening, and agrees to one of the methods below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from methods used consistently and correctly (i.e., in accordance with the local approved product label and per study investigator discretion and the instructions of the physician from 30 days prior to the first dose of study medication and until to follow-up contact):

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

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

- Contraceptive subdermal implant that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label

- Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label [Hatcher, 2007a]
- Oral Contraceptive, either combined or progestogen alone
- Injectable progestogen
- Contraceptive vaginal ring
- Percutaneous contraceptive patches
- 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.
- 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.

[5] **Diagnosis:**

A diagnosis of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society [Celli, 2004].

[6] **Smoking History:**

Current or former cigarette smokers with a history of cigarette smoking of ≥ 10 pack-years [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.

[7] **Severity of Disease:**

A pre and post-albuterol/salbutamol FEV_1/FVC ratio of <0.70 and a post-albuterol/salbutamol FEV_1 of ≤70% to ≥ 50 % of predicted normal values at Visit 1. Predicted values will be based upon the ERS Global Lung Function Initiative [Quanjer, 2012].

[8] **Dyspnea:**

A score of ≥2 on the Modified Medical Research Council Dyspnea Scale (mMRC) at Visit 1.

5.2. Exclusion Criteria

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

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

[2] **Asthma:**
A current diagnosis of asthma. (Subjects with a prior history of asthma are eligible if they have a current diagnosis of COPD, which is the primary cause of their respiratory symptoms).

[3] **Other Respiratory Disorders:**
α1-antitrypsin deficiency: Subjects with α1-antitrypsin deficiency as the underlying cause of COPD **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] **Other Diseases/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.
[5] **Severe Hepatic Impairment**:
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). *Notes:* • *Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.* • *Chronic stable hepatitis B and C (e.g., presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment) are acceptable if subject otherwise meets entry criteria*

[6] **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

[7] **Contraindications:**
Any history of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, sympathomimetic, lactose/milk protein or magnesium stearate.

[8] **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.

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

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

[11] **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 nonsustained ventricular tachycardia
- Second degree heart block Mobitz type II or third degree heart block (unless pacemaker or defibrillator had been inserted)

[12] **Medication Prior to Spirometry:**

Unable to withhold albuterol/salbutamol for the 4 hour period required prior to spirometry testing at each study visit.

[13] **Medications Prior to Screening:**

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

Medication	Time interval
Depot corticosteroids	12 weeks
Systemic, oral or parenteral corticosteroids[1]	6 weeks
Antibiotics (for lower respiratory tract infection)	6 weeks
LABA/Inhaled Corticosteroid (ICS) combination products	30 days
ICS	30 days
Phosphodiesterase 4 (PDE_4) Inhibitor (roflumilast)	14 days
Inhaled long acting $beta_2$ agonists (LABAs): -salmeterol, formoterol -olodaterol, indacaterol, vilanterol	 48 hours 14 days
Long-acting muscarinic antagonists (LAMAs): tiotropium, aclidinium, glycopyrronium, umeclidinium	7 days
LAMA/LABA combination products	Apply whichever mono component has the longest washout
Theophyllines	48 hours
Oral $beta_2$-agonists Long-acting Short-acting	 48 hours 12 hours
Inhaled short acting $beta_2$-agonists[2]	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)

1. Localized corticosteroid injections (e.g., intra-articular and epidural) are permitted.
2. Use of study provided albuterol/salbutamol is permitted during the study, except in the 4-hour period prior to spirometry testing

[14] **Oxygen**:

Use of long-term oxygen therapy (LTOT) described as resting oxygen therapy >3L/min at screening. (Oxygen use ≤3L/min flow is not exclusionary, and patients may adjust oxygen levels as needed during the study.)

[15] **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).

[16] **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.

[17] **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.

[18] **Affiliation with Investigator Site**:
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.

[19] **Inability to Read**:
In the opinion of the investigator, any subject who is unable to read and/or would not be able to complete a questionnaire.

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

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. Data for screening failure will be collected in source documentation at the site and will be transmitted to GSK. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events related to study participation or concomitant medication.

5.4. Randomization Criteria

Subjects must meet the following randomisation criteria at Day 1 (Visit 2), in order to be randomised to study medication:

1. **COPD Exacerbation:** 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. **Prohibited Medications:** No use of any prohibited medications during the run-in period or at Visit 2.

5.5. Withdrawal/Stopping Criteria

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

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

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

5.5.1. Study Specific Withdrawal Criteria

A subject must be withdrawn from the study if any of the following criteria are met:

- **Pregnancy**: Positive pregnancy test
- **Liver Chemistry**: Meets any of the protocol-defined liver chemistry stopping criteria as defined in Section 7.5.4. 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.

5.5.2. Reasons 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 (and sub-reason, if applicable) will be categorized as:

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

5.5.3. Early Withdrawal Visit

The definition of an early subject withdrawal from the study will be any subject who is randomized to blinded medication and, for any reason, is withdrawn prior to completion of the Visit 7 procedures.

A subject may voluntarily discontinue participation in the study at any time. The investigator may also, at his/her discretion; discontinue the subject from participating in the study at any time. In addition, the investigator must make every effort to have the subject return to the clinic as soon as possible after discontinuation of study drug for an

Subjects that withdraw from the study should return to the clinic return to the clinic as soon as possible after discontinuation of study drug for an Early Withdrawal Visit. At the Early Withdrawal Visit, the following evaluations and procedures should be completed and recorded in the eCRF as required:

- Concomitant medication assessment
- Adverse event assessment

- COPD exacerbation assessment
- Physical examination (recorded in source documents only)
- Collect/review electronic diary
- Collect used study medication (blinded study medication and rescue albuterol/salbutamol)
- Assess compliance with investigational product
- Urine pregnancy test for females of childbearing potential
- Inhaler ease of use questionnaire
- Smoking status and smoking cessation counseling
- Contact the RAMOS IRT to report subject's early withdrawal from the study

A follow-up contact as described in Section 5.6 should be conducted 5 to 10 days following completion of the Early Withdrawal Visit.

5.6. Follow-up Contact

A safety follow-up contact should be conducted 7±3 days following the completion of Visit 7 or the Early Withdraw 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

For determination of subject disposition, subjects will be considered to have completed the study upon completion of Visit 7.

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 investigational product for use in this study.

The following study medications will be used in this study:

- UMEC/VI 62.5/ 25mcg administered via ELLIPTA
- TIO/OLO 5/5mcg administered via Respimat

Subjects will be instructed to take one dose of medication each morning from either the ELLIPTA (one inhalation to equal one dose) or the Respimat (inhalation of two inhalations to equal one dose.) Subject instructions and details on how to use the ELLIPTA and Respimat are provided in the SPM.

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 DPI 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.

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

GSK will also supply commercial stock TIO/OLO Inhalation Spray delivered via Respimat as manufactured by Boehringer Ingelheim (Headquarters in Ingelheim, Germany). Each actuation from the Respimat inhaler delivers 3.124mcg tiotropium bromide monohydrate (equivalent to 2.5mcg tiotropium) and 2.736mcg olodaterol hydrochloride (equivalent to 2.5mcg olodaterol) from the mouthpiece. Each TIO/OLO carton will contain a Respimat cartridge as an aluminum cylinder with a tamper protection seal on the cap and a Respimat inhaler. The Respimat inhaler is a cylindrical shaped inhaler with a gray colored body and a clear base. The clear base is removed to insert the cartridge. The Respimat contains a dose counter and will provide 60 metered inhalations

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. If not available or not appropriate locally, GSK will source centrally.

6.2. Medical Devices

Subject to availability, medical devices (eMDI devices) are being provided by GSK for use in this study. These devices, which are fitted on to albuterol/salbutamol MDI to electronically record rescue medication usage, have US FDA 510(K) clearance to market (Class II device) and EU CE marking (Class I device).

6.3. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Subjects who meet the eligibility criteria will be randomly assigned to one of the following sequences shown in Table 2 in equal proportion:

Table 2 Treatment Sequences

Sequence	Period 1	Period 2
1	UMEC/VI Inhalation Powder 62.5/25mcg, (as 1 inhalation) administered once daily via the Ellipta inhaler 8 weeks	TIO/OLO 5/5mcg, (as 2 inhalations of 2.5/2.5mcg per inhalation) administered once daily via Respimat 8 weeks
2	TIO/OLO 5/5mcg, (as 2 inhalations of 2.5/2.5mcg per inhalation) administered once daily via Respimat 8 weeks	UMEC/VI Inhalation Powder 62.5/25mcg, (as 1 inhalation) administered once daily via the Ellipta inhaler 8weeks

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

The duration of treatment for each subject in each period is 8 weeks. On the morning of each clinic study visit, subjects will refrain from taking their morning dose of study medication 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 medication each morning.

During the washout period, subjects will discontinue use of the study medication and will continue use of study provided albuterol to manage breakthrough symptoms. Additionally, short-acting anticholinergics will be allowed for use during the washout periods.

This study will utilize an IVR/IWR 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 IVR/IWR to register and randomize subjects is provided in the SPM.

6.4. Blinding

This is an open label study with no blinding of IP due to lack of availability of placebo Respimat.

6.5. Packaging and Labelling

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

6.6. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

6.6.1. Storage

All Ellipta DPI study medication 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.

The TIO/OLO should be stored at 25°C (77°F). Avoid freezing.

Sites must maintain a daily temperature log for the investigational products.

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

6.6.2. Study Medication Return

All used and unused Ellipta DPIs, and Respimat 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 SPM.

All study medication will be collected at Visit 4 and 7 or at the IP discontinuation visit, if applicable.

For any Ellipta DPI or Respimat 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 IVRS IRT to obtain a new treatment pack number for the subject and dispense a new study medication kit from the site's investigational product supply as instructed by the IVR/IWR

In addition, any Ellipta DPI that fails to function properly must be identified and returned to GSK for testing. Details of the failure will be documented in the eCRF.

6.7. Compliance with Study Treatment Administration

Study drug administration at clinic visits will be observed by study personnel to ensure the proper administration of study drug. Subject compliance with UMEC/VI (one inhalation per day equals one dose) will be assessed at the appropriate Week 4 and Week 8 clinic visits by reviewing the dose counter on the Ellipta inhaler. Subject compliance with TIO/OLO will be assessed at the appropriate Week 4 and Week 8 clinic visits by reviewing the number of inhalations/day (2 inhalations/day to equal one dose) as recorded in the eDiary.

If study medication compliance with either inhaler is determined to be < 80% or > 120%, the subject must be re-educated on proper dosing per protocol. This re-education should be documented in the subject's source document. Overall compliance with either inhaler during an entire period that is not within the range of be >=80% and <=120% will be identified as a protocol deviation. Subjects with overall compliance not within the range of be >=80% and <=120% during the first treatment period will be allowed to continue in the study provided re-education on proper dosing is provided.

6.8. Treatment of Study Treatment Overdose

An overdose is defined as a dose greater than the total doses described above which results in clinical signs and symptoms. These should be recorded by the investigator on the AE/SAE pages. In the event of an overdose of study 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 not be limited to, the approved product label for TIO/OLO, albuterol 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.

6.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because the indication being studied is not life threatening or seriously debilitating and/or other treatment options are available.

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

6.10. Concomitant Medications and Non-Drug Therapies

All COPD medications used within 30 days prior to Visit 0 and onwards should be recorded in the eCRF including any changes. Beginning at Screening (Visit 1) and throughout the rest of the study, all non-COPD medications should be recorded in the eCRF including any changes. The minimum requirement includes but is not limited to drug name, dose, route and the dates of administration. Study provided albuterol/salbutamol and study drug should not be recorded in the eCRF. Medications initiated after completion of Visit 7 will not be recorded in the eCRF, with the exception of those used to treat a COPD exacerbation or SAE that occurs between Visit 7 and the follow-up contact.

6.10.1. 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
- Short-acting inhaled muscarinic antagonists during washout period only, provided they are washed out for ≥ 4 hours prior to Visit 5
- Mucolytics such as acetylcysteine
- Medications for rhinitis (e.g. intranasal corticosteroids, antihistamines, cromolyn, nedocromil, nasal decongestants)
- Influenza vaccine
- Pneumonia 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 oxygen use (i.e. ≤12 hours per day)
- Pulmonary rehabilitation program in maintenance phase
- Smoking cessation treatment, including a stable regimen of nicotine replacement
- Use of positive airway pressure for sleep apnea
- 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

6.10.2. Prohibited Medications and Non-Drug Therapies

Use of the medications listed in Table 3 is not permitted during the study.

Table 3 Prohibited Medications

Medication
Depot corticosteroids
Systemic, oral or parenteral corticosteroids[1]
Antibiotics >14 days
LABA/ICS combination products
ICS
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)
LAMA/LABA combination products except for study drugs
Theophyllines
Oral beta$_2$-agonists
Inhaled short acting beta$_2$-agonists[2]
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 Use of study provided albuterol/salbutamol is permitted during the study, except in the 4-hour period prior to spirometry testing. Inhaled short-acting anticholinergics are allowed during the washout period and must be discontinued for ≥ 4 hours prior to Visit 5

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 at screening.
- Regular (prescribed for daily/regular use, not for as-needed use) therapy with albuterol/salbutamol.
- Initiation of pulmonary rehabilitation during the study.

Acetaminophen should not be used in patients with acute viral hepatitis.

7. STUDY ASSESSMENTS AND PROCEDURES

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

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

		Screen/Run-in		Treatment 1			Wash-Out	Treatment 2			Post-Treatment	
Visit		**0 Prescreen[1]**	**1 (Screen)**	**2 (Rand)**	**3**	**4**		**5**	**6**	**7**	**EW Visit[2]**	**Follow up Contact[11]**
Treatment Day			**14 ± 3 days prior to Visit 2**	**1 ± 3 days**	**28 ± 3 days**	**56 ± 3 days**	**21 days ± 3 days**	**1 21 ± 3 days after V4**	**28 ± 3 days after V5**	**56 ± 3 days after V5**		**7 ± 3days after V7 or EW Visit**
Week			**-1**	**N/A**	**4**	**8**		**N/A**	**4**	**8**		
Screen / Baseline	Written informed consent	X										
	Demography	X										
	Medical/COPD history		X									
	Smoking history/status		X							X	X	
	Smoking cessation counselling		X							X	X	
	Verify Inclusion/exclusion criteria		X									
	Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X
	Verify Randomization criteria			X								
	Physical examination		X							X	X	
	Screening 12-Lead ECG		X									
	Screening spirometry (including post-bronchodilator testing)[3]		X									
	mMRC dyspnea scale		X									
	Training on use of inhalers[13]			X				X				
	Training in the use of eDiary and eMDI		X									
	Register visit IVRS	X	X	X	X	X	X	X	X	X	X	X

		Screen/Run-in		Treatment 1			Wash-Out	Treatment 2			Post-Treatment	
Visit		**0 Prescreen[1]**	**1 (Screen)**	**2 (Rand)**	**3**	**4**		**5**	**6**	**7**	**EW Visit[2]**	**Follow up Contact[11]**
Treatment Day			**14 ± 3 days prior to Visit 2**	**1 ± 3 days**	**28 ± 3 days**	**56 ± 3 days**	**21 days ± 3 days**	**1 21 ± 3 days after V4**	**28 ± 3 days after V5**	**56 ± 3 days after V5**		**7 ± 3days after V7 or EW Visit**
Week			**-1**	**N/A**	**4**	**8**		**N/A**	**4**	**8**		
Efficacy/ Inhaler Evaluations	Pre dose Spirometry (FEV_1, FVC and IC)[4]			X				X				
	Trough Spirometry (FEV_1, FVC and IC)[5]				X	X			X	X		
	CAT[12]		X	X	X	X		X	X	X		
	EXACT-PRO (14 item questionnaire)		→	→	→	→	→	→	→	→		
	Inhaler Ease of use assessment			X				X				
	Inhaler Errors assessment[13]			X				X				
Safety	Adverse event assessment[6]		X	X	X	X	X	X	X	X	X	X
	COPD exacerbation assessment	X	X	X	X	X	X	X	X	X	X	X
	Urine pregnancy test[7]		X	X				X		X	X	
	Observed dose in clinic[14]				X				X			
Medication/ Supplies	Dispense rescue albuterol/salbutamol[8] with eMDI		X	X	X	X		X	X	X		
	Collect rescue albuterol/salbutamol[9] with eMDI			X	X	X		X	X	X	X	
	Dispense period 1 study medication			X	X							

		Screen/Run-in		Treatment 1			Wash-Out	Treatment 2			Post-Treatment	
Visit		**0 Prescreen[1]**	**1 (Screen)**	**2 (Rand)**	**3**	**4**		**5**	**6**	**7**	**EW Visit[2]**	**Follow up Contact[11]**
Treatment Day			**14 ± 3 days prior to Visit 2**	**1 ± 3 days**	**28 ± 3 days**	**56 ± 3 days**	**21 days ± 3 days**	**1 21 ± 3 days after V4**	**28 ± 3 days after V5**	**56 ± 3 days after V5**		**7 ± 3days after V7 or EW Visit**
Week			**-1**	**N/A**	**4**	**8**		**N/A**	**4**	**8**		
	Collect period 1 study medication					X					X	
	Dispense period 2 study medication							X	X			
	Collect period 2 study medication									X	X	
	Assess drug compliance[10]				X	X			X	X	X	
	Dispense eDiary		X									
	Collect eDiary									X	X	

1. Pre-screen Visit must be completed prior to or on the same day as Screening Visit.
2. Early Withdrawal Visit: Subjects that withdraw should return to the clinic as soon as possible for the Early Withdrawal Visit.
3. Spirometry at screening for FEV_1 and FVC assessments to be conducted as follows: pre-bronchodilator testing followed by post-albuterol/salbutamol testing. Post-albuterol/salbutamol testing conducted 10 to 30 minutes after subject self-administration of 4 Inhalations of albuterol/ salbutamol. IC will not be obtained at Screening.
4. Spirometry: On Day 1 of each period (Visits 2 and 5 respectively), pre-dose IC, FEV_1, and FVC measurements should be conducted 30 minutes and 5 minutes prior to dosing.
5. Trough IC, FEV_1, and FVC measurements on Weeks 4 and 8 of each treatment period should be done 23 hours and 24 hours after the previous day's dose of study medication.
6. Adverse events and Serious Adverse Events to be collected from the start of study drug (Visit 2) until the follow-up contact. However, any serious adverse events assessed as related to study participation or related to a GSK concomitant medication will be recorded from the time of consent. Subjects will use eDiary to record any medical problems experienced during the study and any medication taken for those medical problems
7. Pregnancy test: for females for child bearing potential only.
8. After Visit 1, albuterol/salbutamol to be used and dispensed on an as-needed basis. Use in inhalations/day to be recorded daily by subjects using the ePro.
9. Collect albuterol/salbutamol: as required (all rescue medication should be collected at Visit 7 or the Early Withdrawal Visit).
10. Compliance with UMEC/VI will be determined by reviewing the dose counter on the Ellipta inhaler. Compliance with the TIO/OLO will be determined by reviewing the number of inhalations/day (2 inhalations/day to equal one dose) as recorded in the e Diary.
11. The follow-up contact will be by telephone 5 to 10 days after V7 or the Early Withdrawal Visit.

12. CAT will be performed at the site on the eDiary.
13. For first dosing of each treatment period the subject will follow the patient information sheet under the observation of the site staff. Before the subject leaves the clinic the site staff will make sure the subject is shown a training video on the use of the inhaler and they will make sure the inhaler is correctly loaded.
14. Dosing by the subject will be observed in the clinic and corrected if necessary. Retraining by showing the training video to take place if dosing not correct. PI to make sure inhaler loader appropriately loaded before subject leaves the clinic.

EW= Early withdrawal
Rand = Randomization

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified.

No study related procedures may be performed until the informed consent form document has been signed by the subject. A pre-screening visit may be required in order to administer the informed consent before any changes are made to the subject's current medication regimen. The investigator should exercise clinical judgment, and is discouraged from changing medications only for the purposes of the clinical study. The informed consent must be signed before any changes are made to the subject's current medication regimen. The informed consent may be given at the screening visit if the subject does not take or has not taken any prohibited medications defined by the protocol.

During the pre-screening visit (Visit 0); each subject will have the following information collected:

- Demographic history (including gender, ethnic origin, race and year of birth)
- Concomitant medication review
- COPD exacerbation assessment
- Cardiovascular medical history/risk factors

The additional following critical baseline assessments will be conducted at Visit 1:

- Medical history including COPD (compromised of 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)
- Inclusion/Exclusion criteria assessment
- Concomitant medication review (COPD concomitant medications in the 3 months prior to Screening)
- Pre- and post-albuterol/salbutamol spirometry (reversibility)
- Physical examination
- 12-Lead ECG
- Urine pregnancy test if applicable

- SAE assessment (if related to study participation)
- mMRC dyspnea scale
- CAT

Assessment of subject's health status will be made at screening using CAT. Patient Reported Outcomes questionnaires must be completed by subjects before any other assessment at each clinic visit, in the order specified. mMRC should be performed prior to CAT at screening as it is an inclusion criterion.

7.2.1. Modified Medical Research Council (mMRC) Dyspnea Scale

At screening the subject's degree of dyspnea to different levels of activity will be rated on the five point mMRC scale. The mMRC, administered by an interviewer, asks subjects to rate how breathless they are using a 0-4 point scale.

The mMRC, administered by an interviewer, asks subjects to rate how breathless they are on a 5-point scale as follows:

- 0 = not troubled by breathlessness except with strenuous exercise
- 1 = troubled by shortness of breath when hurrying on the level or walking up a slight hill
- 2 = Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
- 3 = stops for breath after walking about 100 yards or after a few minutes on the level
- 4 = too breathless to leave the house or breathless when dressing or undressing

7.2.2. 12-Lead ECG

ECG measurements will be obtained with equipment provided by the investigation site. A 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.

ECGs are only required at Visit 1 (Screening) only for eligibility assessment.

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

7.3. Efficacy

7.3.1. Spirometry

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

All subjects will have spirometry performed at Screening and at Visits 2, 3, 4, 5, 6, and 7 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) ≥4 hours and after withholding short-acting inhaled anticholinergics taken during washout for ≥4 hours prior to Visit 5
- At Visit 1, after withholding COPD medications as specified in the exclusion criteria in Section 5.
- At Visit 3 and 6 after withholding the morning dose of study drug (note study drug will not be administered at visits 4 and 7).
- Pre dose assessments performed prior dosing

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

On Day 1 of each treatment period (Visits 2 and 5 respectively), pre-dose spirometry measurements should be conducted 30 minutes and 5 minutes prior to dosing. Trough measurements on Weeks 4 (Visits 3 and 6) and Week 8 (Visits 4 and 7) of each treatment period should be done 23 hours and 24 hours after the previous day's dose of study medication. Any trough FEV_1 measurement collected outside 22.0-25.0 hours after the previous day's dose will be considered protocol deviations with data exclusion from the Per Protocol population analysis of trough FEV_1.

7.3.2. Albuterol/Salbutamol Reversibility Assessment

At Visit 1, both pre- and post-albuterol/salbutamol spirometry will be obtained to determine subject eligibility. Failure to obtain both pre- and post- post-albuterol/salbutamol spirometry at Visit 1 will be considered a protocol deviation. Bronchodilator responsiveness testing will be completed as follows: Following pre-albuterol/salbutamol spirometry (three acceptable spirometry efforts), the subject will

self-administer 4 Inhalations of albuterol/salbutamol MDI. Three acceptable spirometry efforts should be obtained approximately 10 to 30 minutes after albuterol/salbutamol administration.

7.3.3. Inspiratory Capacity (IC)

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; 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 and 5 (30 and 5 min prior to dosing) and at trough at Visits 3, 4, 6 and 7 (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 TLC (Total Lung Capacity) 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 and after withholding short-acting inhaled anticholinergics taken during washout for ≥4 hours prior to Visit 5
- At Visit 3 after withholding the morning dose of study drug (note study drug will not be administered at visits 4 and 7).

7.4. Electronic Diary

Electronic diary will be used to collect the following: E-RS, rescue use, CAT and Inhaler questionnaires and potential medical problems.

7.4.1. 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.

7.4.2. Supplemental Albuterol/Salbutamol Use

Subjects should be instructed that study-provided albuterol/salbutamol should be used on an 'as-needed' basis only.

Rescue medication will be captured in the electronic Diary as well as eMDI as data allow. Details on how to place the eMDI on the MDI is described in the SPM.

Rescue inhaler use will be captured each day (during run-in, washout and treatment periods) by means of an eDiary and if available and possible in an eMDI device . The eDiary will be used as the primary analysis measure. eMDI attaches to the actual MDI inhaler and that gets activated every time there is an actuation. The device should be attached to the MDI inhaler at the first subject visit. If the subject requires a replacement rescue inhaler the eMDI device can be transferred from the old inhaler to the new on. This should be performed at the study site by the Investigator or designee.

Use of rescue albuterol/salbutamol should **not** be recorded as a concomitant medication in the eCRF.

The following Clinic visit Questionnaires will also be collected on the electronic diary:

7.4.3. COPD Assessment Test (CAT)

COPD-related health status will be assessed using the CAT at Visit 1 for subject characterisation and then Visits 2, 3, 4, 5, 6 and Visit 7.

The COPD Assessment Test (CAT) is a patient-completed instrument designed to provide a simple and reliable measure of health status in COPD. The CAT is designed to measure overall COPD-related health status for the assessment and long-term follow-up of individual patients. The instrument consists of eight items; each formatted as a semantic six-point differential scale, and is completed by the patient [Jones, 2009; Jones, 2012].

CAT will be completed at each visit on the eDiary. Additional instructions for completion of the CAT are provided in the SPM.

CAT evaluations must be performed before any other visit procedures.

7.4.4. Inhaler questionnaires

7.4.4.1. Inhaler Ease of Use

An investigator (or designee)-administered questionnaire will be completed at Visits 2 and 5, or Early Withdrawal if applicable, to determine the ease of use of the ELLIPTA and Respimat. Six questions will be asked and the subject will be required to select only one response for each question.

A sample of the inhaler ease of use questionnaire is included in the SPM. Additional instructions for completion of this questionnaire are provided in the SPM.

7.4.4.2. Inhaler Errors

Inhaler errors will be assessed using the Inhalers Errors Checklist at Visit 2 and Visit 5 to assess the critical and overall (critical and non-critical) errors made by subjects with the ELLIPTA and Respimat inhalers.

The investigator (or designee)-administered inhaler errors checklist is based on the steps listed in the Patient Information Leaflets (PIL) for each inhaler. The proportion of subjects reported by the investigator or designee as making at least one critical error (defined as an error that is most likely to result in no or only minimal medication being inhaled) or overall error (includes a critical and non-critical error) will be evaluated in this study.

The inhaler errors checklist will be administered by the investigator or designee.

At Visit 2 and 5, the subject will prepare his or her inhaler for first use and self-administer their first dose of the study medication in the clinic under the supervision of the investigator or designee. The subject will simply follow the instructions in the patient information leaflet without prior instruction on the day. Any errors (critical or non-critical) made by the subject while using the inhaler will be recorded by the investigator or designee. If the subject makes no errors, this will also be recorded. Any errors (critical or non-critical) made by the subject while using the inhaler will be recorded by the investigator or designee. If the subject makes no errors, this will also be recorded. The investigator or designee will demonstrate the correct use of the inhaler to the subject and will make sure the inhaler is loaded properly before the subject leaves the clinic.

Additional instructions for completion of the inhaler errors checklist are provided in the SPM.

7.4.5. Any Medical Problems Experienced and any Medications used to Treat those Medical Problems

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

7.5. Safety

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

Safety endpoints include the following:

- Incidence of COPD exacerbations
- Incidence of adverse events

7.5.1. COPD Exacerbations

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.

If a subject experiences a moderate or severe COPD exacerbation, the COPD exacerbation page of the eCRF should be completed. COPD exacerbations should not be recorded as an Adverse Event, unless they meet the definition of a Serious Adverse Event.

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

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. COPD exacerbations after randomization through follow-up will be recorded on the COPD exacerbation page of the eCRF.

7.5.2. Adverse Events (AE), Serious Adverse Events (SAEs) and sentinel events

The definitions of an AE or SAE and sentinel event can be found in Section 12.4.

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

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

- AEs will be collected from the start of study treatment and until the follow up contact.
- AEs and SAEs will be collected at the time points specified in the Time and Events Table (Section 7.1).

- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- 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.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in.
- 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 Section 7.5.2.1

7.5.2.2. Method of Detecting AEs and SAEs

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

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

7.5.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 7.5.2) 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).

7.5.2.4. Cardiovascular Events

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

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

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

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

7.5.2.5. 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.

7.5.2.6. Death Events

In addition, all deaths will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

7.5.2.7. 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.

7.5.2.8. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK or designee of SAEs and non-serious AEs 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.

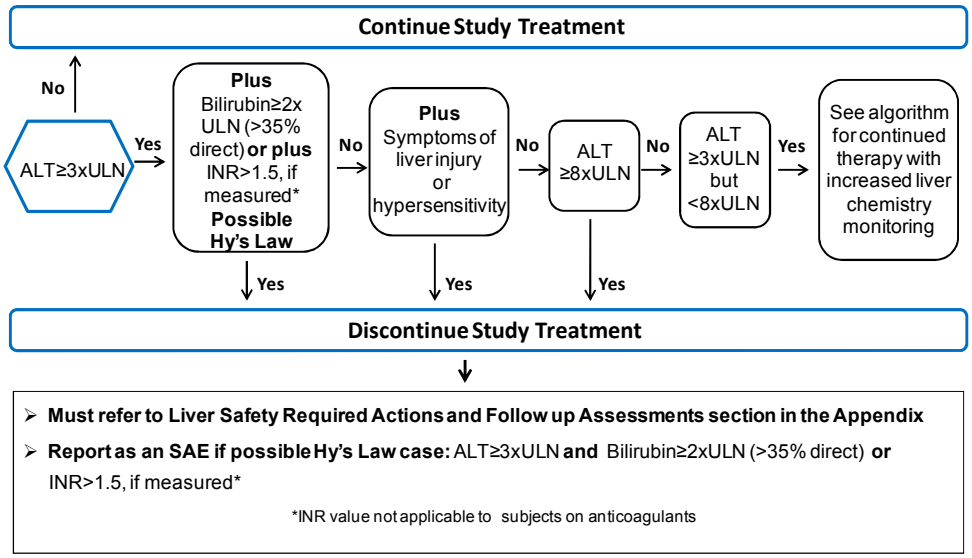
7.5.3. Pregnancy

- Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.
- Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.
- 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 6.

7.5.4. Liver Chemistry Stopping Criteria

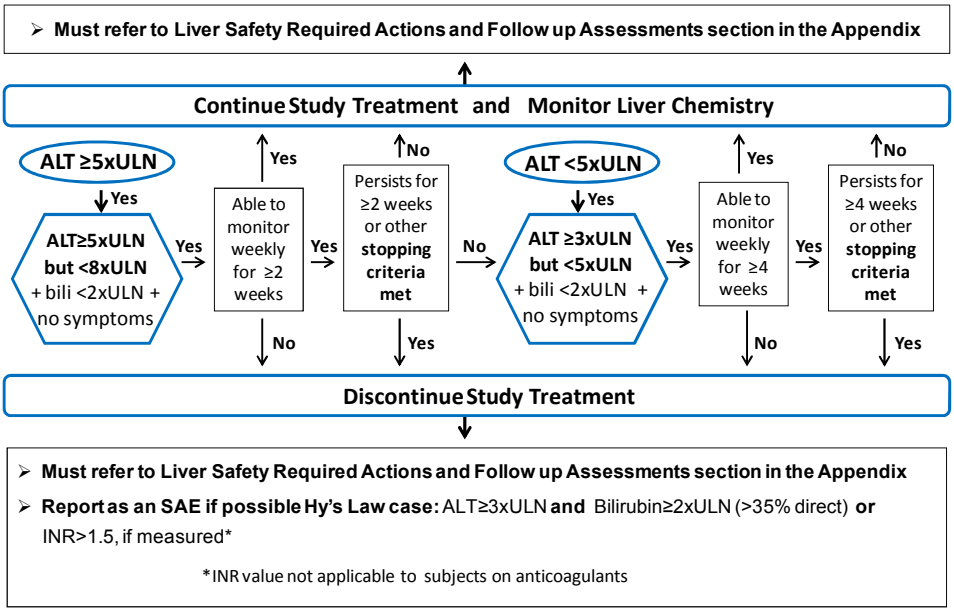
A protocol-defined liver chemistry stopping criteria and increased monitoring algorithm is provided in Figure 2.

Figure 2 Phase III/Phase IV Liver Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2

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



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2

Note: This study does not require laboratory assessments, therefore the liver chemistry criteria apply to any laboratory assessments obtained outside of the protocol-specified safety evaluations.

7.5.5. Medical Device Incidents (Including Malfunctions)

Procedures for Documenting Medical Device Incidents are provided in Appendix 5

7.5.6. Physical Exams

A complete physical examination will be performed at Visit 1 screening and at Visit 7 or Early Withdrawal Visit if appropriate.

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

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined electronic case report forms (eCRFs), transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- 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 objective of this study is to compare UMEC/VI 62.5/25 mcg with TIO/OLO 5/5 mcg in moderate COPD subjects. The primary endpoint is trough FEV_1 at Week 8. The primary analysis is the comparison of this endpoint for UMEC/VI 62.5/25 mcg vs. TIO/OLO 5/5 mcg.

The null hypothesis is that the difference in trough FEV_1 between treatment groups is less than or equal to a pre-specified non-inferiority margin Δ:

H_0: $T_1 - T_2 \leq \Delta$

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

H_1: $T_1 - T_2 > \Delta$

where T_1 and T_2 are the treatment means for UMEC/VI 62.5/25 mcg and TIO/OLO 5/5 mcg, respectively.

The non-inferiority margin has been set at -50mL, which is consistent with the non-inferiority margins used for trough FEV_1 or 0 to 24 hour weighted mean FEV_1 in previous studies comparing long-acting bronchodilators or long-acting bronchodilator/ICS combinations [Ichinose, 2010; Vogelmeier, 2010; Agustí, 2014].

If the lower bound of the 95% confidence interval around the (UMEC/VI 62.5/25 mcg vs. TIO/OLO 5/5 mcg) treatment difference is above -50mL then UMEC/VI 62.5/25 mcg will be considered non-inferior to TIO/OLO 5/5 mcg.

If the lower bound of the 95% confidence interval around the (UMEC/VI 62.5/25 mcg vs. TIO/OLO 5/5 mcg) treatment difference is above 0 then UMEC/VI 62.5/25 mcg will be considered superior to TIO/OLO 5/5 mcg.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The sample size calculations use a one-sided 2.5% significance level and an estimate of within-subject standard deviation (SD) for trough FEV_1 of 140 ml. The estimate of SD is based on a mixed model repeated measures (MMRM) analyses of two previous cross-over studies in COPD subjects evaluating trough FEV_1 at Week 2. The observed SD from these studies (133ml in DB2116132 and 113ml in DB2116133) has been increased to allow for additional variability that may be observed during an 8 week treatment period.

A study with 168 evaluable subjects for the primary analysis on the per-protocol (PP) population will have 90% power to detect non-inferiority of UMEC/VI to TIO/OLO based on trough FEV_1 at Week 8, when the margin of non-inferiority is -50mL and the true mean treatment difference is assumed to be 0mL.

It is estimated that approximately 10% of subjects who will provide a Week 8 assessment will be excluded from the PP population, which would require 186 subjects with a Week 8 assessment in the ITT population. Allowing for a 15% withdrawal rate, a total of 220 subjects will be randomised.

9.2.2. Sample Size Sensitivity

The within-subject SD of 140 ml for trough FEV_1 used for the sample size calculations was based on two previous cross-over responder studies in COPD subjects evaluating trough FEV_1 at Week 2. If the standard deviation observed in this study is different from the estimated value used in the sample size calculation, the power to determine non-inferiority based on trough FEV_1 at Week 8 will be affected. Table 4 illustrates the power which would be obtained with various standard deviations, assuming the number of evaluable subjects remains constant at 168 and the non-inferiority margin is -50 mL.

Table 4 Impact on Power of Different Estimates of Standard Deviation for Trough FEV_1

Within-subject SD (mL)	Power for Margin of -50 mL
100	>99%
120	97%
140	90%
160	81%
180	72%

If the within subject SD increased to 180 mL, the study would have 72% power to conclude non-inferiority based on a margin of -50 mL. If the SD were 100 mL then the study would have >99% power to conclude non-inferiority.

Based on a within subject SD of 140 mL and a sample size of 168 evaluable PP subjects, the lower confidence bound for the treatment difference would be greater than 0 at an observed treatment difference of 30 mL [detectable effect].

Based on a within subject SD of 140 mL and a sample size of 186 ITT subjects, the study would conclude superiority (i.e. lower confidence bound > 0) with a treatment difference of 29mL [detectable effect].

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

Three subject populations will be identified.

The **All Subjects Enrolled** Population will comprise all subjects for whom a record exists on the study database, including screen failures and any subject who was not screened but experienced a serious adverse event (SAE) between the date of informed consent and the planned date of the Screening Visit. This population will be used for reporting subject disposition, reasons for withdrawal prior to randomization, and inclusion, exclusion and randomization criteria deviations and SAEs for non-randomised subjects.

The **Intent-to-treat** (ITT) Population will comprise all subjects randomized to treatment, excluding those who were randomized in error. A subject who is recorded as a screen or run-in failure and also randomized will be considered to be randomized in error. Any other subject who receives a randomization number will be considered to have been randomized. Randomized subjects will be assumed to have received study medication unless definitive evidence to the contrary exists. Outcomes will be reported according to the randomized treatment allocation. This population will be the used for all efficacy and safety displays unless specified otherwise.

The **Per Protocol** (PP) Population will comprise all subjects in the ITT Population who do not have a full protocol deviation considered to impact efficacy. Receipt of a study treatment other than the randomised treatment will be considered a full protocol deviation. Subjects with partial protocol deviations considered to impact efficacy will be included in the PP Population but will have their data excluded from PP analyses from the time of deviation onwards. Subjects with time-point specific or period specific protocol deviations will be included in the PP population but will have the data affected excluded from PP analyses. The definition of full, partial, time-point specific and period specific deviations considered to impact efficacy will be included in the Reporting and Analysis Plan (RAP). This population will be used for the primary comparison between the treatments to determine NI. It will also be used for the primary comparison between treatments to assess superiority, assuming that the primary analysis on the PP population supports the conclusion of NI.

9.3.2. Interim Analysis

No interim analysis is planned.

9.4. Key Elements of Analysis Plan

Since this is an 8 week non-inferiority study with two active comparators, the number of withdrawals is expected to be low. In particular, subjects who experience an exacerbation whilst in the study will be allowed to continue participating if possible. Furthermore, the primary comparison is non-inferiority on the per protocol population (a De Jure estimand) and inclusion of data from subjects post-withdrawal would likely bias the results towards a conclusion of non-inferiority. Hence data from subjects post-withdrawal will not be collected. Where possible, data from subjects who withdraw prematurely from the study will be included in any relevant analyses. Specific details for inclusion will be detailed in the RAP, but in general the minimum data required will be a baseline evaluation and at least one on-treatment evaluation. Tipping Point analyses will however be conducted to assess robustness of conclusions. Data collected during a clinic visit will be reported by the visit at which the data were collected and will not be excluded from any analysis for being collected outside of an assessment window.

For the purposes of analyses, a completed subject is defined as anyone completing the last treatment visit for each period (Visit 4 and 7).

It is anticipated that approximately 30 centres (worldwide) will participate in the study. Centres enrolling a small number of subjects may be pooled with another centre. All amalgamations will be finalised and documented in the RAP. These amalgamations will be used wherever region is incorporated into the analysis.

Baseline values for each endpoint will be those used from Visit 1 (screening) or pre-treatment in period 1 at Visit 2 (randomisation) or pre-treatment in period 2 at Visit 5 and will be defined in the RAP.

9.4.1. Efficacy Analyses

All efficacy data will be summarized using means, SDs and ranges for continuous data and frequencies and percentages for categorical data.

Primary Endpoint

The primary endpoint of trough FEV_1 at week 8 will be analysed using a repeated measures model including data recorded at each of Week 4 and Week 8 for the PP population. Treatment group (categorical) will be fitted as the explanatory variable, with period baseline, mean baseline, period, and visit fitted as covariates. Visit (nominal) will be fitted as a categorical variable and visit by period baseline, visit by mean baseline and visit by treatment interaction terms will be included. Treatment effects will be estimated at each visit separately. The variance-covariance matrix will be assumed unstructured. Missing data are not imputed in this analysis; however, all non-missing data will be used within the analysis to estimate the treatment effect at Week 8.

Estimated treatment differences for UMEC/VI vs. TIO/OLO will be presented together with 95% confidence intervals (CIs) for the difference and p-values (for test of superiority).

The MMRM analysis of the primary endpoint will be repeated for the ITT Population testing for superiority in order to ensure consistent results with those from the PP population. These analyses will include data from protocol deviators. In addition, a tipping point analysis will be carried out as a sensitivity analysis for the primary endpoint of trough FEV_1 at Week 8 on the PP and ITT population in order to assess the impact of missing data. Full details will be given in the RAP.

Other Endpoints

FVC and IC at Week 4 and Week 8 will be analysed separately using the same methodology as that for the primary endpoint. The mean number of Inhalations of rescue medication per day for Weeks 1-2, 3-4, 5-6 and 7-8 will be analysed using a mixed model repeated measures analysis including covariates of period baseline, mean baseline, period, treatment, two-weekly period, two-weekly period by period baseline interaction and two-weekly period by mean baseline interaction. The model will use all available values recorded during Weeks 1-2, 3-4, 5-6 and 7-8. Missing data are not directly imputed in this analysis; however, all non-missing data for a subject will be used within the analysis to estimate the treatment effect for the mean number of Inhalations of rescue medication over Weeks 1-8. Two models will be fitted; one with a response variable of mean number of Inhalations, and one with a response variable of change from baseline in mean number of Inhalations. The variance-covariance matrix will be assumed unstructured.

Estimated treatment differences for UMEC/VI vs. TIO/OLO will be presented together with 95% confidence intervals (CIs) for the difference and p-values.

The percentage of rescue-free days will be analysed similarly. If the assumption for normality is not satisfied a non-parametric analysis will be used instead. Full details will be given in the RAP.

The CAT endpoint at Week 4 and Week 8 will be analysed using an MMRM analysis as described for the primary endpoint of trough FEV_1.

Responder analyses for trough FEV_1 and CAT will be analysed using a logistic regression analysis for Week 4 and Week 8 separately. Further details will be given in the RAP.

9.4.2. Safety Analyses

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

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

The proportion of subjects experiencing a COPD exacerbation will be tabulated.

Full details of the analyses to be performed on all efficacy and 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 CRF 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	Time to 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- PRO	Evaluating respiratory Symptoms of COPD Tool
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
IE	Inhaler Errors
IEC	Independent Ethics Committee
IP	Investigational product
INR	International normalized ratio
IRB	Independent Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine System
LABA	Long Acting Beta-Agonist

LAMA	Long-acting Muscarinic Receptor Antagonists
LDH	Lactate dehydrogenase
LTOT	Long Term Oxygen Therapy
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
NI	non-inferiority margins
NYHA	New York Heart Association
TIO/OLO	Tiotropium/Olodaterol as fixed dose combination
OTC	Over the Counter
PDE	Phosphodiesterase
PGx	Pharmacogenetic
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PP	Per Protocol
prn	As required
QTc	QT interval corrected for heart rate
QTc(F)	QT interval corrected for heart rate according to Fridericia formula
RAP	Reporting and Analysis Plan
RNA	Ribonucleic acid
SABA	Short Acting Beta-Agonist
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SPM	Study Procedures Manual
SRT	Safety Review Team
TDI	Transition Dyspnea Index
ULN	Upper Limit of Normal
UMEC	Umeclidinium (GSK573719)
UMEC/VI	Umeclidinium & Vilanterol as a fixed dose combination
VI	Vilanterol Trifenate

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ANORO
CAT
ELLIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
Respimat
Stiolto

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

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event 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 stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria - Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥ 8xULN</td></tr>
<tr><td>ALT Increase</td><td colspan="2">ALT ≥ 5xULN but <8xULN persists for ≥2 weeks
ALT ≥ 3xULN but <5xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin1, 2</td><td colspan="2">ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR2</td><td colspan="2">ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td colspan="2">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>Symptomatic3</td><td colspan="2">ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th colspan="2">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 baseline (see MONITORING below)
• Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval is</td><td colspan="2">• 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</td></tr>
</table>

granted (refer to Appendix 3) • If restart/rechallenge **not allowed or not granted**, 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 liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<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 baseline	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 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.

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

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

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

SAEs, cardiovascular, pneumonia, death events, pregnancies, medical device incidents, non-serious AEs related to study treatment and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Cardiovascular or Pneumonia and/or death event (s)[4]	Initial and follow up reports to be completed within one week of when the cardiovascular, Pneumonia and or death event (s) is reported	"Cardiovascular (CV)", "Pneumonia" and/or "death" event(s) data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event Pneumonia and/or death event (s) is reported	Updated "CV, Pneumonia," and/or "death" event (s) data collection tool(s) if applicable
Medical Device Incident	24 hours	"Medical Device Incident Report Form"	24 hours	Updated "Medical Device Incident Report Form"
Pregnancy	2 weeks	"Pregnancy Notification Form"	2 weeks	"Pregnancy Follow-up Form"
Non-serious adverse events related to study treatment	5 calendar days	"Adverse Reaction" data collection tool	2 weeks	Updated "Adverse Reaction" data collection tool
Liver chemistry abnormalities for Phase I to IV:				
ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) (or ALT≥3xULN **and** INR>1.5, if INR measured)[1]	24 hours[2]	"SAE" data collection tool. "Liver Event CRF" and "Liver Imaging" and/or "Liver Biopsy" CRFs, if applicable[3]	24 hours	Updated "SAE" data collection tool/"Liver Event" Documents[3]

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
Remaining liver chemistry abnormalities Phase III to IV:				
ALT≥8xULN; ALT≥3xULN with hepatitis or rash or ≥3xULN and <5xULN that persists≥4 weeks	24 hours[2]	"Liver Event" Documents (defined above) [3]	24 hours	Updated "Liver Event" Documents[3]
ALT≥5xULN plus bilirubin <2xULN	24 hours[2]	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks[3]	24 hours	Updated "Liver Event" Documents, if applicable[3]
ALT≥5xULN and bilirubin <2xULN that persists ≥2 weeks	24 hours[2]	"Liver Event" Documents (defined above) [3]	24 hours	Updated "Liver Event" Documents[3]
ALT≥3xULN and <5x ULN and bilirubin <2xULN	24 hours[2]	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[3]	24 hours	Updated "Liver Event" Documents, if applicable[3]

1. INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants.
2. GSK must be contacted at onset of liver chemistry elevations to discuss subject safety
3. Liver Event Documents (i.e., "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible.
4. The SRT (or Study Team, if there is no SRT) should determine the appropriate time frame, *if one is needed,* for completion of DRE CRF pages.

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

12.3. Appendix 3: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

Not applicable

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. • 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. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes 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 and 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.

- Refer to Appendix 2 for the required liver chemistry follow-up instructions

12.4.3. Definition of Sentinel Events

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. Medical monitor review of all SAEs for possible Sentinel Events is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review.:

The current GSK-defined Sentinel Events
• Acquired Long QT Syndrome • Agranulocytosis/Severe Neutropenia • Anaphylaxis & Anaphylactoid Reactions • Hepatotoxicity • Acute Renal Failure • Seizure • Stevens Johnson syndrome/Toxic epidermal necrosis

12.4.4. 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

12.4.5. 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.

12.4.6. 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.

12.4.7. 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.

SAE reporting to GSK via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail
- Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via PIMS

- Facsimile transmission of the following PIMS listings for the corresponding subject is the preferred method to transmit SAE information to the Medical Monitor:
  - SAE listing
  - Demographic listing
  - Study treatment listing
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of all required information sent by overnight mail.
- If the PIMS system is unavailable when the SAE occurs, the site will use the paper SAE form and fax that to the Medical Monitor. The site will enter the SAE data into PIMS as soon as the system becomes available.

12.5. Appendix 5: Definition of and Procedures for Documenting Medical Device Incidents

12.5.1. 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

12.5.2. 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 • 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.

12.6. Appendix 6: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

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

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

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a]
- Injectable progestogen [Hatcher, 2007a]
- Contraceptive vaginal ring [Hatcher, 2007a]
- Percutaneous contraceptive patches [Hatcher, 2007a]
- Male partner 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, 2007a].
- Male condom plus partner use of one of the contraceptive options below:
    - Contraceptive subdermal implant
    - Intrauterine device or intrauterine system
    - Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a] Injectable progestogen [Hatcher, 2007a]
    - Contraceptive vaginal ring [Hatcher, 2007a]
    - Percutaneous contraceptive patches [Hatcher, 2007a]

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

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

12.6.2. 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 discontinue study medication
- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner’s pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

12.7. Appendix 7 - Country Specific Requirements

No country-specific requirements exist.