TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A 24- week randomised, double-blind and placebo-controlled study to evaluate the efficacy and safety of 62.5 mcg Umeclidinium Inhalation Powder delivered once-daily via a Novel Dry Powder Inhaler in subjects with Chronic Obstructive Pulmonary Disease

Compound Number: GSK573719

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Author (s):

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Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2013N159587_00	2013-NOV-13	Original
2013N159587_01	2014-APR-03	Amendment No.: 01
To update eligibility criteria, revise some minor errors		
2013N159587_02	2014-MAY-09	Amendment No. 02
To define variables used in statistical assessment to meet authority's requirement.		
2013N159587_03	2015-NOV-11	Amendment No. 03
• Removed Thailand and Taiwan from involved countries/areas. • Changed randomization ratio from 1:1 to 2:1. • Updated sample size based on the latest difference and SD. Updated analysis plan. • Dispense of rescue sulbutamol was moved up from V1 to V0. • Updated wordings in cardiovascular events, death events, liver stop/follow, and AE/SAE according to the latest protocol template. • Developed a China specific requirement on SAE collection period. • Pharmacogenetic research sections removed. • Updated the 12-Lead ECG Exclusion Criteria and 12-Lead ECG Withdrawal Criteria. • Novel Dry Powder Inhaler (NDPI) has been replaced with ELLIPTA. • Some minor revisions.		

SPONSOR SIGNATORY

PPD

11 November 2015

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SPONSOR INFORMATION PAGE

Clinical Study Identifier: AC4117410

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol AC4117410

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

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

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

Investigator Name:		
Investigator Signature		Date

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LIST OF ABBREVIATIONS

Ach	Acetylcholine
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
ATS	America Thoracic Society
AV	Atrioventricular
BDI	Baseline Dyspnea Index
CI	Confidence Interval
CAT	COPD Assessment Test
CPK	Creatine Phosphokinase
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
EW	Early Withdrawal
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
FEV_1	Forced Expiratory Volume in One Second
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
IB	Investigator's Brochure
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IRB	Independent Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LABA	Long Acting Beta-Agonist
LAMA	Long Acting Muscarinic Antagonist
LDH	Lactate Dehydrogenase
LTOT	Long Term Oxygen Therapy
Mcg	Micrograms
MDI	Metered Dose Inhaler
MedRA	Medical Dictionary for Regulatory Activities
mMRC	Modified Medical Research Council Dyspnea Scale
MMRM	Mixed Models Repeated Measures
MSDS	Material Safety Data Sheet
mV	Millivolt
NHANES III	National Health and Nutrition Examination Survey III
PGx	Pharmacogenetics
PDE4	Phosphodiesterase 4
PK	Pharmacokinetic
PP	Per Protocol

RAMOS NG	Randomization And Medication Ordering System Next Generation
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SGRQ	St George's Respiratory Questionnaire
SPM	Study Procedures Manual
TDI	Transitional Dyspnea Index
ULN	Upper Limit of Normal
UMEC	Umeclidinium

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ELLIPTA

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PROTOCOL SUMMARY

Rationale

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of poor health, resulting in millions of deaths annually worldwide and contributing significantly to health care costs and morbidity. As of 2001, COPD was the fifth leading cause of death and the eleventh leading cause of disability worldwide. By the year 2020, COPD is expected to be the third leading cause of death and the fifth leading cause of disability. It has been estimated that over a 30 year period in China (up to 2033), 65 million deaths will be attributable to COPD.

COPD is a preventable and treatable disease characterized by airflow limitation that is not fully reversible. The airflow limitation of COPD is primarily due to small airways disease and parenchymal destruction associated with an abnormal inflammatory response of the lungs. This is mainly caused by cigarette smoking, although in many countries, air pollution resulting from burning of wood and other biomass fuels has also been identified as a COPD risk factor. Chinese smokers account for about one third of all smokers worldwide. In China the prevalence of COPD was reported to be 8.2 % for those ≥ 40 years of age and is expected to rise.

Pharmacological management of chronic, stable COPD is primarily aimed at improving symptoms and quality of life, optimizing lung function, reducing exacerbations and improving exercise tolerance. Inhaled bronchodilators, including $beta_2$-agonists and anticholinergics, together with inhaled corticosteroids (ICS) are the mainstays of therapy in patients diagnosed with COPD. Inhaled bronchodilators are recommended as a standalone treatment for patients in GOLD group A and B with long acting bronchodilators recommended as disease progresses. This is often followed by use as an 'add on' to steroid for more severe patients.

Anti cholinergic bronchodilators (muscarinic receptor antagonists) exert their bronchodilator activity by inhibiting the binding of neurotransmitter acetylcholine (Ach) with muscarinic Ach receptors on airway smooth muscle. This blocks endogenous airway smooth muscle tone allowing bronchodilation and reducing mucus hypersecretion.

Treatment with muscarinic antagonists has been shown to significantly improve Forced Expiratory Volume in One Second (FEV_1), resting and dynamic lung hyperinflation, symptoms, exercise capacity, health status, and reduce COPD exacerbations. However, a significant number of subjects are thought to continue to have symptoms, as reported in a primary care, cross-sectional study.

Umeclidinium (UMEC) is an orally inhaled, potent, pan-active long acting muscarinic antagonist (LAMA) in development for use as an inhaled product in the treatment of COPD as a monotherapy once-daily product and also in combination with the long acting beta agonist (LABA), vilanterol, as a once-daily treatment of COPD.

Studies to date provide substantial evidence for the effectiveness for UMEC 62.5 mcg as a long term maintenance therapy for the treatment of COPD. The purpose of this 24-week

study is to further evaluate the efficacy and safety of UMEC 62.5 mcg administered once-daily in Asian subjects with COPD.

Objective(s)

The primary objective of the study is to evaluate the efficacy and safety of Umeclidinium Inhalation Powder at 62.5 mcg compared with placebo administered once- daily via an ELLIPTA™ over 24 weeks in subjects with COPD.

Study Design

This is a 24-week, phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group study.

288 eligible subjects will be randomized to the UMEC 62.5 mcg and placebo treatment groups in a 2:1 ratio, approximately 192 subjects in active arm and 96 subjects in placebo arm. All treatments will be administered once-daily in the morning by inhalation using an ELLIPTA.

There will be a total of 10 study clinic visits conducted on an outpatient basis. A pre-screening visit (V0) will be conducted to sign the informed consent form (ICF), dispense the rescue medication and review demography, COPD history and concomitant medications. Once the ICF is signed the subject will be assigned a subject identifier. At Visit 0, any medications changes made by the investigator will be recorded. Subjects who meet the eligibility criteria at Screening (Visit 1) will complete a 7 to 14 day Run-in period. At the end of the Run-in period, subjects will be assessed and those who meet the randomisation criteria will enter a 24-week double-blind Treatment Period. Clinic visits (1 through 9) will be at Screening, Randomization (Day 1), Day 2, Day 28 (Week 4), Day 56 (Week 8), Day 84 (Week 12), Day 112 (Week 16), Day 168 (Week 24) and Day 169. A follow-up contact for adverse event (AE) assessment will be conducted by telephone approximately 7 days after the Treatment period or the Early Withdrawal (EW) Visit.

The total duration of subject participation, including follow-up will be approximately 27 weeks. All subjects will be provided with albuterol/salbutamol for use on an “as-needed” basis throughout the Pre-screen, Run-in and study Treatment periods.

Study End-point Assessments

Primary

Clinic visit trough (pre-bronchodilator) FEV_1 on Treatment Day 169

Trough FEV_1 on Treatment Day 169 is defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Treatment Day 168 (i.e. at Week 24).

Secondary

- Transition Dyspnea Index (TDI) focal score at Week 24.
- Weighted mean clinic visit FEV_1 over 0 to 6 hours post-dose at visit 2 (Day 1)

Others

- Trough FEV_1 and TDI focal score at other time points
- Rescue albuterol/salbutamol use (percentage of rescue-free days and puffs/day)
- Time to onset (defined as an increase of 100mL above baseline in $FEV_{1)}$ during 0-6hr post-dose on Treatment Day 1 (Visit 2)
- Proportion of subjects achieving an increase in FEV_1 of ≥12% and ≥200mL above baseline at any time during 0 to 6hr post-dose on Treatment Day 1 (Visit 2)
- Proportion of subjects achieving an increase in FEV_1 of ≥100mL above baseline in trough FEV_1
- Serial FEV_1 over 0 to 6 hours post-dose (on day 1)
- Serial and trough FVC
- Proportion of responders to TDI. (a responder to TDI will be defined as a subject with TDI score of 1 unit or more)
- Time to first COPD exacerbation

Safety

- Incidence of AEs
- Vital signs (pulse rate, systolic and diastolic blood pressure)
- 12-lead electrocardiogram (ECG) parameters
- Clinical chemistry and haematology parameters and routine urinalysis

Health- Related Quality of Life

- St. George's Respiratory Questionnaire (SGRQ)
- COPD Assessment Test (CAT)
- Healthcare resource utilisation

1. INTRODUCTION

1.1. Background

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of poor health, resulting in millions of deaths annually worldwide [GOLD,2015] and contributing significantly to health care costs and morbidity [Chapman, 2006; Jung, 2011; Lopez, 2006]. As of 2001, COPD was the fifth leading cause of death and the eleventh leading cause of disability worldwide. By the year 2020, COPD is expected to be the third leading cause of death and the fifth leading cause of disability [Rennard, 2002]. It has been estimated that over a 30 year period in China (up to 2033), 65 million deaths will be attributable to COPD [Lin, 2008].

COPD is a preventable and treatable disease characterized by airflow limitation that is not fully reversible [Celli, 2004]. The airflow limitation of COPD is primarily due to small airways disease and parenchymal destruction associated with an abnormal inflammatory response of the lungs. This is mainly caused by cigarette smoking [Celli, 2004], although in many countries, air pollution resulting from burning of wood and other biomass fuels has also been identified as a COPD risk factor.

Chinese smokers account for about one third of all smokers worldwide. In China the prevalence of COPD was reported to be 8.2% for those ≥40 years of age [Zhong, 2007] and is expected to rise.

COPD is characterized by symptoms of chronic and progressive breathlessness (or dyspnea), cough and sputum production which can be a major cause of disability and anxiety associated with the disease. Pharmacological management of chronic, stable COPD is primarily aimed at improving symptoms and quality of life, optimizing lung function, reducing exacerbations and improving exercise tolerance [Celli, 2004; GOLD, 2015].

1.2. Rationale

Inhaled bronchodilators, including beta$_2$-agonists and anticholinergics, together with inhaled corticosteroids (ICS) are the mainstays of therapy in patients diagnosed with COPD. Inhaled bronchodilators are recommended as a standalone treatment for patients in GOLD group A and B with long acting bronchodilators recommended as disease progresses.

Dominant autonomic control of the airways is provided by the parasympathetic nerves, which control a variety of airway functions. Release of the neurotransmitter acetylcholine (ACh) from parasympathetic nerves stimulates muscarinic receptors, causing bronchoconstriction and mucus secretion. Anti cholinergic bronchodilators (muscarinic receptor antagonists) exert their bronchodilator activity by inhibiting the binding of ACh with muscarinic Ach receptors on airway smooth muscle. This blocks endogenous airway smooth muscle tone allowing bronchodilation and reducing mucus hypersecretion.

Muscarinic receptor antagonists have been in use since 1975 and have become well established as safe and effective bronchodilators for the treatment of COPD [Decramer, 2013; Niewoehner, 2005; Aaron, 2007]. Commonly used inhaled long acting muscarinic antagonists (LAMAs) are poorly absorbed orally, limiting the troublesome effects observed with the more systemically available atropine [Decramer, 2013].

Treatment with muscarinic antagonists has been shown to significantly improve Forced Expiratory Volume in One Second (FEV_1), resting and dynamic lung hyperinflation, symptoms, exercise capacity, health status, and reduce COPD exacerbations [O'Donnell, 1998; O'Donnell, 2004; Tashkin, 2008a; Tashkin, 2008b]. However, a significant number of subjects are thought to continue to have symptoms, as reported in a primary care, cross-sectional study [Dransfield, 2011].

Umeclidinium is an orally inhaled, potent, pan-active long acting muscarinic anatagonist (LAMA) for use as an inhaled product in the treatment of COPD as a stand-alone once-daily product and with the long acting beta agonist (LABA), vilanterol, as a once-daily combination product for the treatment of COPD. Both Umeclidinium monotherapy and combination with vilanterol have been approved by FDA and EMA.

Studies to date provide substantial evidence for the effectiveness for UMEC 62.5 mcg as a long term maintenance therapy for the treatment of COPD. The purpose of this 24 week study is to further evaluate the efficacy and safety of UMEC 62.5 mcg administered once-daily in Asian subjects with COPD.

1.3. Summary of Risk Management

GlaxoSmithKline (GSK) has assessed this study for potential risks that a subject may experience. The investigational product, UMEC, has an acceptable safety profile for clinical use and there are no significant associated risks. This conclusion is supported by the results of previously performed clinical studies with the products in healthy volunteers and subjects with COPD [GlaxoSmithKline Document Number RM2006/00835/11, Investigator's Brochure (IB) 2015].

Subjects will be routinely monitored for safety throughout the duration of the study. Adverse effects associated with the use of LAMAs will be closely monitored. Stringent safety criteria outlining details for subject withdrawal is included in the protocol [Section 4.5, Withdrawal Criteria]. A thorough summary and evaluation of the available preclinical data can be found in the investigators brochure [GlaxoSmithKline Document Number RM2006/00835/11, IB 2015]. Routine safety analysis of this study will be conducted by the company.

Summaries of findings from both clinical and non-clinical studies conducted with GSK573719 can be found in the Investigator's Brochure. The following sectionoutlines the risk assessment and mitigation strategy for this protocol:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GSK573719]		
Cardiovascular effects such as cardiac arrhythmia, e.g. atrial fibrillation and tachycardia.	A potential class effect associated with anti-muscarinic therapies. The clinical significance of these arrhythmias is unknown. Clinical experience with UMEC to date in completed studies has did not show any association with major cardiovascular events. Data available to date in the IB for UMEC [GlaxoSmithKlineDocument Number RM2006/00835/11 effective date 10-AUG-2015)	Exclusion criteria have been set for subjects with uncontrolled or severe cardiovascular disease according to the PI's opinion where the potential risk may outweight the benefit. An abnormal and significant ECG finding from the 12-lead ECG conducted at Visit 1, including the presence of a paced rhythm on a 12-lead ECG which causes the underlying rhythm and ECG to be obscured will be excluded. Specific ECG findings that precluded subject eligibility are listed in Appendix 2: The study investigator will determine the medical significance of any ECG abnormalities not listed in Appendix 3.
Narrow-angle glaucoma, urinary	No association has been found to date, in completed studies with UMEC on glaucoma or urinary retention. However, glaucoma or urinary retention have been observed with other antimuscarinic agents, and could potentially be due to the pharmacology. Data available in the IB for UMEC [GlaxoSmithKline Document Number RM2006/00835/11 effective date 10-AUG-2015)	Exclusion criterion states that subjects with medical conditions such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Paradoxical bronchospasm	Known effect associated	If paradoxical

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
that may occur with an immediate increase in wheezing after dosing.	with inhalation therapy.	bronchospasm occurs following dosing with IP, this treatment should be discontinued immediately and alternative therapy should be instituted
Pregnancy	There is no experience to date of pregnancy during the use of UMEC.	The study inclusion criteria Ensure that female subjects enrolled, who are of Child bearing potential, have a negative pregnancy test at screening, and agree to a reliable contraceptive method, used consistently and correctly (i.e. in accordance with the approved product label and the instructions of the physician for the duration of the study).
Severe hepatic impairment	UMEC has not been studied in severe hepatic impairment.	Exclusion criterion states that subjects with severe hepatic impairment should only be included if, in the opinion of the study physician, the benefit outweighs the risk.
Study Procedures		
Spirometry procedures	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	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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other (if applicable)		
Side effects of rescue salbutamol	Class effects associated with SABAs	Subjects should call their study doctor if they experience any of these symptoms Adverse events (AEs) seen in clinical studies to date are consistent for the beta2-adrenergic class of compounds.
	Subjects' condition may worsen since not on active treatment.	Subjects will be provided with rescue albuterol/salbutamol use throughout the study.

2. OBJECTIVE(S) and Endpoints

Objectives	Endpoints
Primary Objectives	
• To evaluate the efficacy of Umeclidinium 62.5 mcg compared with placebo when administrated once-daily via the ELLIPTA™ over a 24-week treatment period in subjects with COPD	**Primary Efficacy Endpoint:** • Clinic visit trough (pre-bronchodilator) FEV_1 on Treatment Day 169 Trough FEV_1 on Treatment Day 169 is defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Treatment Day 168 (i.e. at Week 24). **Secondary Efficacy Endpoint:** 1. TDI focal score at Week 24. 2. Weighted mean FEV_1 over 0 to 6 hours post-dose at visit 2 (Randomisation visit) **Other Efficacy Endpoint:** 1. Trough FEV_1 and TDI focal score at other time points 2. Rescue albuterol/salbutamol use (percentage of rescue-free days and puffs/day) 3. Time to onset (defined as an increase of 100mL above baseline in $FEV_{1)}$ during 0-6hr post-dose on Treatment Day 1 (Visit 2) 4. Proportion of subjects achieving an increase in FEV_1 of ≥12% and ≥200mL above baseline at any time during 0 to 6hr post-dose on Treatment Day 1 (Visit 2) 5. Proportion of subjects achieving an increase in FEV_1 of ≥100mL above baseline in trough FEV_1 6. Serial FEV_1 over 0 to 6 hours post-dose at Visit 2(Day 1) 7. Serial and trough Forced Vital Capacity (FVC) 8. Proportion of responders to TDI. (a responder to TDI will be defined as a

Objectives	Endpoints
	subject with TDI score of 1 unit or more) 9. Time to first COPD exacerbation
Secondary Objectives	
• To evaluate the safety of Umeclidinium 62.5 mcg compared with placebo when administrated once-daily via ELLIPTA over a 24-week treatment period in subjects with COPD	1. Incidence of AEs 2. Vital signs (pulse rate, systolic and diastolic blood pressure) 3. 12-lead ECG parameters 4. Clinical chemistry and haematology parameters and routine urinalysis
• To evaluate health-related quality of life Umeclidinium 62.5 mcg compared with placebo when administrated once-daily via ELLIPTA over a 24-week treatment period in subjects with COPD	1. 1. St. George's Respiratory Questionnaire (SGRQ) 2. COPD Assessment Test (CAT) 3. Healthcare resource utilisation

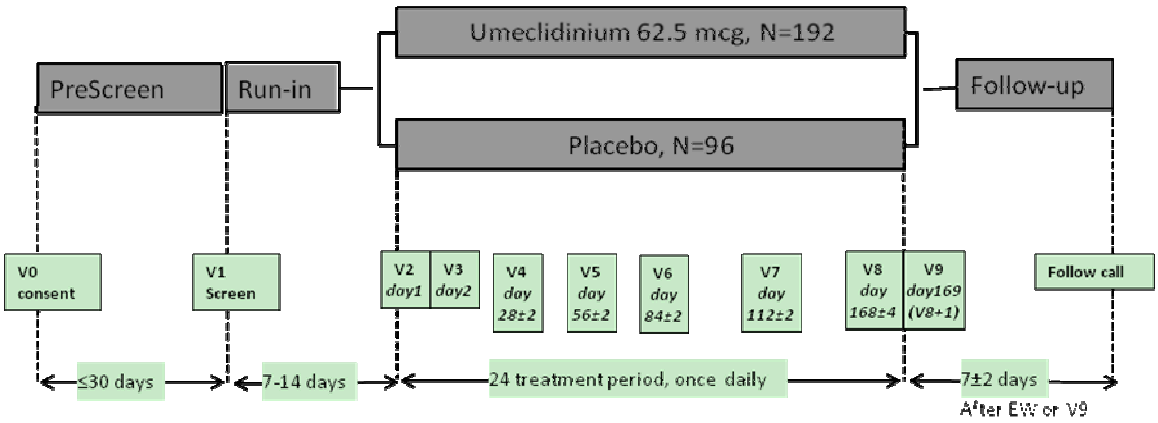
3. INVESTIGATIONAL PLAN

3.1. Study Design

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

This is a multicenter, randomized, double-blind, parallel group study to evaluate the efficacy and safety of umeclidinium 62.5 mcg administered once-daily via an ELLIPTA compared with placebo over 24 weeks in subjects with COPD. Eligible subjects will be randomized 2:1 to receive one of the two following treatments:

- Umeclidinium (GSK573719) 62.5 mcg Inhalation Powder administered QD via an ELLIPTA in the morning
- Placebo administered QD via an ELLIPTA in the morning



There will be a total of 10 study clinic visits conducted on an outpatient basis. A pre-screening visit (V0) will be conducted to sign the informed consent form (ICF), dispense rescue medication and review demography, COPD history and concomitant medications. Once the ICF is signed the subject will be assigned a subject identifier. At Visit 0, any medications changes made by the investigator will be recorded. Subjects who meet the eligibility criteria at Screening (Visit 1) will complete a 7 to 14 day run-in period followed by a 24 week treatment period. Clinic visits will be at Prescreening (visit 0), Screening, Randomization (Day 1), Day 2 and 4, 8, 12, 16, and 24 weeks, and 1 day after the Week 24 visit (Visit 0 to Visit 9, respectively). Additionally a safety Follow-Up assessment will be conducted by phone call approximately 7 days after the end of the study treatment (Visit 9 or Early Withdrawal, if applicable). The total duration of subject participation, including the Follow-Up, will be approximately 27 weeks. All subjects will be provided with albuterol/salbutamol for use on an "as-needed" basis throughout the pre-screen, run-in and study treatment periods.

Spirometry will be conducted at Screening and each on-treatment clinic visit. Pre- and post-albuterol/salbutamol spirometry will be conducted at Screening (Visit 1) for determination of eligibility and calculation of reversibility. To further characterize bronchodilator responsiveness, post-ipratropium testing will be conducted following completion of post- salbutamol/albuterol spirometry. Baseline spirometry will be conducted at Visit 2 prior to randomization. Pre-dose trough spirometry will be conducted at every on-treatment clinic visit after randomization. Additionally, six hour post-dose serial spirometry will be conducted at Visit 2 (Day 1).

The Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) will be used to measure the severity of breathlessness. It will be administered by study personnel trained on the proper administration of the set of questionnaires. The BDI and TDI should be obtained prior to performing any other study-related procedures including spirometry testing. The BDI will be administered at Visit 2 while TDI will be administered at Visits 4, 6 and 8.

Disease specific health status will be evaluated using the St. George's Respiratory Questionnaire (SGRQ) and CAT. SGRQ and CAT will be administered at baseline (Day 1- Visit 2) and Visits 4, 6 and 8. Vital signs (blood pressure and pulse rate), 12-lead ECGs and standard clinical laboratory tests (hematology and blood biochemistry) will be obtained at selected clinic visits.

The occurrence of AEs will be evaluated throughout the study, beginning at Visit 2. SAEs will be collected over the same time period as for AEs. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication (e.g. Run-in medications, rescue medications provided by GSK), will be recorded from the time a subject consents to participate in the study up to and including any follow up contact (China sites should Section 11.1, Appendix 1)

Subjects will be provided with a diary for daily completion in the morning throughout the run-in period and 24-week treatment period. Subjects will use the diary to record daily use of supplemental albuterol/salbutamol. All unscheduled COPD-related visits to a physician's office, urgent care facility, or emergency department, and COPD-related hospitalizations associated with the subject's condition will be recorded on the COPD-related healthcare resource utilisation assessment worksheet within the diary.

For determination of subject disposition, subjects will be considered to have completed the study upon completion of Day 169 (Visit 9). There is no plan to provide any of the active study treatments for compassionate use following study completion.

The Modified Intent-to-Treat (ITT) population will be the primary population of interest, and is defined as all randomised subjects who have received at least one dose of the randomised study medication during the Treatment Period.

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

3.2. Discussion of Design

A randomized, double-blind, placebo-controlled, parallel group study is a standard, well-established design to evaluate the efficacy and safety of an investigational drug. A placebo arm is included in this study to allow for an absolute assessment of efficacy and safety of the active treatment.

Duration of 24 weeks is considered adequate for assessment of lung function and symptoms in response to treatment intervention with bronchodilators, and is consistent with regulatory guidance on clinical studies in COPD. The choice of a lung function endpoint, trough FEV_1, as the primary efficacy endpoint is a robust, well established, and objective means of demonstrating bronchodilator efficacy and duration of effect at the end of 24 hours after dosing. Post-dose assessments of lung function on day 1 will provide for an assessment of treatment response over the 0 to 6 hour post-dose period which represents the beginning of the treatment effect.

A randomisation ratio of 2:1 will reduce the number of subjects randomised to placebo arm, as well as to reduce drop-outs.

3.2.1. Dose Selection

Data from two dose ranging studies, AC4113073 and AC4113589, demonstrated significant improvements in lung function for UMEC as measured by FEV_1 over 24 to 28 hours. However, there was no clear dose differentiation over the range of once-daily doses tested (62.5 mcg and 1000 mcg). A third dose ranging study (AC4115321), evaluating lower doses of UMEC monotherapy once and twice daily in COPD, demonstrated a FEV_1 dose response across the range of once-daily doses of UMEC tested (15.6 to 125 mcg) supporting the dose selection for Phase IIIa. This third study further substantiated the findings from the previous dose ranging study (AC4113073) by showing twice-daily doses did not provide added benefit over once-daily dose, supporting a once-daily dosing interval. Based on a favourable therapeutic index, two doses of UMEC were selected to be taken to Phase III, 62.5 mcg and 125 mcg.

Integrated analysis of Phase IIIa study lung function parameters and rescue medication data indicates that differences in response to the 125 mcg dose and the 62.5 mcg dose, were modest, were not always consistently observed and were not considered clinically meaningful. TDI score and SGRQ changes also did not show an advantage for the 125 mcg dose versus 62.5 mcg and the sub-group analysis did not identify a group who benefited from UMEC 125 mcg versus the 62.5 mcg. Therefore, the 62.5 mcg is the most appropriate dose for the treatment of COPD patients.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

Based on an early withdrawal rate of 18% of randomized subjects, approximately 288 study subjects will be randomized in 2:1 to the double blind medication, that means 192 subjects in active arm and 96 subjects in placebo arm, to ensure approximately 236 subjects complete the 24 week treatment period.

4.2. Inclusion Criteria

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

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

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

1. **Type of subject:** outpatient, Asian ancestry.
2. **Informed Consent:** A signed and dated written informed consent prior to study participation.
3. **Age:** 40 years of age or older at Screening (Visit 1).
4. **Gender:** Male or female subjects are eligible to participate in the study.

   A female is eligible to enter and participate in the study if she is of:

   Non-child bearing potential (i.e. physiologically incapable of becoming pregnant, including any female who is post-menopausal or surgically sterile). Surgically sterile females are defined as those with a documented hysterectomy and/or bilateral oophorectomy or tubal ligation. Post-menopausal females are defined as being amenorrhoeic for greater than 1 year with an appropriate clinical profile, e.g. age appropriate, >45 years, in the absence of hormone replacement therapy. However, in questionable cases, post-menopause status may be confirmed by analysis of a blood sample with Follicle Stimulating Hormone (FSH) >40MIU/ml and estradiol <40pg/ml (<140 pmol/L) as confirmatory.

   OR

   Child bearing potential, provided the subject has a negative pregnancy test at screening, and agrees to one of the following acceptable contraceptive methods 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 – Screening to Follow-Up contact):

   - Abstinence
   - Oral contraceptive either combined or progestogen alone

- Injectable progestogen
- Implants of levonorgestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS)
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study and this male is the sole partner for that subject.
- Double barrier method condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository).

5. **COPD History:** An established clinical history of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society [Celli, 2004] as follows:

   Chronic obstructive pulmonary disease is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.

6. **Tobacco Use and 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.

   Note: Pipe and/or cigar use cannot be used to calculate pack-year history. COPD patients who only use a pipe and/or cigar are not eligible.

7. **Severity of Disease:** A pre and post-salbutamol/albuterol FEV_1/FVC ratio of <0.70 and a pre and post-salbutamol/albuterol FEV_1 of ≤70% of predicted normal values calculated using National Health and Nutrition Examination Survey (NHANES) III reference equations at Visit 1 [Hankinson, 1999, Hankinson, 2010].

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

4.3. Exclusion Criteria

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

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

1. **Pregnancy:** Women who are pregnant or lactating or are planning on becoming pregnant during the study.
2. **Asthma:** A current diagnosis of asthma.
3. **Other Respiratory Disorders:** Known α-1 antitrypsin deficiency, active lung infections (such as tuberculosis) and lung cancer are absolute exclusionary conditions. A subject, who in the opinion of the investigator has any other significant respiratory conditions in addition to COPD should be excluded. Examples may include clinically significant bronchiectasis, pulmonary hypertension, sarcoidosis or interstitial lung disease.
4. **Other Diseases/Abnormalities:** Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or haematological abnormalities that are uncontrolled and/or a previous history of cancer in remission for <5 years prior to Visit 1 (localized carcinoma of the skin that has been resected for cure is not exclusionary). Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.
5. **Chest X-Ray:** A chest X-ray or computed tomography (CT) scan that reveals evidence of clinically significant abnormalities not believed to be due to the presence of COPD. A chest X-ray must be taken at Visit 1 if a chest X-ray or CT scan is not available within 6 months prior to Visit 1.
6. **Contraindications:** A history of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, $beta_2$-agonist, lactose/milk protein or magnesium stearate or a medical condition such as of narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the study physician contraindicates study participation or use of an inhaled anticholinergic.
7. **Hospitalization:** Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1.
8. **Lung Resection:** Subjects with lung volume reduction surgery within the 12 months prior to Screening (Visit 1).
9. **12-Lead ECG:** An abnormal and significant ECG finding from the 12-lead ECG conducted at Visit 1, including the presence of a paced rhythm on a 12-lead electrocardiogram (ECG) which causes the underlying rhythm and ECG to be obscured. Investigators will be provided with ECG reviews conducted by a centralized independent cardiologist to assist in evaluation of subject eligibility. Specific ECG findings that precluded subject eligibility are listed in Appendix 3: The study investigator will determine the medical significance of any ECG abnormalities not listed in Appendix 3.
10. **Screening Labs:** Significantly abnormal findings from clinical chemistry and haematology tests at Visit 1.
11. **Medications Prior to Spirometry:** Unable to withhold albuterol/salbutamol for the 4 hour period required prior to spirometry testing at each study visit.

12. Medications Prior to Screening: Use of the following medications according to the following defined time intervals prior to Visit 1; (Table 1)

Table 1 Time Interval for Prohibited Medication Prior to Visit 1

Medication	Time Interval Prior to Visit 1
Depot corticosteroids	12 weeks
Systemic, oral, parenteral (intra-articular) corticosteroids	4 weeks
Antibiotics (for lower respiratory tract infection)	4 weeks
ICS/LABA combination products if ICS/LABA therapy is discontinued completely	30 days
Use of ICS at a dose >1000mcg/day of fluticasone propionate or equivalent[1]	30 days
Initiation or discontinuation of ICS use[1]	30 days
Phosphodiesterase 4 (PDE4) inhibitors (e.g.roflumilast)	14 days
Long-acting anticholinergics (e.g.,tiotropium and aclidinium, glycopyronium)	7 days
Theophyllines[2]	12 hours (stable dose of theophylline alone is allowed during the study but must be withheld 12 hours prior to each study visit)
Oral leukotriene inhibitors (zafirlukast, montelukast, zileuton)	48 hours
Oral $beta_2$-agonists Long- acting Short –acting	 48 hours 12 hours
Olodaterol and Indacaterol (inhaled long-acting $beta_2$-agonist)	14 days
Salmeterol, formoterol, (inhaled long-acting $beta_2$-agonist)	48 hours
LABA/inhaled corticosteroid (ICS) combination products only if discontinuing LABA therapy and switching to ICS monotherapy[3]	48 hours for LABA component
Inhaled sodium cromoglycate or nedocromil sodium	24 hours
Inhaled short acting beta2-agonists[4]	4 hours
Inhaled short-acting anticholinergics[2] (e.g. ipratropium bromide)	4 hours (stable dose of ipratropium alone is allowed during the study, provided that the subject is on a stable dose regimen from Screening (Visit 1 and remains so throughout the study) but must be withheld 4 hours prior to each study visit)
Inhaled short-acting anticholinergic/short-acting $beta_2$-agonist combination products	4 hours

Medication	Time Interval Prior to Visit 1
Any other investigational drug	30 days or 5 half lives, whichever is longer

1. Use of ICS is permitted provided the dose not exceed 1000mcg of fluticasone propionate or equivalent; ICS use not to be initiated or discontinued within 30 days prior to Visit 1
2. Ipratropium bromide or theophylline is permitted, provided that the subject is on a stable dose from Screening (Visit 1) and remains on the stable dose throughout the study; however, Ipratropium bromide must be withheld for 4 hours; theophylline must be withheld for 12 hours prior to and during each clinic visit.
3. The dose of ICS must be equivalent to that contained in the ICS/LABA combination product (the study procedures manual will have equivalence guidelines)
4. Use of study provided albuterol/salbutamol is permitted during the study, except in the 4-hour period prior to spirometry testing

13. **Oxygen:** Use of long-term oxygen therapy (LTOT) described as oxygen therapy prescribed for greater than 12 hours a day. As-needed oxygen use (i.e., ≤12 hours per day) is not exclusionary.
14. **Nebulized Therapy:** Regular use (prescribed for use every day, not for as-needed use) of short-acting bronchodilators (e.g., albuterol/salbutamol) via nebulized therapy.
15. **Pulmonary Rehabilitation Program:** Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1. Subjects who are in the maintenance phase of a pulmonary rehabilitation program are not excluded.
16. **Drug or Alcohol Abuse:** A known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1.
17. **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.
18. **Compliance**: A subject will not be eligible if he/she has any infirmity, disability, illiteracy, disease, or geographical location which seems likely (in the opinion of the Investigator) to impair compliance with any aspect of this study protocol, including visit schedule and completion of daily diaries or questionnaires.

4.4. Randomization Criteria

In order to be randomized to double-blind study drug the subject must continue to meet the inclusion/exclusion criteria above. In addition the following criteria must also be met at Visit 2:

1. **Pre-Dose 12-Lead ECG at Visit 2:** There is **no** evidence of a significantly abnormal 12-lead ECG finding at the pre-dose ECG at Visit 2. ECG reviews conducted by a centralized cardiologist will **not** be available at Visit 2 for evaluation of subject eligibility. Eligibility of the subject is based on Visit 1 (screening) overread ECG.
2. **COPD Exacerbation:** Subjects must not have experienced a COPD exacerbation (defined as worsening of symptoms of COPD requiring the use of any additional

treatment other than study medication or rescue salbutamol) or a lower respiratory tract infection during run-in or at Visit 2.

3. **Inhaled Corticosteroids:** Subjects using ICS must have maintained a regular use of a stable dose of ICS during the run-in period at a dose ≤ 1000 mcg/day fluticasone propionate or equivalent.
4. **Prohibited Medications.** Subjects must not have used any prohibited medication [as listed in Section 5.6.2] during the run in period or at Visit 2.

4.5. Withdrawal Criteria

A subject will also be withdrawn from the study if any of the following withdrawal criteria are met:

1. **COPD exacerbation:** Subjects who experience a COPD exacerbation during the treatment period requiring the use of any systemic/oral corticosteroids, with prescribed or non-prescribed (self administered) antibiotics, and/or emergency treatment or hospitalization need to be withdrawn from the study.

   Note: However, subjects who experience a COPD exacerbation requiring **only** the use of either prescribed or non-prescribed (self-administered) antibiotics may continue to participate in study.

   If a subject is withdrawn due to a COPD exacerbation, the exacerbation section of the electronic Case Record Form (eCRF) should be completed.

2. **Pneumonia** : Presumptive diagnosis or radiographically confirmed. Pneumonia needing the treatment of oral antibiotics or/and systemic steroid and/or emergency treatment or hospitalisation.
3. **Laboratory measurements:** Demonstrate a clinically important change(s) in a laboratory parameter(s) as determined by the study investigator
4. **ECG:** An abnormal and significant ECG finding identified during the study. Specific ECG findings that would result in subject withdrawal are listed in Section 11.3. The study investigator will determine the medical significance of any ECG abnormalities not listed in Section 11.3.
5. **Liver Chemistry**: Meets any of the protocol-defined liver chemistry stopping criteria in Section 6.3.4
6. **Pregnancy**: Positive pregnancy test

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

If study drug is permanently discontinued during the course of the study, the subject must be withdrawn from the study. A subject that is withdrawn early from the study after being randomised to treatment cannot be re-screened.

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

1. adverse event
2. withdrew consent
    - subject relocated
    - frequency of visits
    - burden of procedures
    - other (specify)
3. lost to follow-up
4. protocol deviation
5. lack of efficacy
    - COPD exacerbation
6. subject reached protocol-defined stopping criteria
    - ECG abnormality
    - Laboratory abnormality
    - pregnancy
7. study closed/terminated

Specific regard should be given to distinguishing withdrawals due to an adverse event, lack of efficacy, and protocol deviation.

In cases where contact cannot be made with the subject, the subject may be considered lost to follow-up after the site has attempted actions for contact, as detailed in the SPM.

4.6. Pre-Screen and Screen Failures

A subject will be assigned a subject number at the time the informed consent is signed (V0).

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

Any subject who performs a Visit 1 procedure but does not continue in the study beyond Visit 1 or any subject who completes Visit 1 and enters the run-in period, but is subsequently found to be ineligible for the study based on procedures (e.g., laboratory, ECG, spirometry) conducted at Visit 1and is not randomized to the study treatment medication, is classified as a ‘screen failure’.

In addition, a subject who experienced an SAE as related to study participation between the date of informed consent and the planned date of Visit 1 will be assigned a subject numbers and considered a prescreening failure.

The following information will be collected for subjects who are pre-screen failures:

1. Date of ICF signature

2. Details of COPD medications within 30 days of Visit 0

3. Summary Status of COPD exacerbation, Yes/No

4. Serious Adverse Events information, if applicable, only for any SAE considered as related to study participation (e.g., study treatment, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication

5. Demographic information including race, age and gender

6. Subject number

7. Investigator signature page

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

1. Date of screening visit
2. Reason subject failed screening

Subjects who are pre-screen failures or screen failures cannot be re-screened.

4.7. Run-in Failures

Subjects who meet the eligibility criteria at Visit 1 and enter the run-in period, but are not randomized will be considered run-in failures. In addition to the information described in Section 4.6, the date of Visit 2 and the reason for the run-in failure will be recorded in the eCRF.

4.8. Premature Discontinuation

The definition of an early subject withdrawal (premature discontinuation) from the study will be any subject who is randomized to double-blind medication and, for any reason, is withdrawn prior to completion of the Visit 9 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 Early Withdrawal Visit. An Early Withdrawal Visit may occur at a regular scheduled clinic visit or between clinic visits. The following evaluations and procedures should be completed and recorded in the eCRF.

1. Concomitant medication assessment

2. AE/SAE assessment

3. COPD exacerbation assessment

4. Physical examination (recorded in source documents only)
5. Vital signs
6. Collect and review paper diary
7. Collect used study medication(blinded study medication and rescue albuterol/salbutamol)
8. Assess compliance with investigational drug
9. 12-Lead ECG
10. Laboratory assessments (including chemistry, haematology, and pregnancy test for females of childbearing potential and routine urinalysis)
11. Evaluation of smoking status and smoking cessation counselling
12. Report subject's early withdrawal from the study via Randomization And Medication Ordering System New Generation (RAMOS NG).

A follow- up contact as described in Section 4.9 should be conducted 7±2 days following completion of the Early Withdrawal Visit.

A subject that is withdrawn from the study after being randomised to treatment cannot be re-screened and subjects who are withdrawn from the study will not be replaced.

4.9. The Follow-up Phone Contact

A follow-up contact will be conducted 7±2 days following completion of Visit 9 (or the Early Withdrawal Visit, if applicable). The following procedures will be performed:

1. AE/SAE assessment
2. COPD exacerbation
3. Pregnancy information (if applicable)
4. Register visit in RAMOS NG

Subjects will be discharged from the study upon completion of the follow-up phone call.

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

GlaxoSmithKline (GSK) will provide the investigational product for use in this study. The investigational product Umeclidinium Inhalation Powder (62.5 mcg), and Placebo Inhalation Powder will each be delivered via an ELLIPTA.

Each ELLIPTA will be comprised of one or two foil, laminate, blister strip/s. Descriptions of the double-blind investigation product for this study are provided in Table 2 (Umeclidinium) and Table 3 (placebo).

The ELLIPTAs containing investigational product and placebo will be identical in appearance. Subjects will be instructed to take one inhalation each morning from their ELLIPTA. Subject instructions and details on how to use the ELLIPTA are provided in the SPM.

All subjects will receive supplemental albuterol/salbutamol (MDI and/or nebules) to be used on an as-needed basis (rescue medication) throughout the study. Albuterol/salbutamol will be sourced from local commercial stock. If not available locally, GSK will source centrally.

Ipratropium bromide MDI for additional responsiveness testing at Visit 1 will be sourced from local commercial stock. If not available locally, then GSK will source centrally.

Table 2 Description of Umeclidinium Inhalation Powder ELLIPTA

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

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

Table 3 Description of Placebo Inhalation Powder ELLIPTA

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

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

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. 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.

5.1.1. Storage

All study medication should be stored up to 25°C (77°F). Each ELLIPTA will be packaged in a foil pouch with a desiccant sachet. The inhaler should not be used for more than 30 days after opening the foil pouch.

The sites must maintain a daily temperature log for the investigational product.

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

5.1.2. Study Drug Return

At the end of the study, all study supplied study medication (used and unused) will be destroyed following local standard operating procedures Details for both destruction and return of study medication are found in the SPM.

In addition, any ELLIPTA that fails to function properly must be identified and returned to GSK for testing. Details of the failure will be documented in the eCRF. If a subject's inhaler fails to function properly, the subject should return to the clinic as soon as possible to obtain a new inhaler. The site will obtain a new treatment pack number for the subject via RAMOS NG and dispense a new study medication kit from the site's investigational product supply as instructed by RAMOS.

5.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the central randomization schedule. The randomisation code will be generated by GSK using a validated computerised system. Subjects will be randomised using RAMOS NG. This is an internet-based system which will be used by the investigator or designee to register the subject (initially at pre-screening, and subsequently at each study visit), randomize the subject, and provide medication assignment information if and when required. Details on how to use RAMOS NG to register and randomize subjects are provided in the SPM.

Once a randomization number has been assigned to a subject, the same number cannot be reassigned to any other subject in the study.

Following completion of the 7 to 14 day Run-In period eligible subjects will be randomized in 2:1 ratio to one of the following treatment regimes in equal proportions

- Umeclidinium Inhalation Powder 62.5 mcg once daily
- Placebo Inhalation Powder once daily

Approximately 192 subjects will be randomised to active treatment and 96 subjects to placebo.

Study drug will be collected at Visit 8 or at the Early Withdrawal Visit (if applicable)

5.3. Blinding

Investigational product taken during the 24-week treatment period will be double-blind. Neither the subject nor the study physician will know which study medication the subject is receiving.

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

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

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

5.4. Product Accountability

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

5.5. Treatment Compliance

Subject compliance with double-blind study medication will be assessed at Visits 3 through to 8 by reviewing the dose counter on the ELLIPTA and at any unscheduled visit where study drug is returned, Subjects should be ≥80% to ≤120% compliant on taking study medication between each pair of consecutive on-treatment visits. Subjects who fall outside this range should be re-educated on treatment compliance by their site. This re-education should be documented in the subject's source document. If the double-blind study medication is prematurely discontinued during the course of study or medication compliance repeatedly falls outside of acceptable ranges, the study sponsor/site monitor must be contacted to discuss subject eligibility for continued participation in the study.

5.6. Concomitant Medications and Non-Drug Therapies

All COPD medications used within 30 days prior to visit 0 and onward should be recorded in the eCRF including any changes. Beginning at visit 1 and throughout the rest of the study, all non COPD medications taken during the study will be recorded in the eCRF, including any changes. Study-provided albuterol/salbutamol should not be recorded in the eCRF. The minimum requirement includes but is not limited to drug name, dose, route and the dates of administration. Medications initiated after completion of Visit 9 or the Early Withdrawal Visit will not be recorded in the eCRF with the exception of those used to treat a COPD exacerbation or SAE that occurs between Visit 9 (or the Early Withdrawal Visit) and the follow-up contact.

5.6.1. Permitted Medications and Non-Drug Therapies

The following relevant medications are permitted during this study.

1. Study-provided albuterol/salbutamol for use as relief medication throughout the Run-in and Treatment periods, except in the 4-hour period prior to spirometry testing
2. Theophylline is permitted, provided that the subject is on a stable dose from Screening (Visit 1) and remains on the stable dose throughout the study; however, theophylline must be withheld for 12 hours prior to and during each clinic visit.
3. Ipratropium bromide is permitted, provided that the subject is on a stable dose from Screening (Visit 1) and remains on the stable dose throughout the study, however, ipratropium bromide must be withheld for 4 hours prior to and during each clinic visit.
4. Inhaled corticosteroids at a dose ≤1000 mcg/day of fluticasone propionate or equivalent are permitted provided the dose remains consistent as defined in the SPM throughout the study. Any ICS product alone (e.g., fluticasone propionate) cannot be initiated or discontinued within 30 days prior to Visit 1
5. If the subject is on an ICS/LABA product for at least 30 days to Visit 1, the subject may switch to an ICS product alone as long as it does not exceed 1000mcg/day of FP or equivalent, and the dose remains consistent, as defined in the SPM, throughout the study. The switch to ICS alone from an ICS/LABA product must occur at least 48 hours prior to screen visit. Discontinuation of the

ICS/LABA product completely in the absence of starting an ICS alone must occur at least 30 days prior to V1.

6. Mucolytics such as acetylcysteine
7. As-needed oxygen use (i.e., ≤12 hours per day)
8. Medications for rhinitis (e.g., intranasal corticosteroids, antihistamines, cromolyn, nedocromil, nasal decongestants)
9. Influenza vaccination
10. Pneumonia vaccination
11. Antibiotics for short term treatment of acute infection (≤2 weeks)
12. Oral anticholinergic for overactive bladder
13. Pulmonary rehabilitation program in maintenance phase
14. Smoking cessation treatment, including a stable regimen of nicotine replacement
15. Use of positive airway pressure for sleep apnoea

5.6.2. Prohibited Medications and Non-Drug Therapies

Use of the medications listed in Table 4 is not permitted during the study and for the washout period indicated prior to Visit 1 refers to Table 1.

Table 4 Prohibited Medications

Depot corticosteroids
Systemic, oral or parenteral corticosteroids
LABA/ICS combination products
Use of ICS at a dose >1000 mcg/day of fluticasone propionate or equivalent[1]
Initiation or discontinuation of ICS use[1]
PDE4 inhibitor (e.g.roflumilast)
Oral leukotriene inhibitors (e.g. zafirlukast, montelukast, zileuton)
Oral $beta_2$-agonists
Inhaled long acting $beta_2$-agonists (LABA, e.g., salmeterol, formoterol, indacaterol, olodacterol)
Inhaled long acting anticholinergics (LAMA, eg; tiotropium, aclidinium, glycopyrronium)
Inhaled sodium cromoglycate or nedocromil sodium
Any other investigational medication

1. Use of ICS is permitted provided the dose not exceed 1000mcg of fluticasone propionate or equivalent; ICS use not to be initiated or discontinued within 30 days prior to Visit 1

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

- LTOT (defined as oxygen therapy prescribed for greater than 12 hours per day)
- Regular nebulized therapy
- Initiation of pulmonary rehabilitation during the study

5.6.2.1. Traditional or herbal medicines

The following categories of traditional or herbal medicines are prohibited prior to Visit 1 and at any time during the study:

- Traditional or herbal medicines used for the treatment of COPD, including those with known effect of bronchodilation.
- Traditional or herbal medicines that have known effects on platelets and that increase the tendency to cause bleeding.

5.7. Treatment after the End of the Study

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

GSK will not provide post-study treatment. Post-treatment COPD therapy should not be entered into the eCRF.

5.8. Treatment of Study Investigational product 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 IB or equivalent document provided by GSK

6. STUDY ASSESSMENTS AND PROCEDURES

This Section provide an outline of the time and completing of all study procedures and a description of specific procedures. A schedule of Time and Events is provided in Table 5

Table 5 Time and Events Table

Detailed procedure and time window please reference to SPM.

		Run-in	Double-blind treatment period									
Visit	**Visit 0 (Pre-Screen)**	**Screening Visit (Visit 1)**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Early With-drawal (EW) Visit**	**Follow-Up (Phone contact)**
Day		**Day -7 to -14**	**Day 1**	**Day 2**	**Day 28±2**	**Day 56±4**	**Day 84±4**	**Day 112±4**	**Day 168±4**	**Day 169 (Visit 8 +1 day)**		**7±2 days after Visit 9 or EW**
Week		**-1**	**0**	**0**	**4**	**8**	**12**	**16**	**24**			
Written Informed Consent[1]	**x**											
Demography/ COPD History	**X**											
Medical History		**X**										
Physical Examination		**X**							**X**		**X**	
Smoking Status		**X**							**X**		**X**	
Smoking Cessation Counselling		**X**							**X**		**X**	
Chest X-ray[2]		**X**										
Inclusion/exclusion criteria		**X**										
Randomization criteria			**X**									
Screening spirometry (including post-bronchodilator testing)[3]		**X**										
mMRC questionnaire		**X**										
Register visit in IWRS[4] (RAMOS NG)			**x**		**x**	**x**	**x**	**x**				
Diary Card Dispense or Collection/Review		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	

		Run-in	Double-blind treatment period									
Visit	**Visit 0 (Pre-Screen)**	**Screening Visit (Visit 1)**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Early With-drawal (EW) Visit**	**Follow-Up (Phone contact)**
Day		**Day -7 to -14**	**Day 1**	**Day 2**	**Day 28±2**	**Day 56±4**	**Day 84±4**	**Day 112±4**	**Day 168±4**	**Day 169 (Visit 8 +1 day)**		**7±2 days after Visit 9 or EW**
Week		**-1**	**0**	**0**	**4**	**8**	**12**	**16**	**24**			
Efficacy assessments												
Trough Spirometry[5]				X	X	X	X	X	X	X		
Serial Spirometry[6]			X									
COPD exacerbation assessment	x	X	X	X	X	X	X	X	X	X	X	X
Baseline Dyspnea Index (BDI)			X									
Transition Dyspnea Index (TDI)					X		X		X			
SGRQ			X		X		X		X			
COPD Assessment Test (CAT)			X		X		X		X			
Healthcare resource utilization[7]			←	—	—	—	—	—	—	—	→	
Safety Assessments												
12-Lead ECG[8]		X	X[8]				X[8]		X[8]		X	
Vital Signs (blood pressure and pulse rate)[9]		X	X	X	X	X	X	X	X	X	X	
Adverse Event			X	X	X	X	X	X	X	X	X	X
Serious Adverse Event /Con-Med Assessment	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments												
Routine urine		X							X		X	
Urine Pregnancy Test		X	X				X		X		X	X
Clinical Laboratory tests[10]		X					X		X		X	
Medication												

		Run-in	Double-blind treatment period									
Visit	**Visit 0 (Pre-Screen)**	**Screening Visit (Visit 1)**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Early With-drawal (EW) Visit**	**Follow-Up (Phone contact)**
Day		**Day -7 to -14**	**Day 1**	**Day 2**	**Day 28±2**	**Day 56±4**	**Day 84±4**	**Day 112±4**	**Day 168±4**	**Day 169 (Visit 8 +1 day)**		**7±2 days after Visit 9 or EW**
Week		**-1**	**0**	**0**	**4**	**8**	**12**	**16**	**24**			
COPD and Concurrent Medication Assessment	**x**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Dispense/collect rescue salbutamol/albuterol	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Dispense double-blind study drug			**X**		**X**	**X**	**X**	**X**				
Collect double-blind study drug					**X**	**X**	**X**	**X**	**X**		**X**	
Assess double-blind study drug compliance					**X**	**X**	**X**	**X**	**X**		**X**	

1. Written informed consent must be obtained prior to performing any Visit 1 procedures or initiating any alterations in a subject's medications. Subjects will be assigned a study number at the time the ICF is signed. Visit 0 and Visit 1 may occur on the same day if applicable.
2. To be performed only if there is no chest X-ray or CT scan available within 6 months prior to Visit 1
3. Spirometry to be conducted as follows: pre-bronchodilator testing following by post-albuterol/salbutamol testing, followed by post-ipratropium testing. Post albuterol/salbutamol testing conducted 10 to 30 min after subject self-administration of 4 puffs of albuterol/salbutmol via MDI with a spacer. Subject will then self administer 4 puffs of ipratropium bromide via MDI and spacer, followed by spirometry testing 30 to 60 min later.
4. IWRS stands for Interactive Web Response System.
5. Trough spirometry obtained twice: at 23 and 24 hours after the previous day's morning dose.
6. 6 hr serial spirometry: Performed post-dose at 15 and 30 min and 1, 3 and 6 hours. At Visit 2 (Day 1), pre-dose measurements will be obtained -30min and -5min pre-dose.
7. Healthcare resource utilization will be collected and entered in the e-CRF as required during the study, collection of this data to be aided by the subject documentation in the paper diary of any contact with the doctor or nurse about their lung condition which was unrelated to study participation.
8. ECG conducted pre-dose and 10 and 45 minutes post-dose
9. Vital signs to be measured pre-dose and 10 and 45 minutes post-dose at visit 2, and measured only pre- dose at other visits (prior to spirometry).
10. Haematology, and clinical chemistry.

6.1. Critical Baseline Assessments

No study related procedures may be performed until the informed consent form document has been signed by the subject or legal deputy. A pre-screening visit may be required in order to administer the informed consent before any changes are made to the subject's current medication regimen. The informed consent 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 protocol excluded medications.

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

- Demographic history (including gender, ethnic origin, age, height and weight)
- COPD history
- COPD exacerbation assessment
- Review of COPD medication

Visit 1: The following critical baseline assessments will be conducted at the screening visit, Visit 1:

- Medical history including COPD (comprised of date of diagnosis and COPD type [emphysema and/or chronic bronchitis]), and smoking history, COPD exacerbations history, smoking status and previous and/or current medical conditions
- Pre-and post-albuterol/salbutamol and post-ipratropium bromide spirometry
- Cardiovascular medical history/risk factors
- 12-Lead ECG
- Review of concomitant medications
- Physical examination
- Pulse rate and blood pressure measurements
- Chest x-ray (or historical CT-Scan obtained within 6 months of Screening or Visit 1)
- Clinical laboratory assessments (including chemistry, hematology, and routine urinalysis)
- mMRC dyspnea scale (The subject's degree of dyspnea to different levels of activity will be rated using a 0 to 4 point mMRC scale).
- Urine pregnancy test
- SAE assessment
- Inclusion/ exclusion criteria

The following critical baseline assessments will be conducted at Visit 2, as specified in Table 5;

- Pre-dose spirometry
- Baseline Dyspnea Index (BDI)
- CAT
- SGRQ

6.2. Efficacy

6.2.1. Primary Efficacy Endpoints

The primary efficacy endpoint is:

- Clinic visit trough (pre-bronchodilator) FEV_1 on Treatment Day 169.

Trough FEV_1 on Treatment Day 169 is defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Treatment Day 168 (i.e. at Week 24).

6.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- TDI Focal score at Week 24
- Weighted mean clinic visit FEV_1 over 0 to 6 hours post-dose at visit 2 (Day 1)

6.2.3. Other Endpoints

Other endpoints include:

- Trough FEV1 and mean TDI score at other time points
- Rescue albuterol/salbutamol use (percentage of rescue-free days and puffs/day)
- Time to onset (defined as an increase of 100mL in FEV_1 above baseline) during 0 to 6h post-dose on Treatment Day 1 (Visit2)
- Proportion of subjects achieving an increase in FEV_1 of $\geq$12% and $\geq$200mL, above baseline at any time point during 0 to 6h post-dose on Treatment Day 1 (Visit 2)
- Proportion of subjects achieving an increase in FEV_1 of $\geq$100mL above baseline in trough FEV_1
- Serial FEV1 over 0 to 6 hours post-dose at Visit 2 (Day 1)
- Serial and Trough FVC
- Proportion of responders to TDI. A responder to TDI will be defined as a subject who reported a TDI score of 1 unit or more.
- Time to first COPD exacerbation

6.2.4. Spirometry and Reversibility Testing

6.2.4.1. Spirometry

Spirometry measurements will be performed using equipment that meets or exceeds the minimum performance recommendations of the America Thoracic Society (ATS) [Miller, 2005]. All sites will use standardized spirometry equipment provided by an external vendor.

Subjects should wear nose clips while performing spirometry manoeuvres. 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; Pelligrino, 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 must be performed as detailed in Table 5, initiated between 8.00am and 12.00pm (noon)
- After completing BDI/TDI, SGRQ and CAT assessments
- At Visit1 after withholding COPD medication as indicated in the exclusion criteria [Section 4.3]
- At Visit 3 through to visit 8 after withholding the morning dose of the double-blind study medication
- At all visits, after withholding the albuterol/salbutamol rescue medication for ≥4 hours
- At all clinic visits after refraining from:
  - smoking for 1 hour
  - drinks with high levels of caffeine such as tea and coffee for at least 2 hours

Details regarding the spirometric procedures are provided in the manual provided by the central spirometry vendor.

Post-dose measurements should be made as close as to the scheduled time points as possible (see Table 5 for timings). Details regarding allowable time windows can be found in the SPM.

6.2.4.2. Bronchodilator Responsiveness Testing

At Visit 1, both pre-and post-albuterol/salbutamol spirometry will be obtained. A pre- and post-albuterol/salbutamol FEV_1 ≤70% of predicted normal and FEV_1/FVC ratio of <0.70 are required for subject eligibility. Additionally, to further characterize the bronchodilator responsiveness, post-ipratropium spirometry testing will be obtained following completion of the post-albuterol/salbutamol spirometry.

Bronchodilator responsiveness testing will be completed as follows:

Following pre-albuterol/salbutamol spirometry (three acceptable spirometry efforts should be obtained), the subject will then self-administer 4 puffs of albuterol/salbutamol via MDI using a spacer. Three acceptable spirometry efforts should be obtained approximately 10 to 30 minutes after albuterol/salbutamol administration.

Following completion of post-albuterol/salbutamol spirometry, the subject will self-administer 4 puffs of ipratropium via MDI using a spacer. Three acceptable spirometry efforts should be obtained approximately 30 to 60 minutes after ipratropium administration.

6.2.4.3. 6-Hour Serial Spirometry

All subjects will be required to perform the 6-hour serial spirometry on Day 1, Visit 2, at 15 and 30 min, 1, 3 and 6h post-dose. Pre-dose measurements will be obtained at 30min and 5 min prior to the dose of study medication.

Post-dose measurements should be made as close as to the scheduled time points as possible (see Table 5 for timings). Details regarding allowable time windows can be found in the SPM.

6.2.5. BDI/TDI

The BDI is used to measure the severity of dyspnea in patients at baseline. The TDI measures changes in the patient's dyspnea from baseline. The BDI and TDI should be performed prior to spirometry testing.

The interviewer should be a physician, nurse, respiratory therapist, or cardiopulmonary technician. The interviewer must be blinded to other parameters evaluated for the patient. It is recommended that the same person conduct all interviews for each patient throughout the study.

A worksheet will be provided to record the comments from the subject which were used to complete the BDI. This worksheet will then be referred to at subsequent visits for completion of the TDI.

Additional instructions for completion of the BDI/TDI are provide in the SPM.

6.2.6. Diary Assessments

6.2.6.1. Paper Diary

Subjects will use paper diary to record the following information:

- Any medical problems experienced and any medications used to treat those medical problems. These entries will be reviewed by the study coordinator at each study visit and recorded in the eCRF as an adverse events/concomitant medication or COPD exacerbations as appropriate.

- The date and time of the morning dose of study medication taken on the days prior to Visit 4, Visit 5, Visit 6, Visit 7, and Visit 8
- Supplemental albuterol/salbutamol used over the previous 24 hours.

Subjects will be asked to bring the paper diary to each clinic visit. The study coordinator will review the paper diary at each clinic visit for completeness, legibility and consistency with subject-reported AEs. Signs and symptoms of COPD recorded on the diary card will not be considered AEs and will not be collected in the eCRF. Additional details for completion of the diary cards are provided in the SPM.

6.2.7. COPD Exacerbations

A COPD exacerbation will be defined as an acute worsening of symptoms of COPD requiring the use of any treatment beyond study medication or rescue albuterol/salbutamol. This includes requiring the use of antibiotics, systemic corticosteroids, and/or emergency treatment or hospitalization. COPD exacerbations will be recorded on the COPD exacerbation page of the eCRF.

Subjects who experience an exacerbation during treatment or run-in period requiring the use of any systemic/oral corticosteroids, with/without either prescribed or non-prescribed (self administered) antibiotics, and/or emergency treatment or hospitalisation will be withdrawn from the study and will not be allowed to re-screen. However, subjects who experience a COPD exacerbation/lower respiratory tract infection requiring only the use of antibiotics, either prescribed or non-prescribed (self-administered), may continue to participate in study.

COPD exacerbations are associated with the disease under study and will not be recorded as AEs unless the exacerbation meets the definition of a "serious" AE as defined in Section 6.3.5.2 of this protocol. Exacerbations that meet the definition of "serious" AEs will be recorded on the appropriate eCRF section and should be reported to GSK for all study subjects regardless of whether or not they are randomized to study medication.

6.3. Safety

Safety endpoints include:

- Incidence of adverse events
- Vital signs (pulse rate and systolic and diastolic blood pressure)
- 12-Lead ECG parameters
- Clinical Chemistry and haematology parameters and routine urinalysis

6.3.1. Vital Signs

Vital signs measurements will include pulse rate and systolic and diastolic blood pressure. Vital signs will be obtained after subjects have rested for approximately 5

minutes and before performing ECG and spirometry testing. A single set of values will be obtained.

Vital signs will be performed using equipment provided by investigational sites and will be obtained at visits and time points as detailed in Table 5.

Additional details of procedures related to vital signs are provided in the SPM.

6.3.2. 12-Lead ECG

A 12-lead ECG measurement and rhythm strip (10 seconds) will be obtained after measurement of vital signs and before spirometry testing. After vital signs are obtained subjects should be placed in the supine position for the ECG measurements.

ECG measurements will be taken at various visits and time points as detailed in Table 5

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

ECG data will be electronically transmitted to an independent cardiologist, contracted by GSK, and evaluated. The independent cardiologist, blinded to treatment assignment, will be responsible for providing ECG measurements required for the study and an interpretation of ECGs findings. A hard copy of these results will be sent to the investigator. The investigator must provide his/her dated signature on the confirmed report, attesting to his/her review of the independent cardiologist's assessment.

Additional details of all 12-lead ECG procedures are provided in the SPM.

6.3.3. Clinical Laboratory Tests

Routine, non fasting clinical laboratory (haematology and chemistry and urinalysis) tests will be performed as detailed in Table 5. At the discretion of the investigator, additional samples may be taken for safety reasons. All samples will be measured at a designated central laboratory.

A urine pregnancy test will be performed for all females of child bearing potential as detailed in Table 5.

The study clinical laboratory tests including analytes for clinical chemistry and haematology are shown below in Table 6.

Table 6 Study Clinical Laboratory Tests

CHEMISTRY	HEMATOLOGY	OTHER
Albumin	Hemoglobin	Hepatitis B surface antigen[1]
Alkaline phosphatase	Hematocrit	Hepatitis C virus antibody[1]
Alanine amino-transferase (ALAT or SGPT)	Platelet count	Urine pregnancy test (in clinic)[2]
Aspartate amino-transferase (ASAT or SGOT)	WBC count	**Routine Urinalysis:**
Bilirubin, direct	Neutrophils, absolute	pH
Bilirubin, indirect	Neutrophils, segs (%)	Protein
Bilirubin, total	Neutrophils, bands (%)	Glucose
Calcium	Basophils (%)	Blood, Bilirubin, and White Cell Count
Chloride	Eosinophils (%)	
CO_2 content/Bicarbonate	Eosinophils , absolute	
Creatinine	Lymphocytes (%)	
Creatine phosphokinase (CPK), total	Monocytes (%)	
Gamma glutamyl transferase (GGT)	RBC count	
Glucose		
Phosphorus		
Potassium		
Protein, total serum		
Sodium		
Urea nitrogen (BUN)		
Uric Acid		

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

Additional details of the clinical laboratory procedures and procedures for sending samples to the central laboratory will be provided by the central laboratory for placement in the SPM.

6.3.4. Liver chemistry stopping and follow up criteria

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

Liver chemistry stopping criteria 1 to 5 are defined below:

1. Alanine Transaminase (ALT) ≥3xUpper Limit of Normal (ULN) and bilirubin ≥2xULN (>35% direct bilirubin) (or ALT ≥3xULN and INR>1.5, if INR measured)

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

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

4. ALT ≥3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
5. ALT ≥5xULN but <8 xULN and cannot be monitored weekly for ≥2 weeks

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

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

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

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

In addition, for criterion 1:

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

For criteria 2, 3, 4 and 5:

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

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

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

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

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

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

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

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week (James, 2009).

  NOTE: not required in China.
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. **NOTE**: if hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) – as outlined in: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793/
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

An algorithm for liver chemistry stopping and follow-up criteria is provided in Appendix 4:

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

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

6.3.5.1. Definition of AEs

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

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE 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 fulfill the definition of an AE or SAE.

Events that **do not** meet the 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.

6.3.5.2. Definition of SAEs

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).

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:

- results in death
- 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.

- 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.

- 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.

- Is a congenital anomaly/birth defect
- Other situations:

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- **Is** associated **with liver injury <u>and</u> impaired liver function defined as:**

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

ALT ≥3xULN and INR** >1.5.

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

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

6.3.5.3. Recording of AEs and SAEs

- 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.

6.3.5.4. Evaluating AEs and SAEs

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.

6.3.5.5. 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.

6.3.6. Cardiovascular Events

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 thrombosis
- Deep Venous Thrombosis
- Revascularisation

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

6.3.7. Death Events

In addition, for all deaths, specific Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

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

COPD exacerbations are associated with the disease to be studied and will not be recorded as AEs unless they meet the definition of an SAE as defined in Section 6.3.5.2. Exacerbations that meet the definition of an SAE will be recorded on the appropriate eCRF section and should be reported to GSK for all subjects regardless of whether or not they are randomized to blinded study medication.

Medications used to treat a COPD exacerbation will be recorded in the eCRF

6.3.9. Pregnancy

Details of all pregnancies in female subjects will be collected after the start of dosing and until follow up call 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.

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 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 reasonably related to the study treatment, must be promptly reported to GSK. 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.

6.3.10. Medical Devices

Medical devices are being provided by GSK for use in this study (spacers for administration of albuterol/salbutamol and ipratropium bromide at screening). GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

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

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

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

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

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

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

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

It is sufficient that

- An incident associated with a device happened and
- The incident was such that, if it occurred again, it might lead to death or serious deterioration in health
- A serious deterioration in state of health can include:
- A life-threatening illness (a)
- Permanent impairment of body function or permanent damage to a body structure (b)
- A condition necessitating medical or surgical intervention to prevent (a) or (b)
- Any indirect harm as a consequence of an incorrect diagnostic or IVD test results when used within the manufacturer's instructions for use
- Fetal distress, fetal death or any congenital abnormality or birth defects

Incidents include, for example:

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

Incidents do not include for example:

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

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

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

6.3.11. Time Period and Frequency of Detecting AEs and SAEs

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact at the timepoints specified in the Time and Events Table. (China sites should follow Section 11.1, Appendix 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. (China sites should follow Section 11.1, Appendix 1)
- All SAEs will be recorded and reported to GSK within 24 hours as indicated in Section 6.3.12.
- 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.

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

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

- 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 SAE contactor.
- 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 SAE contactor by telephone.

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

Table 7 Reporting of SAE and Other Events to GSK

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Device Incident	24 hours	"Medical Device Incident Report Form"	24 hours	Updated "Medical Device Incident Report Form"
Liver chemistry abnormalities Phase III-IV:				
ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) (or ALT≥3xULN **and** INR>1.5, if INR measured)***	24 hours*	SAE data collection tool. **Liver Event CRF and liver imaging and/or biopsy CRFs if applicable	24 hours	Updated SAE data collection tool. **Updated Liver Event CRF
ALT≥8xULN; ALT≥3xULN with hepatitis or rash or ≥3xULN and <5xULN that persists ≥4 weeks	24 hours*	**Liver event CRF	24 hours	**Updated Liver Event CRF
ALT≥5xULN plus bilirubin <2xULN	24 hours*	**Liver event CRF does not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks	24 hours	
ALT≥5xULN and bilirubin <2xULN that persists ≥2 weeks	24 hours*	**Liver event CRF	24 hours	Updated liver event CRF
ALT≥3xULN and <5x ULN and bilirubin <2xULN	24 hours*	**Liver event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks		

1. *GSK to be notified at onset of liver chemistry elevations to discuss subject safety.
2. ** Liver event documents should be completed as soon as possible.
3. *** INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants.

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

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

6.3.12.1. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK 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.

The Named Safety Contact (NSC) is responsible for individual expedited reports submission to SFDA within 15 days from GSK first receipt (7 days for death case).

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

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

6.4. Health Outcome Assessments Not Included as Primary or Key Secondary Endpoints

6.4.1. St George's Respiratory Questionnaire

The St. George's Respiratory Questionnaire (SGRQ) will be completed by study subjects at study visits as shown in Table 5.

The SGRQ [Jones, 1992] is a disease-specific questionnaire designed to measure the impact of respiratory disease and its treatment on the subject's health-related quality of life. As well as producing an overall summary score, it is also possible to calculate scores for the individual domains of symptoms, activity and impacts. It has been widely used in studies of COPD subjects and has been translated and validated for use in most major

languages. Research has demonstrated that it is sensitive to change and interpretation of the results has been enhanced by determination of the score change necessary to achieve a clinically meaningful improvement in quality of life [Jones, 1991; Jones, 2002]. The SGRQ is self-completed by subjects, taking on average 20 minutes.

The SGRQ should be completed prior to spirometry.

Additional, instructions for completion of the SGRQ are provided in the SPM.

6.4.2. Healthcare Resource Utilisation

All unscheduled COPD-related visits to a Physician's office, urgent care facility, or emergency department, and COPD-related hospitalisations associated with the subject's condition will be recorded on the COPD-related healthcare resource use assessment worksheet within the diary, by the subject

At Visits 2 through 9 or at the Early Withdrawal Visit, the resource utilisation worksheet completed by the subject to record all health care contacts since the last visit will be reviewed by the investigator (or designee). The investigator (or designee) should ask the subject if any of the health care contacts recorded on the worksheets were due to COPD exacerbation. The investigator can refer to his/her records to verify or supplement information given by the subject if necessary.

If any unscheduled healthcare contact was due to a COPD exacerbation, then the COPD Exacerbation section of the eCRF must be completed.

6.4.3. COPD Assessment Test (CAT)

The CAT (www.CATestonline.org) is a validated, short and simple patient completed questionnaire which has been developed for use in routine clinical practice to measure the health status of patients with COPD. The development of the CAT has involved well accepted methodologies used to develop psychometric tools [Jones, 2009a; Jones, 2009b]. The process of generating the CAT item pool was patient centred and also involved literature reviews and physician interviews [Jones, 2009b]. Following initial studies using this item pool in the US and Europe, a structured, rigorous scientific approach was used in the item reduction process to select the best items and generate the final 8-item questionnaire [Jones, 2009a]. The CAT has been validated in prospective studies conducted in the USA [Jones, 2009a] and China.

The CAT is an 8-item questionnaire suitable for completion by all patients diagnosed with COPD. When completing the questionnaire, subjects rate their experience on a 6-point scale, ranging from 0 to 5 with a maximum score of 40. The implications of CAT scores need to be considered in relation to an individual's disease severity. Patients with more severe COPD (as defined by GOLD, 2015) would be expected to have higher CAT scores than patients with milder disease, although many studies have shown that the relationship between GOLD stage (measured by FEV_1) and health status as perceived by physicians and patients is generally very weak. CAT was developed as a measure of health status to aid communication between physicians and patients and does not replace diagnostic spirometry. Research is currently ongoing to define ranges of CAT score in

relation to severity and to better understand the minimal clinically relevant change (often referred to as the Minimum Clinically Important Difference or MCID) in a CAT score from one visit to the next.

The CAT should be completed by all patients at the time points specified in the Time and Events Table. Patients should complete the 8 questions independently and without supervision. The CAT should be administered before any other study procedures are performed (including concurrent medication assessment or adverse event assessment, etc.).

7. DATA MANAGEMENT

For this study subject data will be entered into GSK defined electronic case report forms (eCRFs), transmitted electronically to GSK and combined with data provided from other sources in a validated data system.

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

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

The objective of this study is to assess the efficacy and safety of 24 weeks' treatment with Umeclidinium 62.5 mcg Inhalation Powder compared with placebo, when administered once-daily in subjects with COPD. The primary endpoint is trough FEV_1 at Day 169. The comparisons of interest for the primary analysis are described in Section 8.3.3.1.

For each test on each efficacy endpoint, the null hypothesis is that there is no difference between treatment groups.

H_0: $T_1 - T_2 = 0$

The alternative hypothesis is there is a difference between treatment groups.

H_1: $T_1 - T_2 \neq 0$

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

The sample size calculation is based on the primary endpoint of trough FEV_1 on Treatment Day 169 which will be analysed using a Mixed Models Repeated Measures (MMRM) analysis. The calculation uses an estimate of residual standard deviation (SD) of 234 mL, based on the residual standard deviation from the MMRM analysis of the meta-analyses from prior studies with UMEC in COPD (studies DB2113361, DB2113373, DB2113374).

Based on the Table 8 of effect sizes from previous studies, a true treatment difference of 115mL has been assumed:

Table 8 Effect Sizes from Previous Studies

Study	Comparison	Treatment Difference
DB2113373 (Day 169)	UMEC vs Placebo	0.115
AC4115408 (Day 85)	UMEC vs Placebo	0.127
UMEC ISE (Day 169) (DB2113361, DB2113373, DB2113374)	UMEC vs Placebo	0.133
DB2114634 (Day 169)	UMEC/VI vs Placebo	0.151
DB2114634 (China) (Day 169)	UMEC/VI vs Placebo	0.167

The sample size needs to include sufficient subjects to satisfy anticipated individual country requirements and the China subgroup is powered at 90% with a minimum of 100 evaluable subjects on UMEC arm. Assuming a treatment difference of 115mL and a residual standard deviation of 234mL gives 132 evaluable subjects on UMEC and 66 evaluable subjects on placebo is needed for China.

It is estimated that approximately 18% subjects will withdraw without providing a Week 24 assessment. Although, in MMRM, all available post-baseline assessments up to endpoint for subjects in the Modified Intent-to-Treat Population are utilized in the analysis, data for subjects who withdraw prematurely from the study are not explicitly imputed.

Allowing an 18% dropout, this would equate to 162 subjects randomised to UMEC and 81 subjects randomised to placebo from China.

45 randomised subjects from Korea will be sufficient, equating to 30 subjects randomised to UMEC and 15 subjects randomised to placebo. With an 18% withdrawal rate, this gives 24 evaluable subjects on UMEC and 12 evaluable subjects on placebo (allowing a 2:1 ratio).

We therefore require a total of approximately 192 randomised subjects on UMEC and 96 subjects randomised to placebo (total randomised 288).

Allowing for 18% dropout, a study with 156 evaluable subjects in active treatment arm and 78 evaluable subjects in placebo arm will have 94% power assuming a true treatment difference of 115mL to show a statistically significant difference between UMEC 62.5mcg and placebo in trough FEV_1. The calculations use a two-sample t-test and a two-sided 5% significance level.

The minimal detectable effect for the final sample size of 156 evaluable subjects on UMEC vs 78 evaluable subjects on placebo is 63.6mL.

8.2.2. Sample Size Sensitivity

If the standard deviation in this study is different from the expected value, the power to detect the planned difference in trough FEV_1 will be affected. Table 9 illustrates the power which would be obtained with different values of SD, assuming the sample size remains constant at 156 evaluable subjects on UMEC vs 78 evaluable subjects on placebo.

Table 9 Power Calculation for Treatment Differences

Parameter	SD	Treatment Difference	Power
Trough FEV_1 (mL)	205	115mL	98%
	240	115mL	93%
	260	115mL	88%

If the SD for trough FEV_1 increased to 260 mL, the study would have 88% power to show a statistically significant difference between UMEC and placebo assuming a true treatment difference of 115 mL. If the SD were as low as 205 mL then the study would have 98% power to show a statistically significant difference of 115 mL.

The true treatment difference for a statistically significant difference with 90% power will also be affected by changes in the SD; this is shown in Table 10.

Table 10 Treatment Differences Detected with 90% Power

Parameter	SD	Power	Treatment Difference
Trough FEV_1 (mL)	205	90%	93 mL
	240	90%	108 mL
	260	90%	117 mL

If the SD increased to 260mL, the study would have 90% power to show a statistically significant difference between UMEC and placebo assuming a true treatment difference of 117mL. If the SD were as low as 205mL then the study would have 90% power to show statistical significance for a true treatment difference of detect a difference of 93mL.

8.2.3. Sample Size Re-estimation

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

8.3. Data Analysis Considerations

The analysis described below will be performed on all subjects enrolled from China and Korea and also a separate analysis will be performed on the subjects enrolled in China alone: A China subgroup analysis.

8.3.1. Analysis Populations

Four 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 an 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-randomized subjects.

The **Screen and Run in Failure** population will comprise all subjects in the All Subjects Enrolled Population who are recorded as screen failures or run-in failures in the electronic case report form (eCRF). It will be used for the tabulation of reasons for screen and run-in failure and for inclusion, exclusion and randomisation criteria failed.

The Modified **Intent-to-treat** (ITT) Population will comprise all subjects randomized to treatment who received at least one dose of randomized study medication in the treatment period. 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 constitute the primary population for all data analyses and displays. All scheduled data collected until the time of study discontinuation will be included in the Modified Intent-to-treat analysis for subjects who withdraw from the study.

The **Per Protocol** (PP) Population will comprise all subjects in the Modified ITT Population who are not identified as full protocol violators. Receipt of a study treatment other than the randomized treatment will be considered a protocol deviation from the time of receiving incorrect treatment onwards. Subjects identified as partial protocol violators will be included in the PP Population but will have their data excluded from PP analyses from the time of violation onwards. The definition of full and partial violations will be included in the Reporting and Analysis Plan (RAP)In addition, details of exclusions from the Per Protocol population/ analyses which are not considered to be protocol deviations, but may have a potential impact on the efficacy data will also be documented in the RAP. This population will be used for confirmatory analyses of the primary efficacy endpoints only, irrespective of how many subjects are in the PP population.

For the China subgroup analysis, four subject populations will be identified as above, but will include only those subjects enrolled in sites from China. More details will be provided in the RAP.

8.3.2. Analysis Data Sets

Details of the analysis datasets will be given in the RAP

8.3.3. Treatment Comparisons

8.3.3.1. Primary Comparisons of Interest

The following treatment comparisons will be performed on trough FEV_1 on Treatment Day 169:

- Umeclidinium 62.5 mcg vs. placebo

8.3.3.2. Other Comparisons of Interest

The comparisons listed in Section 8.3.3.1 will be performed on the following secondary endpoints:

- Mean TDI focal score at Week 24
- Weighted mean clinic visit FEV_1 over 0 to 6 hours post-dose at Visit 2

The same treatment comparisons will be performed for the other efficacy endpoints.

8.3.4. Interim Analysis

No interim analysis is planned.

8.3.5. Key Elements of Analysis Plan

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.

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 (Visit 9).

It is anticipated that approximately 50 centres 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 prior to unblinding the treatment codes. These amalgamations will be used wherever centre groupings are incorporated into the analysis.

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

An overall analysis will be carried out including all countries, and also a China subgroup analysis.

8.3.5.1. 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

Primary analysis:

The primary endpoint of change from baseline trough FEV_1 on Day 169 will be analysed for the Modified Intent-to-treat Population using a mixed model repeated measures (MMRM) analysis [Siddiqui, 2009], including trough FEV_1 recorded at each of Days 2, 28, 56, 84, 112, 168 and 169.

Treatment group (categorical) will be fitted as the explanatory variable with baseline FEV_1, day, country, day by baseline interaction and day by treatment interaction fitted as covariates. Baseline FEV_1 is defined as the mean of the two assessments made pre-dose at Visit2. Day (nominal) will be fitted as a categorical variable and day by baseline and day by treatment interaction terms will be included to allow treatment effects to be estimated at each day separately. The variance-covariance matrix will be assumed unstructured (based on previous experience, no issues are expected with fitting models with this matrix structure).

Estimated treatment differences for each treatment comparison will be presented together with 95% confidence intervals (CIs) for the difference and p-values.

This analysis will be repeated for the Per Protocol Population.

Sensitivity analyses – interactions:

An assessment of whether the effect of treatment on trough FEV_1 is modified by each of the following factors will be performed:

Center grouping, reversibility and ICS use.

Separate models will be fitted for each factor, which are identical to the primary efficacy analysis model but including an additional term for the factor and treatment by factor interaction. If these interaction terms demonstrate statistical significance at the 10% level then further investigation and characterization of the interaction will be undertaken.

Further factors may also be considered for investigation and will be detailed in the RAP.

Secondary Endpoints

The analysis of the TDI focal score on Days 28, 84 and 168 will use the same methodology as that for the primary endpoint, but adjusting for BDI score instead of baseline FEV_1.

Weighted mean clinic visit FEV_1 over 0 to 6 hours post-dose at Visit 2 (Day 1) will be analysed using analysis of covariance (ANCOVA). Treatment group (categorical) will be fitted as the explanatory variable with baseline FEV_1, and country fitted as covariates. Baseline FEV_1 is defined as the mean of the two assessments made pre-dose at Visit2.

Estimated treatment differences for each treatment comparison will be presented together with 95% confidence intervals (CIs) for the difference and p-values.

Secondary endpoints will be analyzed for the Modified Intent-to-treat Population only.

Other Endpoints

Serial FEV_1 at 15mins, 30mins, 1, 3 and 6 hours after dosing will be analysed using a repeated measures model, including baseline FEV1, country, treatment, time, time by treatment interaction and time by baseline interaction fitted as covariates. Baseline FEV1 is defined as the mean of the two assessments made pre-dose at Visit2. This analysis will be performed for Day 1 only.

Time to onset of bronchodilation (defined as an increase of 100 mL in FEV_1 above baseline on Treatment Day 1 (Visit2)) and time to first COPD exacerbation will be compared between treatment groups using Cox's proportional hazards model.

Other endpoints will be analysed for the Modified Intent-to-treat Population only. Full details of the analyses to be performed will be provided in the RAP.

8.3.5.2. 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, during active treatment and post-treatment will be summarized separately. The number and percentage of subjects experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be presented for each treatment group. Separate summaries will be provided for all AEs, drug related AEs, SAEs and AEs leading to withdrawal.

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

Clinical laboratory evaluations (hematological and clinical chemistry), vital signs (pulse rate, systolic blood pressure and diastolic blood pressure) and 12-lead will be summarized by treatment group. Pulse rate, systolic and diastolic blood pressure and derived ECG parameters QTc(F), PR interval, and heart rate will be analyzed at each time point at which they were recorded (10 minutes and 45 minutes post-dose on Day 1, for vital signs pre-dose on Days 2, 28, 56, 84, 112, 168 and 169, for ECG pre-dose on Days 1, 84, and 168, and 10 minutes and 45 minutes post-dose on Day 1, 84 and 168) separately, using an ANCOVA model with predefined effects including baseline.

Estimated treatment differences for all comparisons performed will be presented together with 95% CIs for the difference and p-values. The baseline value will be that recorded pre-treatment on Day 1.

8.3.5.3. Health Outcomes Analyses

Full details of the analysis to be performed will be given in the RAP.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

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

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

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

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

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

9.3. Quality Control (Study Monitoring)

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

GSK will monitor the study to ensure that the:

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

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

9.4. Quality Assurance

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

9.5. Study and Site Closure

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

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

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

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

9.6. Records Retention

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

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

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

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

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

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

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

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

The results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was

examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

9.8. Independent Data Monitoring Committee (IDMC)

There is no IDMC in this study.

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11. APPENDICES

11.1. Appendix 1: Country Specific Requirements

For sites located in China, SAEs should be recorded from the time the consent form is signed until the follow-up contact.

The requirement on SAE collecting time period in Section 3.1, Section 4.6 and Section 6.3.11 is not appropriate for sites in China.

11.2. Appendix 2: 12-Lead ECG Exclusion Criteria

An abnormal and clinically significant finding that would preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:

- Sinus tachycardia ≥120 bpm

*Note: sinus tachycardia ≥120bpm should be confirmed by two additional readings at least 5 minutes apart

- Sinus bradycardia <45bpm

*Note: Sinus bradycardia <45bpm should be confirmed by two additional readings at least 5 minutes apart.

- Multifocal atrial tachycardia
- Supraventricular tachycardia (>100bpm)
- Atrial fibrillation with rapid ventricular response (rate >120bpm)
- Atrial flutter with rapid ventricular response (rate >120bpm)
- Ventricular tachycardias (non sustained, sustained, polymorphic, or monomorphic)
- Ventricular flutter
- Ventricular fibrillation
- Torsades de Pointes
- Evidence of Mobitz type II second degree or third degree atrioventricular (AV) block
- AV dissociation
- Trifascicular Block
- For subjects **with QRS duration <120 ms**: QTc(F) ≥450msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).
- For subjects **with QRS duration>120**: QTc(F) ≥480msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).
- Myocardial infarction (acute or recent) * Note: Evidence of an old (resolved) myocardial infarction is not exclusionary.

11.3. Appendix 3: 12-Lead ECG Withdrawal Criteria

An ECG finding that would result in subject withdrawal post-randomization is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:

- Sinus tachycardia ≥120 bpm

*Note: sinus tachycardia ≥120bpm should be confirmed by two additional readings at least 5 minutes apart

- Sinus bradycardia <37bpm

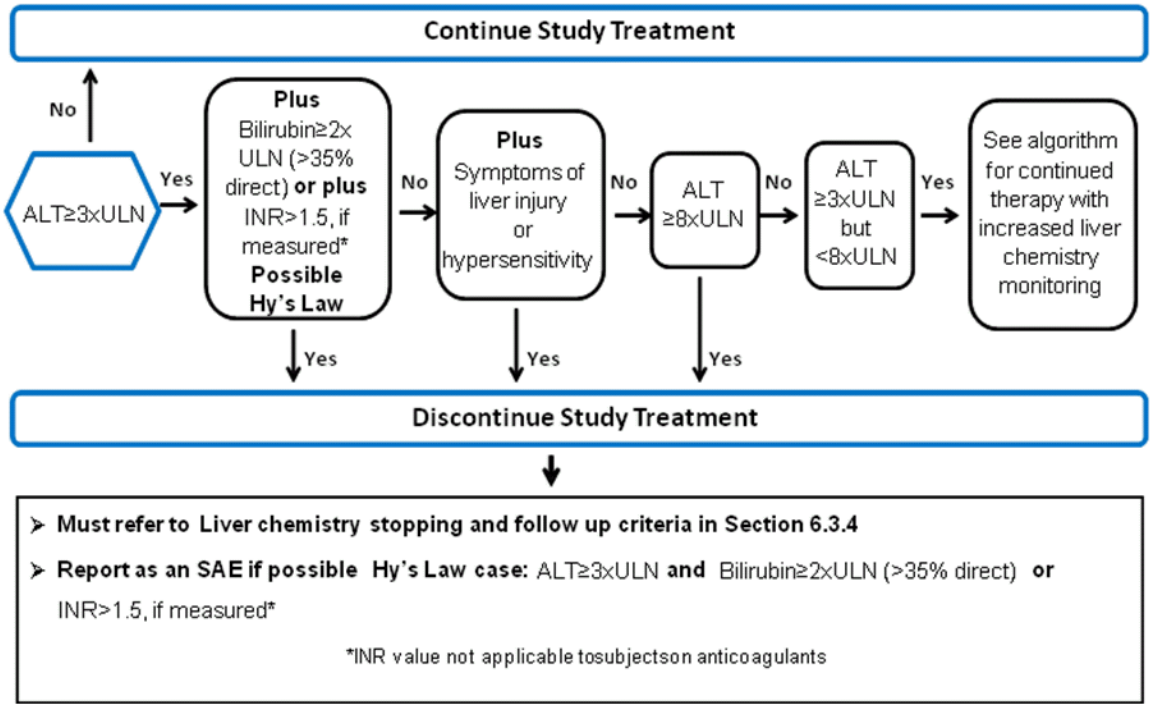
*Note: Sinus bradycardia <37 bpm should be confirmed by two additional readings at least 5 minutes apart.

- Increase in heart rate ≥40bpm relative to baseline

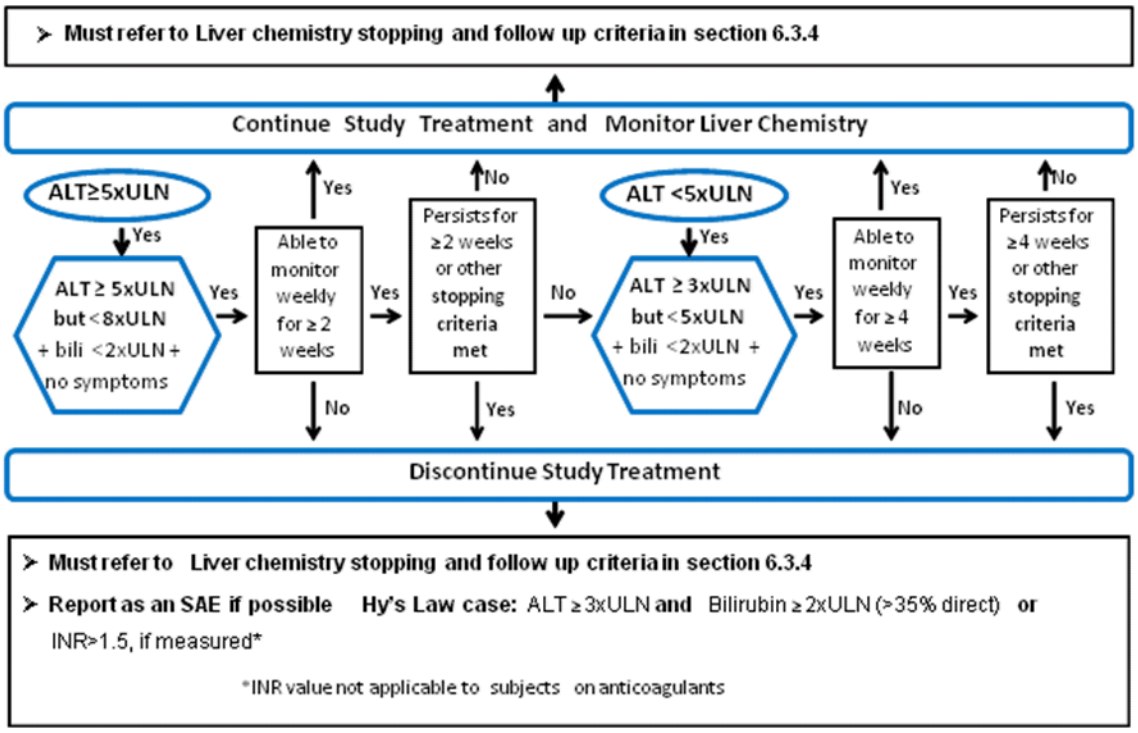
*Note: increase in heart rate ≥40bpm should be confirmed by two additional readings at least 5 minutes apart

- Multifocal atrial tachycardia
- Supraventricular tachycardia (>100bpm)
- Atrial fibrillation with rapid ventricular response (rate >120bpm)
- Atrial flutter with rapid ventricular response (rate >120bpm)
- Ventricular tachycardias (non sustained, sustained, polymorphic, or monomorphic)
- Ventricular flutter
- Ventricular fibrillation
- Torsades de Pointes
- Evidence of Mobitz type II second degree or third degree atrioventricular (AV) block
- AV dissociation
- Trifascicular Block
- An increase in QTcF>60 msec from baseline ECG
- Uncorrected QT>600 msec
- For subjects **with QRS duration <120 ms**: QTc(F) ≥500 msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).
- For subjects **with QRS duration>120 ms**: QTc(F) ≥530 msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).
- Myocardial infarction (acute or recent) Note: Evidence of an old (resolved) myocardial infarction is not exclusionary

11.4. Appendix 4: Liver Chemistry Stopping and Increased Monitoring Algorithm



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



11.5. Appendix 5: Protocol changes in Amendment 01

This amendment applies all sites.

Summary of Amendment Changes with Rationale

The following revisions were made:

- Author(s) updated.
- Inclusion Criteria updated. Asian ancestry is required.
- Exclusion criteria updated. Remove CYP3A4 washout, add exclusive compliance.
- Pre-Screen and Screen Failures updated. Required information is clarified.
- Permitted Medications and Non-Drug Therapies revised.
- Prohibited medications updated. Remove cytochrome P450 3A4 strong inhibitor
- Time and Events Table revised.
- COPD exacerbation revised.
- Clinical Laboratory Tests revised.
- Data Analysis Considerations revised on population and key elements.
- 12-Lead ECG Exclusion Criteria updated. Added 2:1 AV block and non-sustained ventricular tachycardia.
- 12-Lead ECG withdrawal criteria updated: Added 2:1 AV block.
- Some minor format revisions.

List of specific changes

Section: Authors

Author(s): PPD (CMD, China); PPD (CMD, China); PPD (DM); PPD (Clinical Statistician, UK); PPD (CMD, China) PPD

Section 3.2 Discussion of Design

A randomized, double-blind, placebo-controlled, parallel group study is a standard, well-established design to evaluate the efficacy and safety of an investigational drug. A

placebo arm is included in this study to allow for an absolute assessment of efficacy and safety of ~~each of~~ the active treatments~~.~~

Section 4.2 Inclusion Criteria

1. Type of subject: outpatient, Asian ancestry

Section 4.3 Exclusion Criteria

Table 1 Time Interval for Prohibited Medication Prior to Visit 1

Medication	Time Interval Prior to Visit 1
Depot corticosteroids	12 weeks
Systemic, oral, parenteral (intra-articular) corticosteroids	4 weeks
Antibiotics (for lower respiratory tract infection)	4 weeks
~~Cytochrome P450 3A4 strong inhibitors[1]~~	~~4 weeks (Grapefruit is allowed up to Visit 1, then limited to no more than one glass of grapefruit juice (250 mL/8 ounces) or one grapefruit per day)~~
ICS/LABA combination products if ICS/LABA therapy is discontinued completely	30 days
Use of ICS at a dose >1000mcg/day of fluticasone propionate or equivalent[2]1]	30 days
Initiation or discontinuation of ICS use[2]1]	30 days
Phosphodiesterase 4 PDE4 inhibitors (roflumilast)	14 days
Long-acting anticholinergics (e.g.,tiotropium and aclidinium, glycopyronium)	7 days
Theophyllines[3]2]	12 hours (stable dose of theophylline alone is allowed during the study but must be withheld 12 hours prior to each study visit)
Oral leukotriene inhibitors (zafirlukast, montelukast, zileuton)	48 hours
Oral beta$_2$-agonists Long- acting Short –acting	 48 hours 12 hours
Olodaterol and Indacaterol (inhaled long-acting beta$_2$-agonist)	14 days
Salmeterol, formoterol, (inhaled long-acting beta$_2$-agonist)	48 hours
LABA/inhaled corticosteroid (ICS) combination products only if discontinuing LABA therapy and switching to ICS monotherapy[4]3]	48 hours for LABA component
Inhaled sodium cromoglycate or nedocromil sodium	24 hours

Medication	Time Interval Prior to Visit 1
Inhaled short acting beta2-agonists~~[5]~~[4]	4 hours
Inhaled short-acting anticholinergics~~[3]~~[2] (e.g. ipratropium bromide)	4 hours (stable dose of ipratropium alone is allowed during the study, provided that the subject is on a stable dose regimen from Screening (Visit 1 and remains so throughout the study) but must be withheld 4 hours prior to each study visit)
Inhaled short-acting anticholinergic/short-acting beta$_2$-agonist combination products	4 hours
Any other investigational drug	30 days or 5 half lives, whichever is longer

~~1. See the study procedures manual (SPM) for a complete list of excluded cytochrome P450 inhibitors~~

~~2.~~ 1.Use of ICS is permitted provided the dose not exceed 1000mcg of fluticasone propionate or equivalent; ICS use not to be initiated or discontinued within 30 days prior to Visit 1

~~3.~~ 2.Ipratropium bromide or theophylline is permitted, provided that the subject is are on a stable dose from Screening (Visit 1) and remains on the stable dose throughout the study; however, Ipratropium bromide must be withheld for 4 hours; theophylline must be withheld for 12 hours prior to and during each clinic visit.

~~4.~~ 3.The dose of ICS must be equivalent to that contained in the ICS/LABA combination product (the study procedures manual will have equivalence guidelines)

~~5.~~ 4.Use of study provided albuterol/salbutamol is permitted during the study, except in the 4-hour period prior to spirometry testing

Section 4.3: Exclusion Criteria

- Compliance: A subject will not be eligible if he/she has any infirmity, disability, illiteracy, disease, or geographical location which seems likely (in the opinion of the Investigator) to impair compliance with any aspect of this study protocol, including visit schedule and completion of daily diaries or questionnaires.

Section 4.6: Pre-Screen and Screen Failures

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

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

Section 5.6.1 Permitted Medications and Non-Drug Therapies

If the subject is on an ICS/LABA product for at least 30 days to Visit 1, the subject may switch to an ICS product alone as long as it does not exceed 1000mcg/day of FP or equivalent, and the dose remains consistent, as defined in the SPM, throughout the study. The switch to ICS alone from an ICS/LABA product must occur at least 48 hours prior to screen visit ~~starting the study~~. Discontinuation of the ICS/LABA product completely in the absence of starting an ICS alone must occur at least 30 days prior to V1.

Section 5.6.2 Prohibited Medications and Non-Drug Therapies

Table 4 Prohibited Medications

Depot corticosteroids
Systemic, oral or parenteral corticosteroids
~~Cytochrome P450 3A4 strong inhibitors[1]~~
LABA/ICS combination products
Use of ICS at a dose >1000 mcg/day of fluticasone propionate or equivalent[2,1]
Initiation or discontinuation of ICS use[2,1]
PDE4 inhibitor (e.g.roflumilast)
Oral leukotriene inhibitors (zafirlukast, montelukast, zileuton)
Oral beta$_2$-agonists
Inhaled long acting beta$_2$-agonists (LABA, e.g., salmeterol, formoterol, indacaterol, olodacterol)
Inhaled long acting anticholinergics (LAMA, eg; tiotropium, aclidinium, glycopyrronium)
Inhaled sodium cromoglycate or nedocromil sodium
Any other investigational medication

~~1. See the SPM for a complete list of excluded cytochrome P450 inhibitors~~

~~2.~~ 1. Use of ICS is permitted provided the dose not exceed 1000mcg of fluticasone propionate or equivalent; ICS use not to be initiated or discontinued within 30 days prior to Visit 1

Section 6 STUDY ASSESSMENTS AND PROCEDURES

Table 5 Time and Events Table

		Run-in	Double-blind treatment period									
Visit	**Visit 0 (Pre-Screen)**	**Screening Visit (Visit 1)**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Early With-drawal (EW) Visit**	**Follow-Up (Phone contact)**
Day		**Day -7 to -14**	**Day 1**	**Day 2**	**Day 28±2**	**Day 56±4**	**Day 84±4**	**Day 112±4**	**Day 168±4**	**Day 169 (Visit 8 +1 day)**		**7±2 days after Visit 9 or EW**
Week		**-1**	**0**	**0**	**4**	**8**	**12**	**16**	**24**			
Written Informed Consent[1]	**x**											
Demography/ COPD History	**X**											
Medical History		**X**										
Physical Examination		**X**							**X**		**X**	
Smoking Status		**X**							**X**		**X**	
Smoking Cessation Counselling		**X**							**X**		**X**	
Chest X-ray[2]		**X**										
Inclusion/exclusion criteria		**X**										
Randomization criteria			**X**									
Screening spirometry (including post-bronchodilator testing)[3]		**X**										
mMRC questionnaire		**X**										
Register visit in IVSR	**x**	**x**	**x**	**x**	**X**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Diary Card Dispense or~~and~~ Collection/Review		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	

Section 6.2.7 COPD Exacerbations

Subjects who experience an exacerbation during treatment or run-in period requiring the use of any systemic/oral corticosteroids, with/without either prescribed or non-prescribed (self administered) antibiotics, and/or emergency treatment or hospitalisation ~~during the run-in~~ will be withdrawn from the study and will not be allowed to re-screen. However, subjects who experience a COPD exacerbation/lower respiratory tract infection requiring only the use of antibiotics, either prescribed or non-prescribed (self-administered), may continue to participate in study.

Section 6.3.3 Clinical Laboratory Tests

Routine, non fasting clinical laboratory (haematology and chemistry and urinalysis) tests will be performed as detailed in Table 5. At the discretion of the investigator, additional samples may be taken for safety reasons. All ~~blood~~ samples will be measured at a designated central laboratory.

Section 6.3.3 Clinical Laboratory Tests

Table 6 Study Clinical Laboratory Tests

CHEMISTRY	HEMATOLOGY	OTHER
Albumin	Hemoglobin	Hepatitis B surface antigen[1]
Alkaline phosphatase	Hematocrit	Hepatitis C virus antibody[1]
Alanine amino-transferase (ALAT or SGPT)	Platelet count	Urine pregnancy test (in clinic)[2]
Aspartate amino-transferase (ASAT or SGOT)	WBC count	**Routine Urinalysis:**
Bilirubin, direct	Neutrophils, absolute	pH
Bilirubin, indirect	Neutrophils, segs (%)	Protein
Bilirubin, total	Neutrophils, bands (%)	Glucose
Calcium	Basophils (%)	Blood, Bilirubin, and White Cell Count
Chloride	Eosinophils (%)	
CO_2 content/Bicarbonate	Eosinophils , absolute	
Creatinine	Lymphocytes (%)	
Creatine phosphokinase (CPK), total	Monocytes (%)	
Gamma glutamyl transferase (GGT)	RBC count	
Glucose		
Phosphorus		
Potassium		
Protein, total serum		
Sodium		
Urea nitrogen (BUN)		
Uric Acid		

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

Section 8.3 Data Analysis Considerations

The analysis described below will be performed on all subjects enrolled from China, Taiwan, Korea and Thailand and also a separate analysis will be performed on the subjects enrolled in China alone: A China subgroup analysis.

Section 8.3.1 Analysis Population

~~Three~~Four 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 an 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-randomized subjects.

The **Screen and Run in Failure** population will comprise all subjects in the All Subjects Enrolled Population who are recorded as screen failures or run-in failures in the electronic case report form (eCRF). It will be used for the tabulation of reasons for screen and run-in failure and for inclusion, exclusion and randomisation criteria failed.

The **Intent-to-treat** (ITT) Population will comprise all subjects randomized to treatment who received at least one dose of randomized study medication in the treatment period. 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 constitute the primary population for all data analyses and displays. Subjects will be included in the analysis of a particular outcome if they provided at least one on-treatment assessment of that outcome.

The **Per Protocol** (PP) Population will comprise all subjects in the ITT Population who are not identified as full protocol violators. Receipt of a study treatment other than the randomized treatment will be considered a full protocol violation. Subjects identified as partial protocol violators will be included in the PP Population but will have their data excluded from PP analyses from the time of violation onwards. The definition of full and partial violations will be included in the Reporting and Analysis Plan (RAP) and the decision to exclude a subject from the PP Population or a subject's data from PP analyses will be made prior to breaking the blind. This population will be used for confirmatory analyses of the primary and secondary efficacy endpoints only, irrespective of how many subjects are in the PP population.

For the China subgroup analysis, four subject populations will be identified as above, but will include only those subjects enrolled in sites from China. More details will be provided in the RAP.

Section 8.3.5 Key Elements of Analysis Plan

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.

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 (Visit 9).

It is anticipated that approximately 50 centres 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 prior to unblinding the treatment codes. These amalgamations will be used wherever centre groupings are incorporated into the analysis.

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

An overall analysis will be carried out including all countries, and also a China subgroup analysis.

Section 11.3 Appendix 3: 12-Lead ECG Exclusion Criteria

An ECG finding that would preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:

- Sinus tachycardia ≥110 bpm

*Note: sinus tachycardia ≥110bpm should be confirmed by two additional readings at least 5 minutes apart

- Sinus bradycardia <45 bpm

***Note**: Sinus bradycardia <45 bpm should be confirmed by two additional readings at least 5 minutes apart.

- Multifocal atrial tachycardia
- Junctional tachycardia (heart rate >100 bpm)
- Junctional escape complexes
- Supraventricular tachycardia (>100 bpm)
- Ventricular tachycardias (non-sustained, sustained, polymorphic, or monomorphic)
- Atrial fibrillation with rapid ventricular response (rate >100 bpm)
- Atrial flutter
- Evidence of bigeminy, trigeminy or multifocal premature ventricular complexes
- Ventricular flutter
- Ventricular fibrillation
- Torsades de Pointes
- R on T phenomenon
- Wide QRS tachycardia (diagnosis unknown)

- Electrical alternans
- Pacemaker
- Idioventricular rhythm – heart rate <100 bpm
- Evidence of Mobitz type II second degree or third degree atrioventricular (AV) block
- 2:1 AV block
- AV dissociation
- Bifascicular block
- Trifascicular block
- Left bundle branch block
- For subjects **without complete right bundle branch block**: QTc(F) ≥450 msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).
- For subjects **with complete right bundle branch block**: QTc(F) ≥480 msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).

*__Note__: All potentially exclusionary QT measurements should be confirmed by two additional readings at least 5 minutes apart.

- Accessory pathway (Wolff-Parkinson-White, Lown-Ganong-Levine)
- Myocardial infarction (acute or recent)

*__Note__: Evidence of an old (resolved) myocardial infarction is not exclusionary.

Section 11.4 Appendix 4: 12-Lead ECG Withdrawal Criteria

An ECG finding that would result in subject withdrawal post-randomization is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:

- Sinus tachycardia ≥110 bpm

*__Note__: sinus tachycardia ≥110 bpm should be confirmed by two additional readings at least 5 minutes apart

- Increase in heart rate ≥40 bpm relative to baseline
- An increase in $QTc_{(F)}$ >60 msec from baseline ECG
- Sinus bradycardia <37 bpm

*__Note__: Sinus bradycardia <37 bpm should be confirmed by two additional readings at least 5 minutes apart.

- Multifocal atrial tachycardia
- Junctional tachycardia (heart rate >100 bpm)

- Junctional escape complexes
- Supraventricular tachycardia (>100 bpm)
- Ventricular tachycardias (non-sustained, sustained, polymorphic, or monomorphic)
- Atrial fibrillation with rapid ventricular response (rate >100 bpm)
- Atrial flutter
- Evidence of bigeminy, trigeminy or multifocal premature ventricular complexes
- Ventricular flutter
- Ventricular fibrillation
- Torsades de Pointes
- R on T phenomenon
- Wide QRS tachycardia (diagnosis unknown)
- Electrical alternans
- Pacemaker
- Idioventricular rhythm – heart rate <100 bpm
- Evidence of Mobitz type II second degree or third degree atrioventricular (AV) block
- 2:1 AV block
- AV dissociation
- Bifascicular block
- Trifascicular block
- Left bundle branch block
- For subjects **without complete right bundle branch block**: QTc(F) >500 msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).
- For subjects **with complete right bundle branch block**: QTc(F) ≥530 msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).

***Note**: All potentially exclusionary QT measurements should be confirmed by two additional readings at least 5 minutes apart.

- Accessory pathway (Wolff-Parkinson-White, Lown-Ganong-Levine)
- QT >600 msec
- Myocardial infarction (acute or recent)

***Note**: Evidence of an old (resolved) myocardial infarction is not exclusionary

11.6. Appendix 6: Protocol changes in Amendment 02

This amendment applies all sites.

Summary of Amendment Changes with Rationale

To provide detailed information on efficacy analyses following authority's requirement.

List of specific changes

Section 8.3.5.1 Efficacy Analysis

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

Primary Endpoint

Primary analysis:

The primary endpoint of change from baseline trough FEV_1 on Day 169 will be analysed for the Intent-to-treat Population using a mixed model repeated measures (MMRM) analysis [Siddiqui, 2009], including trough FEV_1 recorded at each of Days 2, 28, 56, 84, 112, 168 and 169.

Treatment group (categorical) will be fitted as the explanatory variable with ~~appropriate predefined variables, including~~ baseline FEV_1, smoking status, day, country, day by baseline interaction and day by treatment interaction fitted as covariates. Baseline FEV_1 is defined as the mean of the two assessments made pre-dose at Visit2. Visit (nominal) will be fitted as a categorical variable and visit by baseline and visit by treatment interaction terms will be included to allow treatment effects to be estimated at each visit separately. The variance-covariance matrix will be assumed unstructured (based on previous experience, no issues are expected with fitting models with this matrix structure).

Estimated treatment differences for each treatment comparison will be presented together with 95% confidence intervals (CIs) for the difference and p-values.

This analysis will be repeated for the Per Protocol Population.

Sensitivity analyses – interactions:

An assessment of whether the effect of treatment on trough FEV_1 is modified by each of the following factors will be performed:

Center grouping, smoking status, reversibility and ICS use.

Separate models will be fitted for each factor, which are identical to the primary efficacy analysis model but including an additional term for the factor and treatment by factor interaction. If these interaction terms demonstrate statistical significance at the 10% level then further investigation and characterization of the interaction will be undertaken.

Further factors may also be considered for investigation and will be detailed in the RAP.

Secondary Endpoints

The analysis of the mean TDI focal score on Days 28, 84 and 168 will use the same methodology as that for the primary endpoint, including all sensitivity analyses but adjusting for (at a minimum) BDI score instead of baseline FEV_1.

Weighted mean clinic visit FEV_1 over 0 to 6 hours post-dose at Visit 2 (Day 1) will be analysed using analysis of covariance (ANCOVA). Treatment group (categorical) will be fitted as the explanatory variable with ~~appropriate predefined variables, including~~ baseline FEV_1, smoking status and country fitted as covariates. Baseline FEV_1 is defined as the mean of the two assessments made pre-dose at Visit2.

Estimated treatment differences for each treatment comparison will be presented together with 95% confidence intervals (CIs) for the difference and p-values.

Secondary endpoints will be analyzed for the Intent-to-treat Population only.

Other Endpoints

Serial FEV_1 at 15 mins, 30 mins, 1, 3 and 6 hours after dosing will be analysed using a repeated measures model, ~~with predefined variables,~~ including baseline FEV_1, country, smoking status, treatment, time, time by treatment interaction and time by baseline interaction fitted as covariates. Baseline FEV_1 is defined as the mean of the two assessments made pre-dose at Visit2. Treatment, time and a time by treatment interaction term will be included. This analysis will be performed for Day 1 only.

Time to onset of bronchodilation (defined as an increase of 100 mL in FEV_1 above baseline on Treatment Day 1 (Visit2)) and time to first COPD exacerbation will be compared between treatment groups using Cox's proportional hazards model.

Other endpoints will be analysed for the Intent-to-treat Population only. Full details of the analyses to be performed will be provided in the RAP.

Section 8.3.3.2 Other Comparisons of Interest

The comparisons listed in Section 8.3.3.1 ~~8.3.3.2~~ will be performed on the following secondary endpoints:

- Mean TDI focal score at Week 24
- Weighted mean clinic visit FEV_1 over 0 to 6 hours post-dose at Visit 2

The same treatment comparisons will be performed for the other efficacy endpoints.

11.7. Appendix 7: Protocol changes in Amendment 03

This amendment applies all sites. Besides, a China specific requirement was developed based on authority requirement.

Summary of Amendment Changes with Rationale

The following revisions were made:

- Removed Thailand and Taiwan from involved countries/areas.
- Changed randomization ratio from 1:1 to 2:1.
- Updated sample size based on the latest difference and SD. Updated analysis plan.
- Dispense of rescue sulbutamol was moved up from V1 to V0.
- Updated wordings in cardiovascular events, death events, pregnancy, liver stop/follow, and AE/SAE according to the latest protocol template.
- Developed a China specific requirement on SAE collection period.
- Pharmacogenetic research sections removed.
- Updated the 12-Lead ECG Exclusion Criteria and 12-Lead ECG Withdrawl Criteria.
- Novel Dry Powder Inhaler (NDPI) has been replaced with ELLIPTA.
- Some minor revisions.

List of specific changes

Novel Dry Powder Inhaler (NDPI) has been replaced with ELLIPTA in throughout the document

The IB version has been updated to IB2015 in throughout the document as velow:

GlaxoSmithKline Document Number ~~RM2006/00835/08~~ RM2006/00835/11, IB ~~2012~~2015.

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Protocol Summary

Rationale

Studies to date provide substantial evidence for the effectiveness for UMEC 62.5 mcg as a long term maintenance therapy for the treatment of COPD. The purpose of this 24-week study is to further evaluate the efficacy and safety of UMEC 62.5 mcg administered once-daily in Asian subjects with COPD.

Study Design

288 ~~E~~eligible subjects will be randomized to the UMEC 62.5 mcg and placebo treatment groups in a 2:1 ~~1:1~~ ratio, ~~such that of the planned total number of 454 randomized subjects, subjects will be equally randomised to the active and placebo treatment group (~~approximately 192 ~~227~~ subjects in active arm and 96 subjects in placebo arm ~~per arm)~~. All treatments will be administered once-daily in the morning by inhalation using an ELLIPTA~~NDPI~~.

There will be a total of 10 study clinic visits conducted on an outpatient basis. A pre-screening visit (V0) will be conducted to sign the informed consent form (ICF), dispense the rescue medication and review demography, COPD history and concomitant medications. Once the ICF is signed the subject will be assigned a subject identifier. At Visit 0, any medications changes made by the investigator will be recorded. Subjects who meet the eligibility criteria at Screening (Visit 1) will complete a 7 to 14 day Run-in period. At the end of the Run-in period, subjects will be assessed and those who meet the randomisation criteria will enter a 24-week double-blind Treatment Period. Clinic visits (1 through 9) will be at Screening, Randomization (Day 1), Day 2, Day 28 (Week 4), Day 56 (Week 8), Day 84 (Week 12), Day 112 (Week 16), Day 168 (Week 24) and Day 169. A follow-up contact for adverse event (AE) assessment will be conducted by telephone approximately 7 days after the Treatment period or the Early Withdrawal (EW) Visit.

The total duration of subject participation, including follow-up will be approximately 27 weeks. All subjects will be provided with albuterol/salbutamol for use on an “as-needed” basis throughout the Pre-screen, Run-in and study Treatment periods.

Study End-point Assessments

Secondary

- ~~(~~Transition Dyspnea Index (TDI) focal score at Week 24.
- Weighted mean clinic visit FEV_1 over 0 to 6 hours post-dose at visit 2 (~~Randomisation visit~~ Day 1)

1.2 Rationale

Treatment with muscarinic antagonists has been shown to significantly improve Forced Expiratory Volume in One Second (FEV_1), resting and dynamic lung hyperinflation, symptoms, exercise capacity, health status, and reduce COPD exacerbations [O'Donnell, 1998; O'Donnell, 2004; Tashkin, 2008a; Tashkin, 2008b]. However, a significant number of subjects are thought to continue to have symptoms, as reported in a primary care, cross-sectional study [Dransfield, 2011].

Umeclidinium is an orally inhaled, potent, pan-active long acting muscarinic anatagonist (LAMA)~~LAMA in development~~ for use as an inhaled product in the treatment of COPD as a stand-alone once-daily product and with the long acting beta agonist (LABA), vilanterol, as a once-daily combination product for the treatment of COPD. Both Umeclidinium monotherapy and combination with vilanterol have been approved by FDA and EMA.

Studies to date provide substantial evidence for the effectiveness for UMEC 62.5 mcg as a long term maintenance therapy for the treatment of COPD. The purpose of this 24 week study is to further evaluate the efficacy and safety of UMEC 62.5 mcg administered once-daily in Asian subjects with COPD.

1.3 Summary of Risk Management

Summaries of findings from both clinical and non-clinical studies conducted with GSK573719 can be found in the Investigator's Brochure. The following section (Table 1*) outlines the risk assessment and mitigation strategy for this protocol:

*The detail of the Table 1 refers to the protocol.

2 Objectives and Endpoints

The objectives and Endpoints are presented together in a table to ensure all endpoints are aligned with an objective as per required of template update.

~~2.1 Primary Objective~~

~~The primary objective of the study is to evaluate the efficacy and safety of Umeclidinium 62.5 mcg compared with placebo when administered once-daily via the Novel Dry Powder Inhaler (NDPI) over a 24-week treatment period in subjects with COPD.~~

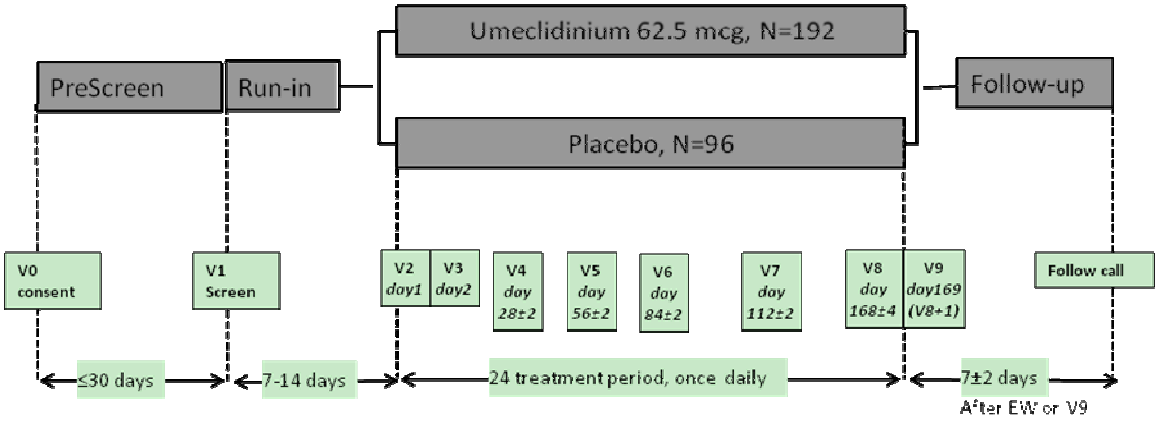
3.1 Study Design

This is a multicenter, randomized, double-blind, parallel group study to evaluate the efficacy and safety of umeclidinium 62.5 mcg administered once-daily via a ELLIPTA

~~novel dry powder inhaler (NDPI)~~ compared with placebo over 24 weeks in subjects with COPD. Eligible subjects will be randomized 2:1~~1:1~~ to receive one of the two following treatments:

- Umeclidinium (GSK573719) 62.5 mcg Inhalation Powder administered QD via a ELLIPTA ~~NDPI~~ in the morning
- Placebo administered QD via a ELLIPTA ~~NDPI~~ in the morning

The schematic diagram in previous protocol has been replaced with the new diagram.



3.1 Study Design

There will be a total of 10 study clinic visits conducted on an outpatient basis. A pre-screening visit (V0) will be conducted to sign the informed consent form (ICF), dispense rescue medication and review demography, COPD history and concomitant medications. Once the ICF is signed the subject will be assigned a subject identifier. At Visit 0, any medications changes made by the investigator will be recorded. Subjects who meet the eligibility criteria at Screening (Visit 1) will complete a 7 to 14 day run-in period followed by a 24 week treatment period. Clinic visits will be at Prescreening (visit 0), Screening, Randomization (Day 1), Day 2 and 4, 8, 12, 16, and 24 weeks, and 1 day after the Week 24 visit (Visit 0 to Visit 9, respectively). Additionally a safety Follow-Up assessment will be conducted by phone call approximately 7 days after the end of the study treatment (Visit 9 or Early Withdrawal, if applicable). The total duration of subject participation, including the Follow-Up, will be approximately 27 weeks. All subjects will be provided with albuterol/salbutamol for use on an "as-needed" basis throughout the pre-screen, run-in and study treatment periods.

The occurrence of adverse events will be evaluated throughout the study, beginning at Visit 2. SAEs will be collected over the same time period as for AEs. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated

procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication (eg Run-in medications, rescue medications provided by GSK), will be recorded from the time a subject consents to participate in the study up to and including any follow up contact (China sites should follow Section 11.1, Appendix 1).

The Modified Intent-to-Treat (ITT) population will be the primary population of interest, and is defined as all randomised subjects who have received at least one dose of the randomised study medication during the Treatment Period.

3.2 Discussion of Design

A randomisation ratio of 2:1 will reduce the number of subjects randomised to placebo arm, as well as to reduce drop-outs.

4.1 Number of Subjects

Based on an early withdrawal rate of 18~~21~~% of randomized subjects, approximately 288~~454~~ study subjects will be randomized in 2:1 to the double blind medication, that means 192 subjects in active arm and 96 subjects in placebo arm, to ensure approximately 236~~360~~ subjects complete the 24 week treatment period.

4.6 Pre-Screen and Screen Failure

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

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

4.8 Premature Discontinuation

- Report subject's early withdrawal from the study via Randomization And Medication Ordring System New Generation (RAMOS NG).

5.1 Investigational Product and Other Study Treatment

Table 2 Description of Umeclidinium Inhalation Powder ELLIPTA

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

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

~~Formulation~~	~~**First strip**~~	~~**Second strip**[1]~~
	~~GSK573719 blended with lactose and magnesium stearate~~	~~N/A~~
~~Dosage Form~~	~~Ellipta with 30 doses (1 strip with 30 blisters)~~	
~~Unit Dose Strengths~~	~~62.5 mcg per blister~~	~~N/A~~
~~Physical Description~~	~~Dry white powder~~	~~NA~~
~~Route of Administration~~	~~Inhaled~~	~~NA~~

~~1. Umeclidinium Inhalation Powder Ellipta will only contain one strip~~
~~N/A= not applicable~~

Table 3 Description of Placebo Inhalation Powder ELLIPTA

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

~~Formulation~~	~~**First strip**~~	~~**Second strip**~~
	~~Lactose with magnesium stearate~~	~~Lactose with magnesium stearate~~
~~Dosage Form~~	~~Ellipta with 30 doses (2 strips with 30 blisters per strip)~~	
~~Unit Dose Strengths~~	~~N/A~~	~~N/A~~
~~Physical description~~	~~Dry white powder~~	~~Dry white powder~~
~~Route of Administration~~	~~Inhaled~~	

~~1. N/A= not applicable~~

5.2 Treatment Assignment

Subjects will be assigned to study treatment in accordance with the central randomization schedule. The randomisation code will be generated by GSK using a validated computerised system ~~RandAll version 2.5~~. Subjects will be randomised using RAMOS

NG ~~IVRS, an Interactive Voice Response System (IVRS)~~. This is a internet ~~telephone-~~based system which will be used by the investigator or designee to register the subject (initially at pre-screening, and subsequently at each study visit), randomize the subject, and provide medication assignment information if and when required. Details on how to use RAMOS NG~~IVRS~~ to register and randomize subjects are provided in the SPM.

Following completion of the 7 to 14 day Run-In period eligible subjects will be randomized at 2:1 ~~1:1~~ ratio to one of the following treatment regimes in equal proportions

- Umeclidinium Inhalation Powder 62.5 mcg once daily
- Placebo Inhalation Powder once daily

Approximately 192 ~~the same number of~~ subjects will be randomised to active treatment ~~(n=227) as~~ and 96 subjects to placebo ~~(n=227)~~.

5.6.2 Prohibited Medications and Non-Drug Therapies

Table 4 Prohibited Medications

Oral leukotriene inhibitors (e.g. zafirlukast, montelukast, zileuton)

6. Study Assessments and Procedures

Table 5 Time and Events Table

		Run-in	Double-blind treatment period									
Visit	**Visit 0 (Pre-Screen)**	**Screening Visit (Visit 1)**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Early With-drawal (EW) Visit**	**Follow-Up (Phone contact)**
Day		**Day -7 to -14**	**Day 1**	**Day 2**	**Day 28±2**	**Day 56±4**	**Day 84±4**	**Day 112±4**	**Day 168±4**	**Day 169 (Visit 8 +1 day)**		**7±2 days after Visit 9 or EW**
Week		**-1**	**0**	**0**	**4**	**8**	**12**	**16**	**24**			
Register visit in ~~IVSR~~ IWRS[4] (RAMOS NG)	~~x~~	~~x~~	x	~~x~~	x	x	x	x	~~x~~	~~x~~	~~x~~	~~x~~
Adverse Event ~~/Con-Med Assessment~~		~~X~~	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event /Con-Med Assessment	X	X	X	X	X	X	X	X	X	X	X	X
Medication												
Dispense/collect rescue salbutamol/albuterol	X	X	X	X	X	X	X	X	X	X	X	

4.IWRS stands for Interactive Web Response System.

6.1 Critical Baseline Assessments

No study related procedures may be performed until the informed consent form document has been signed by the subject or legal deputy.

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

- Demographic history (including gender, ethnic origin, age, height and weight)
- COPD history
- COPD exacerbation assessment
- Review of COPD medication

6.3.4 Liver chemistry stopping and follow up criteria

- 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.

6.3.5 Adverse Events (AE) and Serious Adverse Events (SAEs)

6.3.5.1 Definition of ~~an~~ AEs

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

Events meeting the definition of an AE include:

- 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 fulfill the definition of an AE or SAE. ~~Also "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.~~

Events that **do not** meet the 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.
- ~~The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition~~.

6.3.5.2 Definition of ~~a~~ SAE**s**

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).

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:

- results in death
- 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.

- Requires hospitalization or prolongation of existing hospitalization~~, or~~

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.

- 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.

- Is a congenital anomaly/birth defect
- Other situations:

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- **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.

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

~~NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported~~

~~as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.~~

6.3.5.3 Recording of AEs and SAEs

- 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.

6.3.5.4 Evaluating AEs and SAEs

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.

6.3.5.5 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.

~~**6.3.6 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs**~~

~~Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs.~~

~~However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.~~

6.3.6 ~~6.3.7~~ Cardiovascular Events

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

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

~~This information should be recorded within one week of when the AE/SAE(s) are first reported.~~ The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

6.3.7 ~~6.3.8~~ Death Events

In addition, for all deaths, specific Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death. ~~will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.~~

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

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

6.3.9 ~~6.3.10~~ Pregnancy

Details of all pregnancies in female subjects will be collected after the start of dosing and until follow up call ~~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.

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. ~~The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child.~~

While pregnancy itself is not considered to be an AE or SAE, any 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 reasonably ~~possibly~~ related to the study treatment, must be promptly reported to GSK. 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.

6.3.11 ~~6.3.12~~ Time Period and Frequency of Detecting AEs and SAEs

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact, at the timepoints specified in the Time and Events Table. (China sites should follow Section 11.~~2~~1, Appendix ~~2~~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. (China sites should follow Section 11.~~2~~1, Appendix ~~2~~1)
- All SAEs will be recorded and reported to GSK within 24 hours as indicated in Section 6.3.12.
- 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.

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

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

~~SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study~~

~~up to and including any follow up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.3.10.~~

6.3.12 ~~6.3.13~~ Prompt Reporting of Serious Adverse Events and Other Events to GSK

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

- 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 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.

6.3.12.1 Regulatory Reporting Requirements for SAEs

Prompt notification ~~of SAEs~~ by the investigator to GSK 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.

6.5 Pharmacogenetic Research

This section was removed with alignment with PGx team.

8.2.1 Sample Size Assumption (TBD)

The sample size calculation is based on the primary endpoint of trough FEV_1 on Treatment Day 169 which will be analysed using a Mixed Models Repeated Measures~~d~~ (MMRM) analysis. The calculation uses an estimate of residual standard deviation of 234 ~~221~~mL, ~~(~~based on the residual standard deviation from the MMRM analysis of the meta-analyses from prior studies with UMEC in COPD (studies DB2113361, DB2113373, DB2113374) ~~HZC113684 study in COPD in North East Asian subjects). The variability observed in the global IIIa UMEC/VI studies (239 mL) was similar to that in the 6 month global FF/VI IIIa studies (248 mL) and therefore we would expect the variability in the UMEC China study to be similar to that in the FF/VI study~~ (~~Table 8~~).

~~Table 8 Studies for sample size calculation~~

~~Study~~	~~Duration~~	~~Centralised Spirometry~~	~~SD Trough FEV_1 at Week 24 (mL) (mean 23 & 24hr FEV_1)~~
~~DB2113360~~	~~24 Weeks~~	~~Yes~~	~~252~~
~~DB2113361~~	~~24 Weeks~~	~~Yes~~	~~224~~
~~DB2113373~~	~~24 Weeks~~	~~Yes~~	~~239~~
~~DB2113374~~	~~24 Weeks~~	~~Yes~~	~~240~~
~~HZC113684~~	~~24 Weeks~~	~~Yes~~	~~221~~
~~HZC112206~~	~~24 Weeks~~	~~Yes~~	~~252~~
~~HZC112207~~	~~24 Weeks~~	~~Yes~~	~~243~~

~~A study with 104 evaluable subjects per arm will have 90% power to detect a 100mL treatment difference between an active treatment and placebo in trough FEV_1.The calculations use a two-sample t-test and a two-sided 5% significance level~~.

Based on the Table 8 of effect sizes from previous studies, a true treatment difference of 115 mL has been assumed:

Table 8 Effect Sizes from Previous Studies

Study	Comparison	Treatment Difference
DB2113373 (Day 169)	UMEC vs Placebo	0.115
AC4115408 (Day 85)	UMEC vs Placebo	0.127
UMEC ISE (Day 169) (DB2113361, DB2113373, DB2113374)	UMEC vs Placebo	0.133
DB2114634 (Day 169)	UMEC/VI vs Placebo	0.151
DB2114634 (China) (Day 169)	UMEC/VI vs Placebo	0.167

The sample size ~~was increased in order~~ needs to include sufficient subjects to satisfy anticipated individual country requirements and the China subgroup is powered at 90% with a minimum of 100 evaluable subjects on UMEC arm gives 132 evaluable subjects on UMEC and 66 evaluable subjects on placebo is needed for China.

It is estimated that approximately 18% subjects will withdraw without providing a Week 24 assessment. Although, in MMRM, all available post-baseline assessments up to endpoint for subjects in the Modified Intent-to-Treat Population are utilized in the analysis, data for subjects who withdraw prematurely from the study are not explicitly imputed.

Allowing an 18% dropout, this would equate to 162 subjects randomised to UMEC and 81 subjects randomised to placebo from China.

45 randomised subjects from Korea will be sufficient, equating to 30 subjects randomised to UMEC and 15 subjects randomised to placebo. With an 18% withdrawal rate, this gives 24 evaluable subjects on UMEC and 12 evaluable subjects on placebo (allowing a 2:1 ratio).

We therefore require a total of approximately 192 randomised subjects on UMEC and 96 subjects randomised to placebo (total randomised 288).

Allowing for 18% dropout, a study with 156 evaluable subjects in active treatment arm and 78 evaluable subjects in placebo arm will have 94% power assuming a true treatment difference of 115mL to show a statistically significant difference between UMEC 62.5mcg and placebo in trough FEV_1. The calculations use a two-sample t-test and a two-sided 5% significance level.

The minimal detectable effect for the final sample size of 156 evaluable subjects on UMEC vs 78 evaluable subjects on placebo is 63.6mL.

~~China will have 90% power to detect a 100 mL treatment differences within the China subgroup, which will have 104 evaluable subjects per arm. Taiwan will include a total of 60 randomised subjects, Korea 100 randomised subjects and 30 subjects for Thailand. Assuming a 21% withdrawal rate (see below), Taiwan would therefore provide approximately 24 evaluable subjects per arm, Korea would provide approximately 40 evaluable subjects per arm and Thailand would provide approximately 12 evaluable subjects per arm. Therefore the total sample size would be 180 evaluable subjects per arm~~.

~~It is estimated that approximately 21% subjects will withdraw without providing a Week 24 assessment. Although, in MMRM, all available post-baseline assessments up to endpoint for subjects in the Intent-to-Treat Population are utilized in the analysis, data for subjects who withdraw prematurely from the study are not explicitly imputed. Hence, to account for a 21% withdrawal rate, approximately 227 subjects will be randomised in equal proportions in each of the two treatment groups. i.e. approximately 454 subjects will be randomised in total~~.

8.2.2 Sample Size Sensitivity

If the standard deviation in this study is different from the expected value, the power to detect the planned difference in trough FEV_1 will be affected. Table 9 illustrates the power which would be obtained with different values of SD, assuming the sample size remains constant at 156 evaluable subjects on UMEC vs 78 evaluable subjects on placebo ~~180 evaluable subjects in each treatment group~~.

Table 9 Power Calculation for Treatment Differences

Parameter	SD	Treatment Difference	Power
Trough FEV_1 (mL)	205	115~~100~~mL	98~~>99~~%
	240	115~~100~~mL	93~~98~~%
	260~~280~~	115~~100~~mL	88~~92~~%

If the SD for trough FEV_1 increased to 260~~280~~ mL, the study would have 88~~92~~% power to show a statistically significant difference between UMEC and placebo assuming a true treatment difference ~~detect a difference~~ of 115~~100~~ mL ~~between each treatment comparison~~. If the SD were as low as 205 mL then the study would have 98~~>99~~% power to show a statistically significant difference ~~detect a difference~~ of 115~~100~~ mL.

The true treatment difference for a statistically significant difference ~~which can be detected~~ with 90% power will also be affected by changes in the SD; this is shown in Table 10.

Table 10 Treatment Differences Detected with 90% Power

Parameter	SD	Power	Treatment Difference
Trough FEV_1 (mL)	205	90%	93~~70~~ mL
	240	90%	108~~82~~ mL
	260~~280~~	90%	117~~96~~ mL

If the SD increased to 260~~280~~ mL, the study would have 90% power to show a statistically significant treatment difference of 117 mL ~~detect a difference of 128 96 mL between each treatment comparison~~. If the SD were as low as 205 mL then the study would have 90% power to show statistical significance for a true treatment difference of 93 mL~~detect a difference of 70 mL~~.

8.3 Data Analysis Considerations

The analysis described below will be performed on all subjects enrolled from China and Korea~~, Taiwan, Korea and Thailand~~ and also a separate analysis will be performed on the subjects enrolled in China alone: A China subgroup analysis.

8.3.1 Analysis Populations

The modified **Intent-to-treat** (ITT) Population will comprise all subjects randomized to treatment who received at least one dose of randomized study medication in the treatment period. 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 constitute the primary population for all data analyses and displays. ~~Subjects will be included in the analysis of a particular outcome if they provided at least one on-treatment assessment of that outcome.~~ All scheduled data collected until the time of study discontinuation will be included in the Intent-to-treat analysis for subjects who withdraw from the study.

The **Per Protocol** (PP) Population will comprise all subjects in the Modified ITT Population who are not identified as full protocol violators. ~~Receipt of a study treatment other than the randomized treatment will be considered a full protocol deviation.~~ Receipt of a study treatment other than the randomized treatment will be considered a protocol deviation from the time of receiving incorrect treatment onwards. Subjects identified as partial protocol violators will be included in the PP Population but will have their data excluded from PP analyses from the time of violation onwards. The definition of full and partial violations will be included in the Reporting and Analysis Plan (RAP) ~~and the decision to exclude a subject from the PP Population or a subject's data from PP analyses will be made prior to breaking the blind~~. In addition, details of exclusions from the Per Protocol population/ analyses which are not considered to be protocol deviations, but may have a potential impact on the efficacy data will also be documented in the RAP. This population will be used for confirmatory analyses of the primary ~~and secondary~~ efficacy endpoints only, irrespective of how many subjects are in the PP population.

8.3.5 Key Elements of Analysis Plan

An overall analysis will be carried out including all countries~~/regions~~, and also a China subgroup analysis.

8.3.5.1 Efficacy Analyses

Primary Endpoint

The primary endpoint of change from baseline trough FEV_1 on Day 169 will be analysed for the Modified Intent-to-treat Population using a mixed model repeated measures (MMRM) analysis [Siddiqui, 2009], including trough FEV_1 recorded at each of Days 2, 28, 56, 84, 112, 168 and 169.

Treatment group (categorical) will be fitted as the explanatory variable with baseline FEV_1, ~~smoking status,~~ day, country~~/region~~, day by baseline interaction and day by treatment interaction fitted as covariates. Baseline FEV_1 is defined as the mean of the two assessments made pre-dose at Visit2. ~~Visit~~Day (nominal) will be fitted as a categorical variable and day ~~visit~~ by baseline and day ~~visit~~ by treatment interaction terms will be included to allow treatment effects to be estimated at each day ~~visit~~ separately. The variance-covariance matrix will be assumed unstructured (based on previous experience, no issues are expected with fitting models with this matrix structure).

Sensitivity analyses – Interactions:

Center grouping, ~~smoking status,~~ reversibility and ICS use.

Secondary Endpoints

The analysis of the mean TDI focal score on Days 28, 84 and 168 will use the same methodology as that for the primary endpoint but adjusting for BDI score instead of baseline FEV_1~~, including all sensitivity analyses but adjusting for (at a minimum) BDI score instead of baseline FEV_1~~.

Weighted mean clinic visit FEV_1 over 0 to 6 hours post-dose at Visit 2 (Day 1) will be analysed using analysis of covariance (ANCOVA). Treatment group (categorical) will be fitted as the explanatory variable with baseline FEV_1, ~~smoking status~~ and country~~/region~~ fitted as covariates. Baseline FEV_1 is defined as the mean of the two assessments made pre-dose at Visit2.

Estimated treatment differences for each treatment comparison will be presented together with 95% confidence intervals (CIs) for the difference and p-values.

Secondary endpoints will be analyzed for the Modified Intent-to-treat Population only.

Other Endpoints

Serial FEV_1 at 15 mins, 30 mins, 1, 3 and 6 hours after dosing will be analysed using a repeated measures model, including baseline FEV1, country~~/region~~, ~~smoking status,~~ treatment, time, time by treatment interaction and time by baseline interaction fitted as covariates. Baseline FEV1 is defined as the mean of the two assessments made pre-dose at Visit2. ~~Treatment, time and a time by treatment interaction term will be included.~~ This analysis will be performed for Day 1 only.

Time to onset of bronchodilation (defined as an increase of 100 mL in FEV_1 above baseline on Treatment Day 1 (Visit2)) and time to first COPD exacerbation will be compared between treatment groups using Cox's proportional hazards model.

Other endpoints will be analysed for the Modified Intent-to-treat Population only. Full details of the analyses to be performed will be provided in the RAP.

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11.1 Appendix 1: Pharmacogenetic Research

This section was removed with alignment with PGx team.

11.1 ~~11.2~~ Appendix 1~~2~~: Country Specific Requirements

For sites located in China, SAEs should be recorded from the time the consent form is signed until the follow-up contact.

The requirement on SAE collecting time period in Section 3.1, Section 4.6 and Section 6.3.11 is not appropriate for sites in China.

~~No country specific requirements exist.~~

The 12-Lead ECG Exclusion and Withdrawal Criteria have been updated as below. The underlined sections are those have been updated from the last version.

11.2 Appendix2: 12-Lead ECG Exclusion Criteria

An abnormal and clinically significant finding that would preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:

- Sinus tachycardia ≥120 bpm

*Note: sinus tachycardia ≥120bpm should be confirmed by two additional readings at least 5 minutes apart

- Sinus bradycardia <45bpm

*Note: Sinus bradycardia <45bpm should be confirmed by two additional readings at least 5 minutes apart.

- Multifocal atrial tachycardia
- Supraventricular tachycardia (>100bpm)
- Atrial fibrillation with rapid ventricular response (rate >120bpm)
- Atrial flutter with rapid ventricular response (rate >120bpm)
- Ventricular tachycardias (non sustained, sustained, polymorphic, or monomorphic)
- Ventricular flutter
- Ventricular fibrillation
- Torsades de Pointes

- Evidence of Mobitz type II second degree or third degree atrioventricular (AV) block
- AV dissociation
- Trifascicular Block
- For subjects **with QRS duration <120 ms**: QTc(F) ≥450msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).
- For subjects **with QRS duration>120**: QTc(F) ≥480msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).
- Myocardial infarction (acute or recent) * Note: Evidence of an old (resolved) myocardial infarction is not exclusionary.

~~An ECG finding that would preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:~~

- ~~Sinus tachycardia ≥110 bpm~~

~~*Note: sinus tachycardia ≥110bpm should be confirmed by two additional readings at least 5 minutes apart~~

- ~~Sinus bradycardia <45 bpm~~

~~***Note**: Sinus bradycardia <45 bpm should be confirmed by two additional readings at least 5 minutes apart.~~

- ~~Multifocal atrial tachycardia~~
- ~~Junctional tachycardia (heart rate >100 bpm)~~
- ~~Junctional escape complexes~~
- ~~Supraventricular tachycardia (>100 bpm)~~
- ~~Ventricular tachycardias (non-sustained, sustained, polymorphic, or monomorphic)~~
- ~~Atrial fibrillation with rapid ventricular response (rate >100 bpm)~~
- ~~Atrial flutter~~
- ~~Evidence of bigeminy, trigeminy or multifocal premature ventricular complexes~~
- ~~Ventricular flutter~~
- ~~Ventricular fibrillation~~
- ~~Torsades de Pointes~~
- ~~R on T phenomenon~~
- ~~Wide QRS tachycardia (diagnosis unknown)~~
- ~~Electrical alternans~~
- ~~Pacemaker~~

- ~~Idioventricular rhythm – heart rate <100 bpm~~
- ~~Evidence of Mobitz type II second degree or third degree atrioventricular (AV) block~~
- ~~2:1 AV block~~
- ~~AV dissociation~~
- ~~Bifascicular block~~
- ~~Trifascicular block~~
- ~~Left bundle branch block~~
- ~~For subjects **without complete right bundle branch block**: QTc(F) ≥450 msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).~~
- ~~For subjects **with complete right bundle branch block**: QTc(F) ≥480 msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).~~

~~***Note**: All potentially exclusionary QT measurements should be confirmed by two additional readings at least 5 minutes apart.~~

- ~~Accessory pathway (Wolff-Parkinson-White, Lown-Ganong-Levine)~~
- ~~Myocardial infarction (acute or recent)~~

~~***Note**: Evidence of an old (resolved) myocardial infarction is not exclusionary.~~

11.3 Appendix 3: 12-Lead ECG Withdrawal Criteria

An ECG finding that would result in subject withdrawal post-randomization is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:

- Sinus tachycardia ≥120 bpm

*Note: sinus tachycardia ≥120bpm should be confirmed by two additional readings at least 5 minutes apart

- Sinus bradycardia <37bpm

*Note: Sinus bradycardia <37 bpm should be confirmed by two additional readings at least 5 minutes apart.

- Increase in heart rate ≥40bpm relative to baseline

*Note: increase in heart rate ≥40bpm should be confirmed by two additional readings at least 5 minutes apart

- Multifocal atrial tachycardia
- Supraventricular tachycardia (>100bpm)
- Atrial fibrillation with rapid ventricular response (rate ≥120bpm)

- Atrial flutter with rapid ventricular response (rate >120bpm)
- Ventricular tachycardias (non sustained, sustained, polymorphic, or monomorphic)
- Ventricular flutter
- Ventricular fibrillation
- Torsades de Pointes
- Evidence of Mobitz type II second degree or third degree atrioventricular (AV) block
- AV dissociation
- Trifascicular Block
- An increase in QTcF>60 msec from baseline ECG
- Uncorrected QT>600 msec
- For subjects **with QRS duration <120 ms**: QTc(F) ≥500 msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).
- For subjects **with QRS duration>120 ms**: QTc(F) ≥530 msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).
- Myocardial infarction (acute or recent) Note: Evidence of an old (resolved) myocardial infarction is not exclusionary

~~An ECG finding that would result in subject withdrawal post-randomization is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:~~

- ~~Sinus tachycardia ≥110 bpm~~

~~***Note**: sinus tachycardia ≥110 bpm should be confirmed by two additional readings at least 5 minutes apart~~

- ~~Increase in heart rate ≥40 bpm relative to baseline~~
- ~~An increase in $QTc_{(F)}$ >60 msec from baseline ECG~~
- ~~Sinus bradycardia <37 bpm~~

~~***Note**: Sinus bradycardia <37 bpm should be confirmed by two additional readings at least 5 minutes apart.~~

- ~~Multifocal atrial tachycardia~~
- ~~Junctional tachycardia (heart rate >100 bpm)~~
- ~~Junctional escape complexes~~
- ~~Supraventricular tachycardia (>100 bpm)~~
- ~~Ventricular tachycardias (non-sustained, sustained, polymorphic, or monomorphic)~~

- ~~Atrial fibrillation with rapid ventricular response (rate >100 bpm)~~
- ~~Atrial flutter~~
- ~~Evidence of bigeminy, trigeminy or multifocal premature ventricular complexes~~
- ~~Ventricular flutter~~
- ~~Ventricular fibrillation~~
- ~~Torsades de Pointes~~
- ~~R on T phenomenon~~
- ~~Wide QRS tachycardia (diagnosis unknown)~~
- ~~Electrical alternans~~
- ~~Pacemaker~~
- ~~Idioventricular rhythm – heart rate <100 bpm~~
- ~~Evidence of Mobitz type II second degree or third degree atrioventricular (AV) block~~
- ~~2:1 AV block~~
- ~~AV dissociation~~
- ~~Bifascicular block~~
- ~~Trifascicular block~~
- ~~Left bundle branch block~~
- ~~For subjects **without complete right bundle branch block**: QTc(F) >500 msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).~~
- ~~For subjects **with complete right bundle branch block**: QTc(F) ≥530 msec or an ECG that is unsuitable for QT measurements (e.g., poor defined termination of the T wave).~~

~~***Note**: All potentially exclusionary QT measurements should be confirmed by two additional readings at least 5 minutes apart.~~

- ~~Accessory pathway (Wolff-Parkinson-White, Lown-Ganong-Levine)~~
- ~~QT >600 msec~~
- ~~Myocardial infarction (acute or recent)~~

~~***Note**: Evidence of an old (resolved) myocardial infarction is not exclusionary~~

11.4 Appendix 4

The algorithm was updated according to new protocol template.