200699: A Clinical Study to Evaluate Four Doses of Umeclidinium Bromide in Combination with Fluticasone Furoate in COPD Subjects with an Asthmatic Component

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Author(s): [Redacted]

Amendment No. 1 This amendment was implemented in order to modify the treatment duration of Phase B and visit windows of Phase B and Phase C. Updates were also made to clarify procedures, update inclusion/exclusion criteria, ensure consistency in the definition of severe exacerbation, and ensure the EXACT endpoint definition was consistent with the EXACT manual. Minor adjustments in wording were made to exploratory endpoints and statistical testing methods.

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FDA IND Number 112510
EudraCT Number: 2014-000883-16
INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 200699

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.

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LIST OF ABBREVIATIONS

ADaM  Analysis Data Model
ADME  Absorption, Distribution, Metabolism, Excretion
AE    Adverse Event
ALT   Alanine aminotransferase
AM    Ante Meridiem, before noon, morning
ANCOVA  Analysis of Covariance
AST   Aspartate aminotransferase
BMI   Body Mass Index
BPM   Beats Per Minute
BUN   Blood Urea Nitrogen
CDISC Clinical Data Interchange Standards Consortium
CI    Confidence Interval
CO2   Carbon dioxide
COPD  Chronic Obstructive Pulmonary Disease
CPK   Creatine Phosphokinase
CRF   Case Report Form
DNA   Deoxyribonucleic Acid
DPI   Dry Powder Inhaler
DRE   Drug-Related Event
E0    baseline effect
ECG   Electrocardiogram
eCRF  electronic Case Report Form
ED50  median Effective Dose
eDiary electronic Diary
EDTA  Ethylenediaminetetraacetic Acid
Emax  maximum Effect
FDA   Food and Drug Administration
FEV1  Forced Expiratory Volume in one second
FF    fluticasone furoate
FP    fluticasone propionate
FSC   FP/salmeterol combination
FVC   Forced Vital Capacity
GCP   Good Clinical Practice
GCSP  Global Clinical Safety and Pharmacovigilance
GGT   Gamma-Glutamyltransferase
GINA  Global Initiative for Asthma
GSK   GlaxoSmithKline
HBsAg Hepatitis B surface Antigen
hCG   human Chorionic Gonadotropin
HCV   Hepatitis C Virus
HIV   Human Immunodeficiency Virus
HPLC  High Performance Liquid Chromatography
IB    Investigator Brochure
ICH   International Conference on Harmonization
ICS   Inhaled Corticosteroid
IEC   Independent Ethics Committee
INN  International Non-proprietary Name
INR  International Normalized Ratio
IOP  Intraocular Pressure
IP   Investigational Product
IRB  Institutional Review Board
ITT  Intent-to-Treat
IUD  Intrauterine Device
IUS  Intrauterine System
IVRS Interactive Voice Response System
LABA Long-Acting Beta2-Agonist
LAMA Long-Acting Muscarinic Antagonist
LDH  Lactate Dehydrogenase
LSLV Last Subject Last Visit
LTRA Leukotriene Receptor Antagonist
MACE Major Adverse Cardiac Event
MAO  Monoamine Oxidase
mcg  Microgram
MDI  Metered Dose Inhaler
MedDRA Medical Dictionary for Regulatory Activities
mm  Millimetre
MSDS Material Safety Data Sheet
msec Millisecond
mV   Millivolt
NHANES National Health and Nutrition Examination Survey
NIH  National Institutes of Health
NYHA New York Heart Association
PEF  Peak Expiratory Flow
PGx  Pharmacogenetics
PK   Pharmacokinetics
PM   Post Meridiem, after noon, evening
RAP  Reporting and Analysis Plan
RNA  Ribonucleic Acid
SABA Short-Acting Beta2-Agonist
SAE  Serious Adverse Event
SDTM Study Data Tabulation Model
SGRQ St. George’s Respiratory Questionnaire
SPM  Study Procedures Manual
SRT  Safety Review Team
SVT  Supraventricular Tachycardia
ULN  Upper Limit of Normal
US   United States
VI   vilanterol trifenatate
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PROTOCOL SUMMARY

Rationale

Fluticasone furoate (FF) is an inhaled corticosteroid (ICS) and umeclidinium bromide (UMEC, GSK573719) is a potent, inhaled long-acting muscarinic antagonist (LAMA), both currently under development as monotherapy or in combination therapy for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Pre-clinical data and clinical studies indicate that FF and UMEC are effective for up to 24 hours. In order to provide a treatment option for COPD patients with an asthmatic component, the combination of a once-daily ICS and a once-daily LAMA is being studied.

The population of patients most likely to respond to the bronchodilatory effects of an inhaled muscarinic antagonist should have a high degree of cholinergic-induced bronchoconstriction. It is postulated that persistent obstruction (post-bronchodilator forced expiratory volume in one second to forced vital capacity \[\text{FEV}_1/\text{FVC}\] ratio <0.7) serves as a marker for high cholinergic tone. In support of these hypotheses, the benefit of LAMA therapy is well established in COPD, where the \[\text{FEV}_1/\text{FVC}\] ratio is diagnostic of the disease, and asthmatic subjects with \[\text{FEV}_1/\text{FVC}\] ratio <0.7 demonstrated greater responses to UMEC treatments than those >0.7 (ILA115938).

Objective(s)

Primary Objective(s)

- The primary objective is to evaluate the dose-response of once-daily umeclidinium bromide (UMEC) in combination with fluticasone furoate (FF) (100/15.6, 100/62.5, 100/125, and 100/250 mcg) compared to FF 100 mcg monotherapy over a 4-week treatment period in COPD subjects with an asthmatic component.

Secondary Objective(s)

- To evaluate the treatment effect of FF/UMEC compared to the combination of FF and vilanterol (VI) over a 4-week treatment period in COPD subjects with an asthmatic component

Exploratory Objective(s)

- To evaluate the treatment effect of VI in COPD subjects with an asthmatic component treated with FF/UMEC
- To evaluate the effect on lung function of discontinuing UMEC in COPD subjects with an asthmatic component
- To explore the relationship of patient reported outcomes (PROs) with patient characteristics such as level of reversibility and obstruction, diagnosis and other measures of disease severity
- To explore the responsiveness of PRO measures to response on other outcomes and determine potential responder definitions
• To determine differential responses and their phenotypic characteristics by exploratory and subgroup analyses

Other Objective(s)

• To evaluate the safety of FF/UMEC therapy.

Study Design

This study is a Phase IIb multicenter, randomized, double-blind, parallel-group design to evaluate the dose-response of 4 doses of UMEC in combination with FF (100/15.6, 100/62.5, 100/125, and 100/250 mcg) compared with FF 100 mcg monotherapy in COPD subjects with an asthmatic component. Subjects on an ICS-containing therapy over the previous 12 weeks, including a stable dose of ICS during the 4 weeks prior to Visit 0, will enter a 4-week run-in period on open-label fluticasone propionate (FP) 250 mcg and salmeterol 50 mcg combination (FSC). After the run-in period, eligible subjects will be stratified by smoking status and age when first treated with an inhaler and randomized to Treatment Phase A in a 1:1:1:1:2:2 ratio to FF 100 mcg, FF/UMEC 100/15.6 mcg, FF/UMEC 100/62.5 mcg, FF/UMEC 100/125 mcg, FF/UMEC 100/250 mcg, or FF/VI 100/25 mcg, respectively. After 4 weeks of treatment, subjects will enter Treatment Phase B and receive either FF/UMEC 100/250 mcg or FF/UMEC/VI 100/250/25 mcg for 1 week. Subjects will then enter Treatment Phase C where they will receive either the same treatment in Treatment Phase B or the same treatment minus the UMEC component for 1 week. All subjects will then complete a follow-up period of 7(±2) days. At this time, investigators should prescribe ongoing medication appropriate to the severity of the subject’s COPD or asthma in accordance with guidelines.

Study Endpoints/Assessments

Primary

• Change from baseline in clinic trough (pre-dose) FEV₁ at the end of Treatment Phase A

Secondary

• Mean change from baseline in rescue medication use at the end of Treatment Phase A
• Mean change from baseline in EXACT-RS score at the end of Treatment Phase A
• Change from baseline in daily morning (AM) PEF (pre-dose and pre-rescue bronchodilator) measured at home and averaged over the last 21 days of Treatment Phase A
• Change from trough in FEV₁ at 3 hours post-study treatment at Visit 5
• Change in clinic FEV₁ following 2 puffs of albuterol/salbutamol given 3 hours post-study treatment dose at Visit 5

Exploratory

• Change from baseline in clinic trough (pre-dose) FEV₁ at the end of Treatment Phase B
- The change from baseline in clinic trough FEV$_1$ at the end of Treatment Phase C (Visit 8) for the subset of subjects who have taken FF/UMEC or FF/UMEC/VI for two weeks over Treatment Phase B and Treatment Phase C
- Change from the end of Treatment Phase B clinic trough (pre-dose) FEV$_1$ to the end of Treatment Phase C
- Change in home daily FEV$_1$ during Treatment Phase C
- Change from baseline in home trough (pre-dose) FEV$_1$ over 1, 2, 3, and 4 weeks of Treatment Phase A
- Change from baseline in home trough (pre-dose) FEV$_1$ at the end of Treatment Phase A
- Change from baseline in daily home trough (pre-dose) FEV$_1$ averaged over Treatment Phase A
- The number of exacerbations during Treatment Phase A
- Incidence of symptom-defined events: Acute, sustained symptomatic worsening of COPD, defined as an increase in EXACT score $\geq$9 points for 3 days or $\geq$12 points for 2 days, above baseline during Treatment Phase A
- Mean change from baseline in EXACT-RS sub-scales of breathlessness, cough and sputum, chest symptoms at the end of Treatment Phase A
- Mean change from baseline in wheeze score at the end of Treatment Phase A
- Percent of patients with an improvement (decrease) of SGRQ $\geq$ 4 points from baseline at the end of Treatment Phase A
- Percent of patients with an improvement (decrease) of SGRQ $\geq$ 4 points from baseline in the domains of Symptoms, Activity and Impacts (Psycho-social) at the end of Treatment Phase A

Other

- Safety will be assessed by monitoring of adverse events (AEs), and physical examinations including vital signs, clinical laboratory assessments, oropharyngeal examination, and ECGs.

Exploratory Markers to Predict Responses

Subjects will be phenotyped during screening and during the randomization visit to assess predictors of response. Phenotyping will include measurement of:

- Baseline lung function and reversibility
- Patient disease history (e.g., exposure to smoke, pets, and family history), baseline demographics, medication history, smoking history, atopic status, presence of co-morbid conditions, and exacerbation history
- Environmental exposures and triggers
- Blood (eosinophils, neutrophils, total IgE)
1. INTRODUCTION

1.1. Background

Chronic obstructive pulmonary disease (COPD) is defined as expiratory airflow obstruction resulting primarily from cumulative exposure over decades to tobacco smoke and to pollution from the burning of biomass fuels [GOLD 2013]. However, as many as 20-23% of COPD patients have no known exposure to these offending agents but demonstrate COPD-like characteristics [Lamprecht, 2011]. This disease subset instead results from longstanding asthma and the airway remodeling that may accompany it. In either case COPD includes varying proportions of small airways disease and parenchymal destruction. In a subset of COPD patients with an asthmatic component (also referred to as partially reversible asthma; asthma with fixed, chronic or irreversible airflow obstruction; mixed asthma-COPD phenotype; or asthma-COPD overlap syndrome), reversibility of airflow obstruction is characteristic yet not sufficient to fully normalize lung function. The persistent obstruction is generally manifested in a post-bronchodilator forced expiratory volume in one second to forced vital capacity (FEV\textsubscript{1}/FVC) ratio of <0.7. Patients with persistent airflow obstruction have more symptoms, increased frequency and severity of exacerbations, increased diurnal variation in peak expiratory flow, increased airway wall thickness, and higher overall mortality than those without persistent obstruction [Hudon, 1997; Ulrik, 1999; ten Brinke, 2001; Diaz-Guzman, 2011; Louie, 2013].

Persistent airflow obstruction is characterized by airway narrowing and smooth muscle contraction as a consequence of the inflammatory process and increased neuronally-mediated airway smooth muscle contraction. The population of patients most likely to respond to the bronchodilatory effects of an inhaled muscarinic antagonist appear to have a high degree of cholinergic-induced bronchoconstriction. It is postulated that persistent airflow obstruction serves as a marker for high cholinergic tone. In support of these hypotheses, it is well known that patients with COPD respond to an anticholinergic, and the literature supports use of inhaled corticosteroid (ICS) therapy in certain COPD patients [Cazzola, 2013]. In a recent GlaxoSmithKline (GSK) study (ILA115938) asthmatic subjects with FEV\textsubscript{1}/FVC ratio <0.7 demonstrated greater responses to UMEC treatment than those with FEV\textsubscript{1}/FVC ratio >0.7. These observations suggest that the combination of a potent ICS and a long-acting muscarinic antagonist (LAMA), simultaneously targeting chronic inflammation and parasympathetic dysfunction, respectively, may be an ideal therapy for patients with persistent airflow obstruction.

1.2. Rationale

The combination of an ICS and a long-acting beta\textsubscript{2} agonist (LABA) is already well-established therapy in both COPD and asthma. It is, however, unclear how this therapy will compare to the ICS/LAMA combination in the management of patients with COPD with an asthmatic component.

Fluticasone furoate (FF) is an ICS and umeclidinium bromide (UMEC) is a potent inhaled LAMA, both currently under development (and approved in some countries in
combination with other agents) for the treatment of asthma and/or COPD. Pre-clinical data and clinical studies indicate that FF and UMEC are effective for up to 24 hours. In order to provide a treatment option for patients with persistent airflow obstruction, the combination of a once-daily ICS and a once-daily LAMA is being studied and its effect compared to the combination of FF and the once-daily LABA vilanterol (VI).

1.3. Benefit:Risk Assessment

GSK has developed an inhaled glucocorticoid (GW685698, fluticasone furoate [FF], International Non-proprietary Name [INN] fluticasone) for the once-daily treatment of asthma. Pre-clinical data indicate that FF has a prolonged duration of action, and this has been supported by the clinical pharmacology and clinical studies conducted to date. GSK has also developed an inhaled LAMA (GSK573719; INN umeclidinium bromide [UMEC]) for the once-daily treatment of COPD. UMEC is an orally inhaled quinuclidine derivative that is a potent, pan-active muscarinic antagonist. Clinical pharmacology studies to date have shown UMEC to be generally safe and well-tolerated and have confirmed that it has significant bronchodilatory activity with a 24-hour duration of action. UMEC is being developed as monotherapy for the treatment of COPD. The Phase III development program for UMEC in combination with VI for the treatment of COPD has been completed.

FF has been developed both as a monotherapy for asthma and in combination with a once-daily LABA, VI, for both asthma and COPD. The Phase III development programs for FF/VI for both asthma and COPD have been completed. FF/VI, UMEC/VI, and UMEC have been approved for COPD in certain countries.

Summaries of findings from both clinical and non-clinical studies conducted with FF/UMEC can be found in the Investigator’s Brochure (IB). Table 1 outlines the risk assessment and mitigation strategy for this protocol:
1.3.1. Risk Assessment

Table 1  Risk Rationale and Mitigation

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<th>Data/Rationale for Risk</th>
<th>Mitigation Strategy</th>
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| Pneumonia in patients with COPD        | Pneumonia is a class concern for any ICS-containing product for the treatment of COPD. In two replicate 12 month studies in the FF/VI clinical program, in a total of 3,255 patients with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia (6%-7%) reported in patients receiving the FF (at strengths of 50, 100, and 200 mcg)/VI 25 mcg combination than in those receiving VI 25 mcg alone (3%). In some instances these pneumonia events were fatal (including one fatality on the FF/VI 100/25 µg dose). Risk factors for pneumonia observed in these studies included current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m\(^2\) and patients with an FEV\(_1\)<50% predicted. These factors should be taken into consideration when using an ICS in patients with COPD. Pneumonia risk will be important in the benefit-risk assessment for FF/UMEC in COPD patients with an asthmatic component, hence a robust risk mitigation strategy is being proposed. | - Exclusion criteria as specified in Section 4.2.2 of the protocol  
- Collection of information on previous history of pneumonia in past 12 months, including hospitalisation at baseline  
- Use of pneumonia electronic case report form (eCRF)  
- All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an adverse event (AE) or serious adverse event (SAE) (if applicable).  
- CXR whenever a subject has suspected pneumonia or severe exacerbations during the study. CXRs for moderate exacerbations will be performed if clinically appropriate.  
- Instream review of blinded data |
<p>| Systemic effects of corticosteroids: bone disorders, bone mineral density decrease | A decrease in bone mineral density and the risk of fractures is a class concern for any ICS-containing product for the treatment of COPD. In two replicate 12 month studies in the FF/VI | - Evaluation of the potential for bone systemic corticosteroid effects will be conducted through assessment of |</p>
<table>
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<th>Mitigation Strategy</th>
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<td>and associated fractures</td>
<td>clinical program, in a total of 3,255 patients with COPD, the incidence of bone fractures overall was low in all treatment groups, with a higher incidence in all FF/VI groups (2%) compared with the VI 25 mcg group (&lt;1%). Although there were more fractures in the FF/VI groups compared with the VI 25 mcg group, fractures typically associated with corticosteroid use (e.g., spinal compression/thoracolumbar vertebral fractures, hip and acetabular fractures) occurred in &lt;1% of the FF/VI and VI treatment arms. As part of the FF/VI development program, a bone mineral density study with FF/VI is being conducted, and this will provide data relevant to FF/UMEC.</td>
<td>reported bone adverse events - Use of bone fracture eCRF</td>
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<td>Systemic effects of corticosteroids: cortisol suppression</td>
<td>Although all steroids are likely to have some impact on the hypothalamic-pituitary-adrenal (HPA) axis, the proposed doses of inhaled FF in this study are unlikely to lead to clinically significant changes. No studies have shown a clinically relevant effect of FF/VI on HPA axis. This includes a formal HPA study in asthma subjects, which assessed the effects of FF/VI 100/25 and 200/25 doses on serum cortisol and 24 hour urinary cortisol excretion, and multiple studies with COPD subjects which monitored 24 hour urinary cortisol. During clinical development of FF and FF/VI, no events of Adrenal Suppression were reported.</td>
<td>- Review AE/SAE reports</td>
</tr>
<tr>
<td>Systemic ocular effects of corticosteroids: glaucoma, cataract, raised intra-ocular pressure</td>
<td>Systemic ocular effects (e.g., cataract and glaucoma) may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. However, these effects are much less likely to occur with inhaled corticosteroids compared with oral corticosteroids. During studies with FF and FF/VI in asthma subjects, and with FF/VI and UMEC/VI in COPD subjects, no associated effect on ocular disorders was observed. In addition, no effects on lens</td>
<td>- As per Section 4.2.2 of the protocol, subjects with known narrow-angle glaucoma that, in the opinion of the study physician, contraindicates study participation or use of an inhaled anticholinergic, will be excluded from participating in this study.</td>
</tr>
<tr>
<td>Potential Risk of Clinical Significance</td>
<td>Data/Rationale for Risk</td>
<td>Mitigation Strategy</td>
</tr>
<tr>
<td>----------------------------------------</td>
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<tr>
<td>opacification were observed on formal ophthalmic assessments in a study with FF/VI, FF and fluticasone propionate (FP) in subjects with asthma.</td>
<td>- Review AE/SAE reports</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular effects of UMEC and VI</td>
<td>UMEC Cardiovascular effects are a potential class effect associated with anti-muscarinic therapies.</td>
<td>Mitigation strategy for UMEC and VI:</td>
</tr>
<tr>
<td></td>
<td>In the UMEC/VI clinical development program in COPD patients, UMEC/VI was generally well tolerated. Overall, a low number of atrial arrhythmias were reported based on 12-lead electrocardiograms (ECGs), Holter ECGs, or AEs, of which some occurred with a higher incidence in active treatment groups compared to placebo. There was no additive effect with the combination over individual components. Few of these findings were reported as SAEs and none were fatal. In a narrow* Major Adverse Cardiac Event (MACE) analysis, the incidence of non-fatal myocardial infarction (MedDRA PTs of myocardial infarction and acute myocardial infarction) was low (&lt;1%) across all treatment groups, although small imbalances in exposure-adjusted frequency were observed between UMEC- and VI-containing treatment groups when compared with placebo and tiotropium. There was no obvious dose relationship or additive effect from the combination. Whether this represents a true effect is difficult to determine due to the small numbers. During clinical studies in COPD (62.5 and 125 mcg daily dose of UMEC) and in Healthy Volunteers (in the thorough QT study, UMEC 500 mcg daily dose), no effect was observed on heart rate, blood pressure or QT.</td>
<td>- Exclusion criteria as specified in Section 4.2.2 of the protocol</td>
</tr>
<tr>
<td></td>
<td>VI</td>
<td>- Collection of cardiovascular risk factors and medical history at baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ECGs as per schedule in Table 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Vital sign assessments (heart rate and blood pressure) as per schedule in Table 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Cardiovascular eCRF for collection of AEs and SAEs (see Section 6.3.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Instream review of blinded data</td>
</tr>
<tr>
<td>Potential Risk of Clinical Significance</td>
<td>Data/Rationale for Risk</td>
<td>Mitigation Strategy</td>
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<tr>
<td></td>
<td>In the FF/VI clinical development program in patients with COPD, the cardiovascular safety profile of VI and FF/VI was broadly consistent with the known pharmacology of LABAs in patients with COPD. VI at doses up to 100 mcg in healthy subjects and subjects with asthma or COPD was not consistently associated with clinically relevant or statistically significant effects on blood pressure after either single or repeat dose administration. Data from Thorough QT (TQT) studies with FF, FF/VI and UMEC/VI suggest that, at the doses to be used in phase III studies, the closed triple (FF/UMEC/VI) is unlikely to cause clinically relevant effects on QTc. No difference in QTcF was observed between UMEC/VI 125/25 mcg or UMEC 500 mcg and placebo. UMEC/VI 500/100 mcg increased QTcF on average by 8.2 msec (90% CI: 6.2, 10.2) at 30 min only. A lack of effect was demonstrated for QTcF with FF/VI 200/25 mcg (for 7 days). At a supratherapeutic dose of FF/VI (800/100 mcg for 7 days), the largest mean time-matched difference from placebo was 9.6 msec (90% CI: 7.2, 12.0) at 30 min only.</td>
<td></td>
</tr>
<tr>
<td>Anticholinergic effects (including constipation nausea, dry mouth, glaucoma, raised intraocular pressure and blurred vision, urinary retention)</td>
<td>In clinical studies in COPD, few anticholinergic effects were associated with UMEC; those observed included dry mouth, constipation and cough. ICS has a similar class risk of glaucoma and elevated IOP; however these effects occur by a different mechanism that is not expected to be synergistic or additive when FF is used in combination with UMEC.</td>
<td>- Subjects with known narrow-angle glaucoma, prostatic hyperplasia or bladder outflow obstruction that in the opinion of the study physician contraindicates study participation or use of an inhaled anticholinergic, will be excluded from participating in the study. - Review AE/SAE reports</td>
</tr>
<tr>
<td>Pregnancy and</td>
<td>There has been limited pregnancy exposure of Females who are</td>
<td></td>
</tr>
</tbody>
</table>
### Potential Risk of Clinical Significance

<table>
<thead>
<tr>
<th></th>
<th>Data/Rationale for Risk</th>
<th>Mitigation Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>lactation</td>
<td>FF in humans. Animal studies have shown reproductive toxicity after administration of corticosteroids. There has been some post-marketing experience with FF in an intranasal formulation. No specific safety issues have been identified in regard to pregnancy. There is a limited amount of data from the use of umeclidinium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There is limited information on the excretion of FF or its metabolites in human milk. However, other corticosteroids are detected in human milk. It is unknown whether umeclidinium is excreted in human milk. The excretion of FF and UMEC in breast milk has not been evaluated. A risk to breastfed newborns/infants cannot be excluded.</td>
<td>pregnant or breast-feeding are not eligible for participating in the study. Females of child-bearing potential will need to follow the contraceptive requirements that are specified in the protocol.</td>
</tr>
</tbody>
</table>

| Hypersensitivity | Although not associated with intranasal FF during the clinical studies, hypersensitivity reactions have been observed, post-marketing, with the licensed intranasal spray, Avamys. In addition during the clinical studies for the FF inhaled formulation there were some reports of hypersensitivity-type reactions. There were few events reported in the asthma studies; however as there was limited, short, exposure to placebo, any comparison is not reliable. | Subjects with known immediate or delayed hypersensitivity reaction to a beta2-agonist, sympathomimetic drug, corticosteroid (i.e., intranasal, inhaled, or systemic therapy) or anticholinergic drug or sensitivity to the constituents of the dry powder inhaler (lactose or magnesium stearate) are excluded from participation in this study. |

### 1.3.2. Benefit Assessment

Currently, corticosteroids are the cornerstone of anti-inflammatory therapy for persistent asthma [GINA, 2012] and are also used in the treatment of COPD. FF is a novel corticosteroid with potent glucocorticoid activity, which in Phase III studies has been shown to be effective in maintaining asthma control. UMEC has been studied previously in the COPD population as a monotherapy and in combination with the LABA vilanterol and has demonstrated improvements in lung function and clinical symptoms in Phase III
Recent GSK clinical data as well as data from the literature [Kerstjens, 2011] demonstrated that the addition of a LAMA to the treatment of subjects with persistent asthma taking ICS-containing controller therapy offered significant improvement in lung function. The results of a Phase IIb dose-ranging study (ILA115938) showed improved lung function in subjects with asthma treated with the FF/UMEC combination, with a modest dose-ordering at higher doses. A pre-defined responder analysis showed the greatest response in subjects who had asthma with persistent obstruction.

The use of FF delivered in combination with a LAMA may provide an important once-daily alternative for the management of COPD patients with an asthmatic component, as not all patients may achieve control with an ICS and LABA combination. Additionally, patients can potentially benefit from a simplification of therapy when medications are combined in a single inhaler and require only once-daily dosing.

1.3.3. Overall Benefit:Risk Conclusion

The efficacy and safety of FF and UMEC in patients with COPD have been demonstrated in prior studies, and there is potential value of using an ICS + LAMA combination as a treatment option for COPD patients with an asthmatic component.

Taking into account the current safety experience with FF and UMEC and the anticipated benefits, the overall risk/benefit analysis supports the evaluation of FF/UMEC in this Phase IIb study for COPD with an asthmatic component.

2. OBJECTIVE(S)

Primary Objective(s)

- The primary objective is to evaluate the dose-response of once-daily UMEC in combination with FF (100/15.6, 100/62.5, 100/125, and 100/250 mcg) compared to FF 100 mcg monotherapy over a 4-week treatment period in COPD subjects with an asthmatic component.

Secondary Objective(s)

- To evaluate the treatment effect of FF/UMEC compared to the combination of FF and VI over a 4-week treatment period in COPD subjects with an asthmatic component

Exploratory Objective(s)

- To evaluate the treatment effect of VI in COPD subjects with an asthmatic component treated with FF/UMEC
- To evaluate the effect on lung function of discontinuing UMEC in COPD subjects with an asthmatic component
- To explore the relationship of patient reported outcomes (PROs) with patient characteristics such as level of reversibility and obstruction, diagnosis and other measures of disease severity
To explore the responsiveness of PRO measures to response on other outcomes and determine potential responder definitions

To determine differential responses and their phenotypic characteristics by exploratory and subgroup analyses

Other Objective(s)

- To evaluate the safety of FF/UMEC therapy

3. INVESTIGATIONAL PLAN

3.1. Study Design Schema

Figure 1 Study Design Schematic

3.2. 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 (Table 12), is essential and required for study conduct.

This study is a Phase IIb multicenter, randomized, double-blind, parallel-group design to evaluate the dose-response of 4 doses of UMEC in combination with FF (100/15.6, 100/62.5, 100/125, and 100/250 mcg) compared with FF 100 mcg monotherapy in COPD subjects with an asthmatic component. The FF/UMEC treatments will also be compared to the once-daily ICS/LAMA combination FF/VI. Subjects on an ICS-containing therapy over the previous 12 weeks, including a stable dose of ICS during the 4 weeks prior to Visit 0, will enter a 4-week run-in period on open-label FP 250 mcg and salmeterol 50 mcg combination (FSC). After the run-in period, eligible subjects will be stratified by smoking status and age when first treated with an inhaler and randomized to Treatment Phase A in a 1:1:1:1:2:2 ratio to FF 100 mcg, FF/UMEC 100/15.6 mcg, FF/UMEC 100/62.5 mcg, FF/UMEC 100/125 mcg, FF/UMEC 100/250 mcg, or FF/VI 100/25 mcg, respectively. After 4 weeks of treatment, subjects will enter Treatment Phase B and receive either FF/UMEC 100/250 mcg or FF/UMEC/VI 100/250/25 mcg for
1 week. Subjects will then enter Treatment Phase C where they will receive either the same treatment in Treatment Phase B or the same treatment minus the UMEC component for 1 week. All subjects will then complete a follow-up period of 7(±2) days. At this time, investigators should prescribe ongoing medication appropriate to the severity of the subject’s COPD or asthma in accordance with guidelines.

For determination of subject disposition, subjects will be considered to have completed the study upon completion of Visit 8 (the last on-treatment clinic visit).

Exploratory analyses will be carried out to better understand the response to UMEC in this patient population. Subjects will be phenotyped at the screening and randomization visits to assess predictors of response. Phenotyping will include measurement of spirometry, reversibility, extensive questionnaires to capture disease history, medication history, family history, smoking history, baseline demographics, environmental exposures, atopy, presence of co-morbid conditions, and exacerbation history. Blood (eosinophils, neutrophils, total IgE) and DNA will be collected and stored for future analysis.

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.

3.3. Discussion of Design

FSC 250/50 mcg has been selected as the run-in medication in order to standardize therapy prior to randomization and to facilitate LABA washout prior to procedures required for eligibility.

The primary study comparison is designed to demonstrate the added benefit of 4 doses of UMEC in combination with FF over FF alone. The safety and efficacy of FF 100 mcg once daily have been established in Phase II and Phase III studies in subjects with asthma and COPD. In addition, studies have demonstrated improvement in lung function with FF monotherapy in patients with COPD and reversible airflow obstruction. It is important to study FF/UMEC against a background of FF monotherapy, because data suggest that UMEC performs differently when used in combination with FF. UMEC doses have been selected as appropriate doses for a bronchodilator in this population based on the Phase IIb study ILA115938. Data from the Phase IIb study were combined with output from modelling and simulation (see Section 8.3.2) to determine the UMEC doses to be studied.

FF/VI has been selected to compare the treatment benefit of an ICS/LAMA to a once-daily ICS/LABA. Because of the severity of disease being studied, a placebo control is not considered appropriate. Similarly because of the use of an ICS monotherapy treatment arm, subjects with an FEV1 <50% of predicted normal are excluded. A dose response is expected to be demonstrated within two weeks. A 4-week treatment period is intended to evaluate that response with a longer treatment period.

Treatment Phase B aims to evaluate the incremental effect of vilanterol in subjects optimally treated with FF/UMEC. The 250 mcg dose of UMEC was selected based on
the known safety profile and the likelihood that this dose will produce maximal bronchodilation in this subject population.

The purpose of Treatment Phase C is to characterize the residual effect of UMEC once UMEC is removed from the therapeutic regimen.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

Approximately 500 COPD subjects with an asthmatic component will be screened in order to randomize 400 subjects. Of these, 320 are expected to be evaluable. This estimate assumes a potential screen-fail rate of approximately 20%.

4.2. Eligibility Criteria

Cigarette smoking history is neither an inclusion nor an exclusion criterion for this study, as the patient population of interest includes both smokers and non-smokers. However, randomization will be stratified by pack-years, capping the \( \geq 10 \) years (former and current) at 30% of the total population. Pack years will be determined by the following equation:

\[
\text{Pack-years} = \frac{\text{cigarettes per day}}{20} \times \text{years smoked}
\]

Example: 10 pack-years = 20 cigarettes/day \( \times \) 10 years or 

\[
= 10 \text{ cigarettes/day} \times 20 \text{ years}
\]

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

Subjects failing to meet eligibility criteria will not be allowed to re-screen for entry into the study. In addition to the study-specific criteria, investigators must exercise clinical discretion regarding selection of appropriate study subjects, taking into consideration any local treatment practices or guidelines and good clinical practice (GCP). When required, the GSK study medical monitor may be consulted for study-related medical questions.

Eligible subjects must:

- be able to understand and comply with protocol requirements, instructions, and restrictions;
- be likely to complete the study as planned (e.g., compliance with medication, ability to use the inhalation device correctly, maintaining visit schedule, completing daily diary record or conducting pulmonary function assessments)
- be considered appropriate candidates for participation in an investigative clinical trial with inhaled medication (e.g., no recent history of unstable COPD or asthma
[defined in Discontinuation Criteria, no historical or active substance abuse and no acute major organ disease]).

- not be affiliated with investigator’s site (e.g., an immediate family member of the participating investigator, sub investigator, study coordinator, or employee of the participating investigator).must have given their written informed consent to participate in the study. Written informed consent must be obtained if a subject’s current medication is changed as a result of study participation (e.g., withholding of albuterol for FEV₁ measurements or withholding of LABA prior to Visit 1) and the subject will be required to return to the clinic to complete the screening visit once the required wash-out has been completed.

### 4.2.1. 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.

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

1. **Age:** 18 years of age or older at Visit 0
2. **Diagnosis:** At the point of screening subjects, have sufficient medical history (e.g., signs and symptoms) to diagnose the subject as having COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society (Celli, 2004), AND evidence of an asthmatic component as demonstrated by spirometry, reversibility and current therapy at Visit 1 as follows:

   A. **Spirometry:**
      1. A best post-bronchodilator morning (AM) FEV₁ ≥50% and ≤80% of the predicted normal value at Visit 1. Predicted values will be based upon the ERS Global Lung Function Initiative [Quanjer, 2012].

      AND

      2. Pre- and post-bronchodilator FEV₁/FVC ratio <0.7 at Visit 1.

   B. **Reversibility of Disease:** defined as: ≥12% and ≥200 mL increase in FEV₁ between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol at Visit 1. If a subject fails to demonstrate an increase in FEV₁ ≥12% and ≥200 mL at Visit 1, then the subject will not be allowed to repeat spirometry at a subsequent visit to determine eligibility.

   C. **Current Therapy:** Subjects are eligible if they have received ICS-containing therapy for at least 12 weeks prior to Visit 1 and if their treatment during the 4 weeks immediately prior to Visit 1 consisted of either of the two regimens (1 or 2) below.

      1. A stable ICS dose taken alone (e.g., FP ≥200-1000 mcg daily or equivalent dose)

      OR
2. A stable dose of ICS (e.g., FP ≤500 mcg daily or equivalent dose) with adjunctive therapy (i.e., LABA, LAMA, leukotriene receptor antagonists [LTRA], theophylline, etc.). Subjects taking Symbicort as needed must switch to Symbicort maintenance dosing with as-needed use of a short acting beta2 agonist (SABA) for symptom relief at least 4 weeks prior to Visit 1.

Examples of acceptable doses of commonly prescribed ICS and ICS/LABA combination medication will be provided. Dosing regimen (once or twice daily to equal the total daily dose) should be restricted to the current local product labels.

3. **Short-Acting β\textsubscript{2} Agonists (SABAs):** All subjects must be able to replace their current SABA inhaler with albuterol/salbutamol aerosol inhaler at Visit 1 as needed for the duration of the study. Subjects may instead use their own nebulized albuterol/salbutamol as needed, if this method is preferred. Subjects must be judged capable of withholding albuterol/salbutamol for at least 4 hours prior to study visits.

4. **Type of Subject:** Outpatient subjects who are smokers or non-smokers

5. **Gender:** Male or Eligible Female, defined as having documentation of non-childbearing potential or childbearing potential as follows:

   - 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).
   
   - OR

   Child bearing potential: Has a negative pregnancy test at screening and agrees to use an acceptable contraceptive method 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).

   The following is the GSK list of acceptable, highly effective methods for avoiding pregnancy with failure rates of less than 1% per year:

   - Abstinence from penile-vaginal intercourse when this is the female’s preferred and usual lifestyle [Hatcher, 2007a]
   - Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a]
   - Injectable progestogen [Hatcher, 2007a]
   - Implants of etonogestrel or levonorgestrel [Hatcher, 2007a]
   - Estrogenic vaginal ring [Hatcher, 2007a]
   - Percutaneous contraceptive patches [Hatcher, 2007a]
   - Intrauterine device (IUD) or intrauterine system (IUS) with a failure rate <1% per year as stated in the product label [Hatcher, 2007a]
   - 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 [Hatcher, 2007a]. For this definition, “documented” refers to the outcome of the investigator's/designee’s medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject’s medical records.

- Male condom combined with a female diaphragm either with or without a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2007b]

Female subjects should not be enrolled if they are pregnant or lactating or if they plan to become pregnant during the time of study participation. Serum and urine pregnancy testing is required of all females of child bearing potential as defined in the Time and Events table (Table 12).

4.2.2. Exclusion Criteria

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

1. History of Life-threatening Respiratory Event: Defined for this protocol as an episode that required intubation and/or was associated with hypercapnea, respiratory arrest or hypoxic seizures within the last 5 years.

2. Respiratory Infection: Any infection of the upper or lower respiratory tract, sinus, or middle ear that is not resolved within 4 weeks of Visit 1 and led to a change in COPD/asthma management or, in the opinion of the investigator, is expected to affect the subject’s COPD/asthma status or the subject’s ability to participate in the study.

3. Severe Exacerbation: A subject must not have had an exacerbation prior to Visit 1 meeting either of the following criteria:
   - Deterioration of COPD or asthma requiring either the use of oral corticosteroids for at least 3 days or parenteral corticosteroids in the previous 3 months.
   - An in-patient hospitalization or emergency department visit due to COPD or asthma that required any oral or parenteral corticosteroids in the previous 6 months

For consistency, courses of corticosteroids separated by 1 week or more should be treated as separate exacerbations.

4. Risk Factors for Pneumonia: Immune suppression (e.g., Human Immunodeficiency Virus [HIV], Lupus) or other risk factors for pneumonia (e.g., neurological disorders affecting control of the upper airway, such as Parkinson’s Disease, Myasthenia Gravis)

Subjects at potentially high risk (e.g., very low body mass index [BMI] or severely malnourished) will only be included at the discretion of the investigator.

5. Pneumonia: Hospitalization for pneumonia within 3 months prior to Visit 1.

6. Concurrent Respiratory Disease: A subject must not have current evidence of the following: pneumonia, pneumothorax, atelectasis (segmental or larger), pulmonary fibrotic disease, bronchopulmonary dysplasia, or other respiratory abnormalities
other than chronic obstructive pulmonary disease (including chronic bronchitis and emphysema) or asthma. 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 is exclusionary. If there is a question, the medical monitor for the study may be contacted.

7. **Other Concurrent Diseases/Abnormalities:** A subject must not have any clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the subject at risk through study participation or would confound the interpretation of the efficacy results if the condition/disease exacerbated during the study. Examples are outlined in the table below. The investigator is encouraged to contact the study medical monitor if further clarification is warranted.

The list of additional excluded conditions/diseases includes, but is not limited to, the following:

### Table 2 Exclusionary Concurrent Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison’s disease</td>
<td>Malignancy¹ (current)</td>
</tr>
<tr>
<td>Alpha 1 antitrypsin deficiency causing COPD</td>
<td>Peptic ulcer (recent or poorly controlled)</td>
</tr>
<tr>
<td>Cushing’s disease</td>
<td>Stroke within 3 months of Visit 1</td>
</tr>
<tr>
<td>Haematological disease</td>
<td>Tuberculosis (current or untreated²)</td>
</tr>
<tr>
<td>Immunologic compromise</td>
<td></td>
</tr>
</tbody>
</table>

1. A history of malignancy is acceptable only if subject has been in remission for one year prior to Visit 1 (remission = no current evidence of malignancy and no treatment for the malignancy in the 12 months prior to Visit 1).
2. Subjects with a history of tuberculosis infection who have completed an appropriate course of antituberculosis treatment may be suitable for study entry provided that there is no clinical suspicion of active or recurrent disease.

8. **Viral Hepatitis and HIV:** A positive Hepatitis B surface antigen or positive Hepatitis C antibody pre-study or at Visit 1. Subjects with HIV-positive history are not eligible.

9. **Hepatic Impairment:** Current or chronic history of liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert’s syndrome or asymptomatic gallstones).

10. **Allergies:**
    - Drug Allergy: Any immediate or delayed hypersensitivity reaction to a β₂ agonist, sympathomimetic drug, corticosteroid (i.e., intranasal, inhaled, systemic therapy) or anticholinergic drug. Known or suspected sensitivity to the constituents of the dry powder inhaler (DPI) (i.e., lactose or magnesium stearate).
    - Milk Protein Allergy: History of severe milk protein allergy.

11. **Concomitant Medication:** Administration of prescription or over-the-counter medication that would significantly affect the course of COPD or asthma, or interact with study drug, such as:
• Anticholinergic medications, with the exception of those used for gastrointestinal or genitourinary conditions such as overactive bladder or those which have minimal systemic effects
• Potent Cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, clarithromycin)
• Anticonvulsants (barbiturates, hydantoins, carbamazepine)
• Polycyclic antidepressants
• Phenothiazines
• Monoamine oxidase (MAO) inhibitors

**Table 3 Concomitant Respiratory Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>No use within the following time interval before visit 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous, intramuscular (including depot), intra-articular, or oral corticosteroids</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Inhaled short-acting anticholinergics</td>
<td>6 hours</td>
</tr>
<tr>
<td>Inhaled short-acting anticholinergics+ Short-acting beta agonist combination</td>
<td>6 hours</td>
</tr>
<tr>
<td>Inhaled long-acting anticholinergics</td>
<td>7 days</td>
</tr>
<tr>
<td>Anti-IgE (e.g., Xolair)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Immunosuppressive medications including immunomodulators</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Allergen immunotherapy for the treatment of allergies</td>
<td>Allowed during the study provided it was initiated at least 4 weeks prior to Visit 1 and the subject remains in the maintenance phase throughout the study</td>
</tr>
<tr>
<td>Inhaled long-acting beta₂-agonists (e.g., salmeterol, formoterol) or combination products containing inhaled long-acting beta₂-agonists (e.g., Seretide, Symbicort) Inhaled very long-acting beta₂-agonists, (Vilanterol, Indacaterol, Olodaterol) Oral long-acting beta₂-agonists (e.g., bambuterol)</td>
<td>Must be withheld after the morning dose on the day before the visit (for Visits 1, 2, and 3)</td>
</tr>
<tr>
<td></td>
<td>10 days for Vilanterol, Indacaterol and Olodaterol component</td>
</tr>
<tr>
<td>Inhaled short-acting beta₂-agonist (rescue albuterol/salbutamol is permitted during the study)</td>
<td>4 hours (including all study visits)</td>
</tr>
<tr>
<td>Theophyllines, anti-leukotrienes, slow-release bronchodilators, ketotifen, nedocromil sodium, sodium cromoglycate, roflumilast</td>
<td>48 hours</td>
</tr>
<tr>
<td>Any other investigational drug</td>
<td>30 days or within 5 drug half-lives of the investigational drug (whichever is longer)</td>
</tr>
</tbody>
</table>

12. **Lung Resection:** Subjects with lung volume reduction surgery within 12 months prior to Visit 1.

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) of short-acting bronchodilators (e.g., albuterol/salbutamol) via nebulized therapy. As-needed nebulized albuterol/salbutamol use is not exclusionary.

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. **Unstable or life-threatening cardiac disease:** Subjects with any of the following at screening (Visit 1) would be excluded:
   - Myocardial infarction or unstable angina in the last 6 months
   - Unstable or life-threatening cardiac arrhythmia requiring intervention in the last 3 months
   - NYHA Class IV Heart failure

17. **Abnormal and clinically significant 12-Lead ECG finding:** Investigators will be provided with ECG reviews conducted by a centralized independent cardiologist to assist in evaluation of subject eligibility. The investigator will determine the clinical significance of each abnormal ECG finding in relation to the subject’s medical history and exclude subjects who would be at undue risk by participating in the trial, and the subject would be considered a run-in failure. An abnormal and clinically significant finding that would preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:
   - AF with rapid ventricular rate >120 BPM
   - Sustained or nonsustained VT
   - Second degree heart block Mobitz type II and third degree heart block (unless pacemaker or defibrillator had been inserted)
   - QTcF ≥500 msec in subjects with QRS ≤120 msec
   - QTcF ≥530 msec in subjects with QRS >120 msec

18. **Diseases Preventing Use of Anticholinergic:** Subjects with medical conditions such as narrow-angle glaucoma, prostatic hyperplasia, or bladder neck obstruction should only be included if, in the opinion of the investigator, the benefit outweighs the risk.

### 4.2.3. Randomization Inclusion Criteria

1. **FEV$_1$:** Post-bronchodilator morning (AM) FEV$_1$ ≥50% and ≤80% of the subject’s predicted normal at Visit 2
2. **FEV$_1$/ FVC Ratio:** Pre- and post-bronchodilator FEV$_1$/ FVC ratio <0.7 at Visit 2
3. **Reversibility of Disease:** Reversibility of Disease defined as: ≥12% and ≥200 mL increase in FEV$_1$ between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol inhalation aerosol at Visit 2. If a subject fails to demonstrate an increase in FEV$_1$ ≥12% and ≥200 mL at Visit 2, then the subject will not be allowed to repeat spirometry at a subsequent visit to determine eligibility.
4. **Medication Compliance**: Subjects must have recorded the use of FSC twice daily during the run-in on \( \geq 5 \) of the last 7 consecutive days of the run-in period.

5. **Diary Compliance**: Subjects must have recorded daily diary assessments for symptoms and rescue medication use on \( \geq 5 \) of the last 7 consecutive days of the run-in period.

### 4.2.4. Randomization Exclusion Criteria

1. **Unacceptable Spirometry**: Spirometry at Visit 2 determined to be unacceptable by the central spirometry overread process.

2. **Abnormal Laboratory Finding**: Evidence of clinically significant abnormal laboratory tests during Visit 1, which are still abnormal upon repeat testing. Each investigator will use his/her own discretion in determining the clinical significance of the abnormality. When in doubt, GSK medical monitor, or designee, should be notified so that a joint decision can be made.

3. **Change in Respiratory Medication**: Changes in COPD or asthma medication occurring between Visit 1 and Visit 3. (This exclusion does not include the changes in the study-supplied medications used during the run-in period.)

4. **Infection**: Occurrence of a culture-documented or suspected infection of the upper or lower respiratory tract, sinus, or middle ear during the run-in period that led to a change in COPD or asthma management or, in the opinion of the investigator, is expected to affect the subject’s COPD or asthma status or the subject’s ability to participate in the study.

5. **Evidence of a Severe Exacerbation**: A subject must not have had an exacerbation between Visit 1 and Visit 3 meeting either of the following criteria:
   - Deterioration of COPD or asthma requiring the use of oral corticosteroids for at least 3 days or parenteral corticosteroids
   - An in-patient hospitalization or emergency department visit due to COPD or asthma that required any oral or parenteral corticosteroids

   For consistency, courses of corticosteroids separated by 1 week or more should be treated as separate exacerbations.

6. **Device Use**: Subject is unable to use the inhaler correctly after three separate demonstrations at Visit 3.

7. **Liver Function Tests at Visit 1** (as below and further defined in the study procedure manual):
   - ALT > 2 x upper limit of normal (ULN)
   - Alkaline Phosphatase > 1.5 x ULN
   - Bilirubin > 1.5 x ULN (isolated bilirubin > 1.5 ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

8. **Change in FEV\(_1\)**: A study subject will be excluded if he/she has experienced a change (increase or decrease) in absolute FEV\(_1\) of \( \geq 25\% \) compared with the FEV\(_1\)
measurement at Visit 1, and in the investigator’s clinical judgment, continuing in the study poses a safety risk to the subject.

9. **Unstable or life threatening cardiac disease:** subjects who experienced any of the following between Visit 1 and Visit 3 will be excluded:
   - Myocardial infarction or unstable angina
   - Unstable or life threatening cardiac arrhythmia requiring intervention
   - NYHA Class IV Heart failure

10. **Abnormal and clinically significant 12-Lead ECG finding at Visit 1:**
    Investigators will be provided with ECG reviews conducted by a centralized independent cardiologist to assist in evaluation of subject eligibility. The investigator will determine the clinical significance of each abnormal ECG finding in relation to the subject’s medical history and exclude subjects who would be at undue risk by participating in the trial. An abnormal and clinically significant finding that would preclude a subject from entering the trial is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:
    - AF with rapid ventricular rate >120 BPM
    - Sustained or nonsustained VT
    - Second degree heart block Mobitz type II and third degree heart block (unless pacemaker or defibrillator had been inserted
    - QTcF ≥500 msec in patients with QRS ≤120 msec and QTcF ≥530 msec in patients with QRS >120 msec.

### 4.3. Permanent Investigational Product (IP) Discontinuation

Subjects have the right to stop taking IP before the end of the study. A subject may also be asked to stop IP at the investigator’s discretion. However, subjects who have permanently discontinued IP are not required to withdraw from the study.

In the event that a subject permanently discontinues IP before the end of the randomized treatment period, every effort will be made by the investigator to encourage the subject to remain in the study and to complete all remaining study visits by telephone contact. In the event a subject discontinues IP at a scheduled visit, all study procedures scheduled for the IP Discontinuation/Early Withdrawal (EW) visit should be performed at this visit instead. In the event a subject discontinues IP between visits, the subject should be asked to return to the clinic as soon as possible to complete the IP Discontinuation/EW visit procedures. The investigator must document the reason for discontinuation of IP in the eCRF. The investigator/site staff should contact the subject by phone at the protocol designated visit time intervals to complete the assessment of exacerbations, SAEs, and concomitant medications.

**General Discontinuation Requirements**

Subjects may be discontinued from IP at any time if it is considered to be detrimental for them to continue study treatment. Reasons for discontinuation can include the following:
an adverse event, lost to follow-up, protocol violation, lack of efficacy, sponsor
terminated study, persistent non-compliance, pregnancy, an abnormal liver function test,
abnormal laboratory results, or any other reasons identified by the investigator or study
sponsor.

Once a subject is randomized to investigational product, at a minimum, the subject’s vital
status will be tracked for the duration of the study via either telephone contact or a
Follow-Up visit.

Subects who are discontinued from IP will not be replaced. A subject who is
discontinued from IP after being randomized to treatment cannot be re-screened.

4.3.1. Protocol-Defined IP Discontinuation Criteria

Discontinuation of IP Required by Investigator

A subject MUST DISCONTINUE IP if any of the following occurs:

1. **Severe Exacerbation** defined as either of the following:
   - Deterioration of COPD or asthma requiring either the use of oral corticosteroids
     for at least 3 days or parenteral corticosteroids
   - An in-patient hospitalization or emergency department visit due to COPD or
     asthma that required any oral or parenteral corticosteroids

2. **Additional Maintenance Therapy:** A subject requires additional therapy for the
   control of COPD or asthma symptoms.

3. **Liver Chemistry:** Liver chemistry stopping criteria are met (See Appendix 3)

4. **Pregnancy:** A subject becomes pregnant

5. **ECG Abnormalities:** An increase in QTcF by >60 msec or to a QTcF >530 msec
   (based on an average of triplicate ECGs)

   **NOTE:** These criteria should be based on the average QTcF value of triplicate ECGs.
   For example, if an ECG demonstrates a prolonged QT interval, two more ECGs will be
   obtained over a brief period and then the averaged QTcF values of the three ECGs will be
   used to determine whether the subject should be discontinued from IP.

6. **Adverse Event:** A subject has an adverse event that would, in the investigator’s
   judgment, make continuing IP an unacceptable risk.

7. **Unblinding:** The treatment blind is broken for a subject by site personnel

8. **Study Discontinued:** GSK discontinues the study

Discontinuation of IP per Investigator Discretion

1. **Signs of Unstable COPD or asthma:** The following are signs and symptoms that
   may suggest worsening COPD or asthma and require the investigator to apply clinical
   judgment to ensure subject safety. A subject’s past medical history, severity and
duration of current symptoms, awareness of symptoms, proximity to emergency care,
   adherence to study medications, and potential study treatments are key considerations
   in determining whether a subject may remain on IP.
2. The investigator should consider, but not be limited by, the following clinical parameters to determine if the subject may continue on IP:

- Excessive albuterol/salbutamol use (i.e., ≥12 inhalations of albuterol/salbutamol in a 24 hour period)
- Decrease in PEF (i.e. 2 or more consecutive days in which the PEF has fallen below the PEF Stability Limit calculated at randomization)
- Severe COPD or asthma symptoms that persist throughout the day
- Persistent nighttime awakening due to COPD or asthma and requiring albuterol/salbutamol
- Clinic FEV$_1$ decreased below the FEV$_1$ stability limit value calculated at randomization.

4.3.2. IP Discontinuation Study Assessments

The investigator must make every effort to have the subject return to the clinic as soon as possible after the subject permanently discontinues IP (or informs him they wish to withdraw from study) in order to complete the IP Discontinuation/EW. The evaluations and procedures as outlined in the Time and Events table (Table 12) should be completed and recorded in the eCRF as required.

A safety follow-up contact as described in Table 12 should be conducted 7 days following completion of the IP Discontinuation/EW visit.

4.3.3. Reasons for Permanent Discontinuation of IP

The primary reason for permanent discontinuation of IP will be recorded in the eCRF. Specific regard should be given to distinguishing permanent discontinuation of IP due to an adverse event from other reasons for permanent discontinuation of IP.

The primary reason for permanent discontinuation of IP will be categorized as:

1. Adverse event
2. Lack of efficacy, including exacerbations not defined as SAEs
3. Protocol deviation
4. Subject reached protocol-defined stopping criteria
   - ECG abnormality
   - Lab abnormality (Liver event or Pregnancy)
   - Non-compliance
5. Study closed/terminated
6. Lost to follow-up
7. Investigator discretion
8. Withdraw consent
   • Subject relocated
   • Frequency of visits
   • Burden of procedures
   • Other (specify)

4.4. Withdrawal Criteria

For this study there are no pre-determined protocol specific study withdrawal criteria (see Section 4.3.1 for protocol defined stopping IP criteria).

If a subject meets IP discontinuation criteria, at a minimum, the subject’s vital status will be tracked for the duration of the study via either telephone contact or a Follow-Up visit. Every effort should be made by the investigator to keep the subject in the study. However a subject may voluntarily withdraw from participation in this study at any time. The investigator may also, at his or her discretion, withdraw a subject from further study participation. Subjects who are withdrawn from the study will not be replaced.

4.4.1. Withdrawal from study

Subjects have the right to withdraw from the study and to withdraw their consent for further participation in the study (i.e., this precludes continued data collection).

The investigator must document the reason (if specified by the subject) for withdrawal of consent in the eCRF. Subjects who wish to withdraw from further participation in the study should be encouraged to return to the clinic as soon as possible to complete the IP Discontinuation/EW Visit and to complete the safety follow-up visit in order to collect important safety information.

No further study visits or study-related telephone contacts can be conducted unless the subject’s consent allows for contact after withdrawing from the study then every effort should be made by the investigator and site to determine the subject’s survival status at the end of the study.

NOTE: If contact is lost with the subject, only the specific additional actions as clearly outlined in each subject’s Informed Consent form (e.g., attempt contact with subject’s listed contact and/or a primary care physician; request access to the subject’s medical record) should be attempted to collect survival status.

4.4.2. Study Withdrawal assessments

Subjects who are on IP and wish to withdraw from further participation in the study should be encouraged to return to the clinic as soon as possible to complete the IP Discontinuation/EW Visit assessments (Table 12) and to complete the safety follow-up contact 7 days later.
Subjects who have previously discontinued IP (and have already completed their IP Discontinuation/EW Visit and safety follow-up contact) but then decide that they no longer wish to participate in the study, may withdraw from the study by contacting the site by telephone to notify the site of their intention to withdraw; no additional safety follow-up visit is required.

4.4.3. Lost to follow-up

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study based on previous non-compliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and, if necessary, a certified letter to the subject’s last known mailing address) so that he/she can appropriately be withdrawn from the study. These contact attempts should be documented in the subject’s medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of “Lost to Follow-up”. For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF. Every effort should be made to collect survival status (whether the subject is still alive).

NOTE: If contact is lost with the subject, only the specific additional actions as clearly outlined in each subjects Informed Consent form (e.g., attempt contact with subject’s listed contact and/or a primary care physician; request access to the subject’s medical record) should be attempted to collect survival status.

4.4.4. Reasons for Study Withdrawal

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

The primary reason for study withdrawal will be categorized as:

1. Adverse event
2. Study closed/terminated
3. Lost to follow-up
4. Investigator Discretion
5. Withdrew consent
   - Subject relocated
   - Frequency of visits
   - Burden of procedures
   - Other (specify)
4.5. **Screening/Run-in Failures**

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

A subject who is assigned a subject number but does not have 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 is classified as a ‘screen failure’. A subject who completes the screening visit (Visit 1) and is dispensed medication and diary cards (eDiary and paper Medical Problems/Medications Taken diary) is considered to have entered the Run-In Period.

A subject who has entered the Run-in Period, but is found to be ineligible for the study based on procedures conducted during Visit 1 through Visit 3 (e.g., laboratory, ECG, spirometry) and is not randomized to the Treatment Phase, is classified as a ‘run-in 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:

1. Date of informed consent form (ICF) signature
2. Details of COPD or asthma medications within 30 days of Visit 0
3. Details of COPD or asthma exacerbation (yes/no status), if applicable
4. SAE 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

The IVRS will be contacted to report screen and run-in failures. In addition to the information above, the following information will be collected for screen and run-in failures:

1. Date of clinic visit
2. Reason for screen or run-in failure (inclusion/exclusion or randomization criteria)

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

4.6. **Premature Discontinuation**

Subjects will be considered to have completed the study upon completion of Visit 8 study procedures. Any subject who is randomized to double-blind medication and, for any reason, withdraws consent prior to completion of the Visit 8 procedures has not completed the study.
5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

All medications will be manufactured by GSK.

The DISKUS™ device will be used for the Run-In Phase of the study. The DISKUS is a plastic inhalation delivery system containing a double-foil blister strip of a powder formulation of FSC intended for oral inhalation only. Each blister on the double-foil strip within the device contains 250 mcg of microfine FP and 72.5 mcg of microfine salmeterol xinafoate salt, equivalent to 50 mcg of salmeterol base, in 12.5 mg of formulation containing lactose. Each blister contains 1 complete dose of both medications.

The ELLIPTA™ device will be used in Treatment Phases A, B, and C. The ELLIPTA DPI is a molded plastic two-sided device that can hold two individual blister strips. For the combination FF/UMEC product one strip will contain FF (blended with lactose) and the other strip will contain umeclidinium (blended with lactose and magnesium stearate). FF monotherapy will contain FF blended with lactose in one strip and a blend of lactose and magnesium stearate in the second strip. For the combination FF/VI product, one strip will contain FF (blended with lactose) and the other strip will contain VI (blended with lactose and magnesium stearate).

For Treatment Phase B the FF/UMEC/VI treatments will be provided in two inhalers, one device containing FF and UMEC as described above and the other device containing VI (one strip containing VI blended with lactose and magnesium stearate and one strip containing lactose). The FF/UMEC treatments in Treatment Phase B will also have two devices; one device with FF/UMEC as described above and the other a dual-strip placebo device.

Treatments in Treatment Phase C will also be delivered in two devices to retain the blind. The FF/UMEC/VI treatment will consist of one device containing FF and UMEC as described above and the other device containing (one strip containing VI blended with lactose and magnesium stearate and one strip containing lactose). The FF/UMEC, FF/VI and FF treatments will be delivered in a device as described at the beginning of this section and one dual-strip placebo device.

<table>
<thead>
<tr>
<th>Table 4 Description of FSC Inhalation Powder DPI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation</strong></td>
</tr>
<tr>
<td>Dosage Form</td>
</tr>
<tr>
<td>Unit Dose Strengths</td>
</tr>
<tr>
<td>Physical description</td>
</tr>
<tr>
<td>Route of Administration</td>
</tr>
</tbody>
</table>
### Table 5  Description of FF Inhalation Powder DPI

<table>
<thead>
<tr>
<th>Formulation</th>
<th>First strip</th>
<th>Second strip</th>
</tr>
</thead>
<tbody>
<tr>
<td>FF blended with lactose</td>
<td>lactose and magnesium stearate</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>DPI with 30 doses (2 strips with 30 blisters per strip)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Unit Dose Strengths</th>
<th>100 mcg per blister</th>
<th>N/A</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Physical Description</th>
<th>Dry white powder</th>
<th>Dry white powder</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Inhaled</th>
</tr>
</thead>
</table>

### Table 6  Description of FF/UMEC Inhalation Powder DPI

<table>
<thead>
<tr>
<th>Formulation</th>
<th>First strip</th>
<th>Second strip</th>
</tr>
</thead>
<tbody>
<tr>
<td>FF Blended with lactose</td>
<td>UMEC blended with lactose and magnesium stearate</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>DPI with 30 doses (2 strips with 30 blisters per strip)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Unit Dose Strengths</th>
<th>100 mcg per blister</th>
<th>15.6, 62.5, 125, or 250 mcg per blister</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Physical Description</th>
<th>Dry white powder</th>
<th>Dry white powder</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Route of Administration</th>
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</tr>
</thead>
</table>

### Table 7  Description of FF/VI Inhalation Powder DPI

<table>
<thead>
<tr>
<th>Formulation</th>
<th>First strip</th>
<th>Second strip</th>
</tr>
</thead>
<tbody>
<tr>
<td>FF blended with lactose</td>
<td>VI blended with lactose and magnesium stearate</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>DPI with 30 doses (2 strips with 30 blisters per strip)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Unit Dose Strengths</th>
<th>100 mcg per blister</th>
<th>25 mcg per blister</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Physical Description</th>
<th>Dry white powder</th>
<th>Dry white powder</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Inhaled</th>
</tr>
</thead>
</table>

### Table 8  Description of VI Inhalation Powder DPI

<table>
<thead>
<tr>
<th>Formulation</th>
<th>First strip</th>
<th>Second strip</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI blended with lactose and magnesium stearate</td>
<td>Lactose</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>DPI with 30 doses (2 strips with 30 blisters)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Unit Dose Strengths</th>
<th>25 mcg per blister</th>
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<th>Dry white powder</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Inhaled</th>
</tr>
</thead>
</table>

### Table 9  Description of Placebo Inhalation Powder DPI

<table>
<thead>
<tr>
<th>Formulation</th>
<th>First strip</th>
<th>Second strip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose and magnesium stearate</td>
<td>Lactose</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>DPI with 30 doses (2 strips with 30 blisters)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Unit Dose Strengths</th>
<th>N/A</th>
<th>N/A</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Physical description</th>
<th>Dry white powder</th>
<th>Dry white powder</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Inhaled</th>
</tr>
</thead>
</table>
Albuterol/salbutamol via metered-dose inhaler (MDI) will be issued for reversibility testing at Visit 1. All subjects will receive supplemental albuterol/salbutamol MDI to be used on an as-needed basis (rescue medication) throughout the study. Albuterol/salbutamol will be sourced from local commercial stock, except in the United States where GSK will supply. If not available locally, GSK will source centrally. The contents of the label will be in accordance with all applicable regulatory requirements.

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

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

### 5.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule. The randomization code will be generated by GSK using a validated computerized system, RandAll. Subjects will be randomized using an IVRS.

Following the completion of the run-in period, eligible subjects will be stratified by smoking status and age when first treated with an inhaler and randomized to 1 of 24 treatment sequences. The strata are as follows:

<table>
<thead>
<tr>
<th>Stratum Code</th>
<th>Stratum Description</th>
<th>Stratum definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Never/Light Smoker Early Treatment</td>
<td>&lt;10 pack years and &lt;30 years of age when first treated with an inhaler</td>
</tr>
<tr>
<td>2</td>
<td>Never/Light Smoker Late Treatment</td>
<td>&lt;10 pack years and ≥30 years of age when first treated with an inhaler</td>
</tr>
<tr>
<td>3</td>
<td>Heavy Smoker Early Treatment</td>
<td>≥10 pack years and &lt;30 years of age when first treated with an inhaler</td>
</tr>
<tr>
<td>4</td>
<td>Heavy Smoker Late Treatment</td>
<td>≥10 pack years and ≥30 years of age when first treated with an inhaler</td>
</tr>
</tbody>
</table>
Subjects will be assigned to study treatment in accordance with the randomization schedule.

Run-In Medication

All subjects will enter the run-in period and receive FSC 250/50 mcg

- Inhaled FSC 250/50 mcg twice daily (morning and evening)

Treatment Phase A Medication:

The possible double-blind treatments are:

- Inhaled FF/UMEC 100 mcg/15.6 mcg once daily in the morning
- Inhaled FF/UMEC 100 mcg/62.5 mcg once daily in the morning
- Inhaled FF/UMEC 100 mcg/125 mcg once daily in the morning
- Inhaled FF/UMEC 100 mcg/250 mcg once daily in the morning
- Inhaled FF 100 mcg once daily in the morning
- Inhaled FF/VI 100 mcg/25 mcg once daily in the morning

After the 4-week Treatment Phase A, subjects will receive one of the following medications provided as two separate inhalers and enter a 1-week Treatment Phase B:
Treatment Phase B Medication:

- Inhaled FF/UMEC 100 mcg/250 mcg & placebo once daily in the morning
- Inhaled FF/UMEC/VI 100 mcg/250 mcg/25 mcg (as two separate inhalers: FF/UMEC 100/250 & VI 25) once daily in the morning

After the 1-week Treatment Phase B, subjects will receive the following medication provided as two separate inhalers and enter a 1-week Treatment Phase C:

Treatment Phase C Medication:

- Subjects on Inhaled FF/UMEC 100 mcg/250 mcg once daily in the morning during Treatment Phase B will receive either:
  - Inhaled FF/UMEC 100 mcg/250 mcg & placebo once daily in the morning
  - Inhaled FF 100 mcg & placebo once daily in the morning
- Subjects on Inhaled FF/UMEC/VI 100 mcg/250 mcg/25 mcg once daily in the morning during Treatment Phase B will receive either:
  - Inhaled FF/UMEC/VI 100 mcg/250 mcg/25 mcg (as two separate inhalers: FF/UMEC 100/250 & VI 25) once daily in the morning
  - Inhaled FF/VI 100 mcg/25 mcg & placebo once daily in the morning

After the 1-week Treatment Phase C, subjects will receive medication as prescribed by the investigator and enter a 1-week follow-up period.

Subjects will withhold their morning dose of study medication on clinic days and return their previously dispensed inhaler to clinic. Subjects will receive the next dose of medication at the clinic.

Trade label albuterol/salbutamol inhalation aerosol will be provided by each country participating in the trial and will be given to subjects as rescue medication to use throughout the study to treat acute COPD or asthma symptoms.

5.3. Blinding

The investigator or treating physician may unblind a subject’s treatment assignment only in the case of an emergency or in the event of a serious medical condition, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject, as judged by the investigator. Investigators have direct access to the subject’s individual study treatment. It is preferred (but not required) that the investigator first contacts the GSK medical monitor or appropriate GSK study personnel to discuss options before unblinding the subject’s treatment assignment. If GSK study personnel are not contacted before the unblinding, 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 fully documented 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.

A subject may not continue in the study if the treatment code is unblinded. The primary reason for discontinuation (the event or condition that 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 the study medication during all treatment phases will be assessed at clinic visits by reviewing the dose counter on the inhaler. Subjects should be ≥ 80% to ≤ 120% compliant on taking study medication between each pair of consecutive on-treatment clinic 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 and asthma medications used within 30 days prior to Visit 0 should be recorded in the eCRF. All concomitant medications taken during the study and any changes to concomitant medications (from Visit 0 through Visit 8) will be recorded in the eCRF. Study-provided albuterol/salbutamol should not be recorded in the eCRF. The minimum requirement is that drug name, dose, route and the dates of administration are to be recorded.

Medications initiated after completion of Visit 8 or the IP Discontinuation/Early Withdrawal Visit will not be recorded in the eCRF unless taken to treat an Adverse Event or COPD exacerbation. Detailed information of permitted and prohibited medications is included in the SPM for your reference. Subjects who have completed the IP discontinuation visit are allowed to use any medications prescribed by the investigator or primary care physician.
5.6.1. Permitted Medications and Non-Drug Therapies

5.6.1.1. Permitted COPD or Asthma Medications

The following relevant medications are permitted as noted.

- Study-provided albuterol/salbutamol will be dispensed at Visit 1 for use as relief medication throughout the duration of the study. Subjects must be judged capable of withholding albuterol/salbutamol for at least 4 hours prior to study visits.

- For a minimum of the 12 weeks prior to Visit 1 subjects must have used or received a prescription for inhaled corticosteroids.

- Subjects must have been maintained on a stable dose (not to exceed the equivalent of 1000 mcg fluticasone propionate daily) of the same ICS for 4 weeks prior to Visit 1.

- Note: If the subject is on an ICS/LABA for at least 4 weeks prior to Visit 1, then after signing informed consent the subject must discontinue LABA therapy after the morning dose on the day before starting the study (prior to Screening/Visit1) and, at the investigator’s discretion, continue appropriate therapy (i.e., the same or equivalent ICS dose as monotherapy).

- Study-provided FSC will be started at Visit 1 if the subject meets screening eligibility. This medication will be used throughout the run-in period, but it must be withheld after the morning dose on the day before Visits 2 and 3 for lung function testing. FSC will be returned at the end of the run-in period to avoid confusion with study medication.

5.6.1.2. Permitted Non-COPD and Non-Asthma Medications

The following medications are permitted during this study:

- Medications for rhinitis (e.g., intranasal corticosteroids, antihistamines [including ocular and intranasal], cromolyn, nedocromil, nasal decongestants)

  Note: Information on the use of these medications should be captured prior to ECG measurements.

- Antibiotics for short term treatment of acute infections other than respiratory

- Decongestants: Subjects may take decongestants during the study, but these are disallowed for 24 hours prior to ECG measurements.

- Immunotherapy: Immunotherapy for the treatment of allergies is allowed during the study provided it was initiated 4 weeks prior to Visit 1 and subjects remain in the maintenance phase for the duration of the study.

- Topical corticosteroids: Subjects may use topical corticosteroids (≤1% hydrocortisone cream) for dermatological diseases. Non-corticosteroid containing creams are permitted.

- Systemic and ophthalmic beta-blockers: Administer with caution as systemic beta-blockers block the pulmonary effect of beta-agonists and may produce severe bronchospasm in patients with reversible obstructive airways disease.
Cardioselective beta-blockers should be considered, although they also should be administered with caution.

- Flu vaccine
- Pneumonia vaccine

All medications for other disorders may be continued throughout the study provided their use would not be expected to affect the subjects’ lung function or safety assessments (e.g., cortisol assessments, cardiac measurements). However, no systemic corticosteroids for other conditions will be permitted.

### 5.6.2. Prohibited Medications and Non-Drug Therapies

Use of the medications listed in Table 11 is not permitted during the study.

#### Table 11 Concomitant Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>No use within the following time interval before Visit 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous, intramuscular (including depot), intra-articular, or oral corticosteroids</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Inhaled short-acting anticholinergics</td>
<td>6 hours</td>
</tr>
<tr>
<td>Inhaled short-acting anticholinergics+ Short-acting beta agonist combination</td>
<td>6 hours</td>
</tr>
<tr>
<td>Inhaled long-acting anticholinergics</td>
<td>7 days</td>
</tr>
<tr>
<td>Anti-IgE (e.g., Xolair)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Immunosuppressive medications including immunomodulators</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Allergen immunotherapy for the treatment of allergies</td>
<td>Allowed during the study provided it was initiated at least 4 weeks prior to Visit 1 and the subject remains in the maintenance phase throughout the study</td>
</tr>
<tr>
<td>Inhaled long-acting beta2-agonists (e.g., salmeterol, formoterol) or combination products containing inhaled long-acting beta2-agonists (e.g., Seretide, Symbicort)</td>
<td>Must be withheld after the morning dose on the day before the visit (for Visits 1, 2, and 3)</td>
</tr>
<tr>
<td>Inhaled very long-acting beta2-agonists, (Vilanterol, Indacaterol, Olodaterol)</td>
<td>10 days for Vilanterol, Indacaterol and Olodaterol component</td>
</tr>
<tr>
<td>Oral long-acting beta2-agonists (e.g., bambuterol)</td>
<td>10 days</td>
</tr>
<tr>
<td>Inhaled short-acting beta2-agonist (rescue albuterol/salbutamol is permitted during the study)</td>
<td>4 hours (including all study visits)</td>
</tr>
<tr>
<td>Theophyllines, anti-leukotrienes, slow-release bronchodilators, ketotifen, nedocromil sodium, sodium cromoglycate, roflumilast</td>
<td>48 hours</td>
</tr>
<tr>
<td>Any other investigational drug</td>
<td>30 days or within 5 drug half-lives of the investigational drug (whichever is longer)</td>
</tr>
</tbody>
</table>

A subject may not concurrently use any other prescription or over-the-counter medication which may affect the course of COPD or asthma or interact with study drug, such as:
- Anticholinergic medications, with the exception of those used for gastrointestinal or genitourinary conditions such as overactive bladder or those which have minimal systemic effects
- Potent Cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole)
- Anticonvulsants (barbiturates, hydantoins, carbamazepine)
- Polycyclic antidepressants
- Phenothiazines
- MAO inhibitors

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 subject’s medical condition whether or not GSK is providing specific post study treatment.

Investigators should prescribe COPD or asthma medication appropriate to the severity of the subject’s COPD or asthma in accordance with guidelines [GOLD, 2013; GINA, 2012; NIH, 2007]

5.8. Treatment of Study Treatment Overdose

An overdose will be defined as the subject receiving any amount of investigational product greater than the maximum dose permitted by the protocol, which results in clinical signs or 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.

In the event of an overdose, the investigators should use their discretion as to whether other treatment may be warranted.

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 Investigator Brochures for FF/UMEC Inhalation Powder, FF Inhalation Powder and UMEC Inhalation Powder and prescribing information for FSC. These should be referenced for any safety concerns.
6. STUDY ASSESSMENTS AND PROCEDURES

Table 12 Time and Events

<table>
<thead>
<tr>
<th>Protocol Activity</th>
<th>Pre-Screen</th>
<th>Screen / Run-In</th>
<th>Run-In</th>
<th>Phase A: Dose-Ranging</th>
<th>Phase B: Benefit of LABA</th>
<th>Phase C: Carryover</th>
<th>IP Discontinuation/Early Withdrawal</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 0a</td>
<td>Visit 1b</td>
<td>Visit 2</td>
<td>Visit 3</td>
<td>Visit 4</td>
<td>Visit 5c</td>
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**Efficacy Assessments**

- Spirometry
- Reversibility
- Peak Pre-/Post-Bronchodilator
- Spirometry
- Subject-initiated Spirometry
- St. George's Respiratory Questionnaire
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<tr>
<td>Visit 0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Visit 1&lt;sup&gt;b&lt;/sup&gt;</td>
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### Protocol Activity

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<tr>
<th>Protocol Activity</th>
<th>Pre-Screen</th>
<th>Screen / Run-In</th>
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<td>Assess Compliance</td>
<td>X</td>
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Visit 0 and Visit 1 can be combined if no washout of medications is required.

Note: All clinical visits will occur between 6 and 11 in the morning except for the pre-screen visit.

The procedures in Visit 5 could take up to 6 hours to complete. Subjects and investigational sites should plan accordingly.

Includes detailed smoking, respiratory, and cardiovascular history.

Reversibility demonstrated by ≥12% and ≥200 mL reversibility of FEV₁ within 20-60 minutes following 4 inhalations of albuterol/salbutamol inhalation aerosol (or equivalent nebulised treatment with albuterol/salbutamol solution) at Screening and Visit 2. Spirometry including reversibility at Visit 2 determines eligibility for randomization at Visit 3.

Subjects who complete the IP Discontinuation /Early Withdrawal Visit for permanent discontinuation of IP, should continue to have telephone contacts according to the visit schedule to assess exacerbations, adverse events, and concomitant medications.

Spirometry measurements for this study will be conducted pre-bronchodilator and pre-dose at each visit. Starting after the randomization visit and throughout the treatment duration, subjects will be required to inform the site staff of the time of the dose prior to the visit and perform trough FEV₁ measurements approximately 24 hours post-dose.

Subject-initiated spirometry will be conducted at home by the subject in the morning and evening each day from Visit 1 through Visit 8.

To be conducted at IP Disc/EW if this visit takes place after Visit 3 and before Visit 5.

Chest x-rays should be performed if pneumonia is suspected.

Includes EXACT and wheeze questionnaires and rescue medication use diary.

All current concomitant medications are to be collected, and COPD and asthma medications taken during the 30 days prior to Visit 0 also are to be collected.

Including oropharyngeal examination.

12-lead ECGs will be performed pre-dose and 10 minutes post-dose at randomization and at the end of 4 weeks.

Informed consent for optional pharmacogenetics (PGx) research should be obtained before collecting a sample. The sample can be obtained any time after randomization.

A pregnancy test is required for all females of child bearing potential.

Albuterol will be dispensed at clinic visits on an individual as-needed basis.
6.1. Critical Screening Assessments

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

- Demographic history (including gender, ethnic origin, date of birth)

**Visit 0 and Visit 1 can be combined if the subject does not require wash-out from prohibited medications. See Table 3 for required wash-out periods.**

The following critical screening assessments will be conducted at Visit 1:

- Height and weight
- COPD and/or asthma diagnosis history (including duration of disease)
- Smoking history
- Exacerbation history
- COPD, asthma, and other concurrent medications
- Medical History including previous and/or concurrent medical conditions, pneumonia, and pneumonia vaccine status
- Reason for screen failure (if applicable)
- Lung function
- Vital signs
- Pre-and post-albuterol/salbutamol lung function (reversibility)
- Inclusion/Exclusion criteria assessment
- Physical examination including oropharyngeal exam
- 12-lead ECG
- Clinical laboratory tests (including hematology, chemistry, Hepatitis B antigen and Hepatitis C antibody testing, urinalysis and pregnancy test)
- SAE assessment

Information collected during this study regarding spirometry and medical and respiratory history will be combined with data from other respiratory studies to further characterize the asthma-COPD overlap syndrome.

See Section 4.5 for any specific data to be collected for screen failures.
6.2. Efficacy

6.2.1. Primary Efficacy

- Change from baseline in clinic trough (pre-dose) FEV$_1$ at the end of Treatment Phase A

6.2.2. Secondary Efficacy

- Mean change from baseline in rescue medication use at the end of Treatment Phase A
- Mean change from baseline in EXACT-RS score at the end of Treatment Phase A
- Change from baseline in daily morning (AM) PEF (pre-dose and pre-rescue bronchodilator) measured at home and averaged over the last 21 days of Treatment Phase A
- Change from trough in FEV$_1$ at 3 hours post-study treatment at Visit 5
- Change in clinic FEV$_1$ following 2 puffs of albuterol/salbutamol given 3 hours post-study treatment dose at Visit 5

6.2.3. Other Efficacy

Exploratory

- Change from baseline in clinic trough (pre-dose) FEV$_1$ at the end of Treatment Phase B
- The change from baseline in clinic trough FEV$_1$ at the end of Treatment Phase C (Visit 8) for the subset of subjects who have taken FF/UMEC or FF/UMEC/VI for two weeks over Treatment Phase B and Treatment Phase C
- Change from the end of Treatment Phase B clinic trough (pre-dose) FEV$_1$ to the end of Treatment Phase C
- Change in home daily FEV$_1$ during Treatment Phase C
- Change from baseline in home trough (pre-dose) FEV$_1$ over 1, 2, 3, and 4 weeks of Treatment Phase A
- Change from baseline in home trough (pre-dose) FEV$_1$ at the end of Treatment Phase A
- Change from baseline in daily home trough (pre-dose) FEV$_1$ averaged over Treatment Phase A
- The number of exacerbations during Treatment Phase A
- Incidence of symptom-defined events: Acute, sustained symptomatic worsening of COPD, defined as an increase in EXACT score ≥9 points for 3 days or ≥12 points for 2 days, above baseline during Treatment Phase A.
• Mean change from baseline in EXACT-RS sub-scales of breathlessness, cough and sputum, chest symptoms at the end of Treatment Phase A
• Mean change from baseline in wheeze score at the end of Treatment Phase A
• Percent of patients with an improvement (decrease) of SGRQ >= 4 points from baseline at the end of Treatment Phase A
• Percent of patients with an improvement (decrease) of SGRQ >= 4 points from baseline in the domains of Symptoms, Activity and Impacts (Psycho-social) at the end of Treatment Phase A

6.2.4. Lung Function Measurements

FEV$_1$ will be measured in the morning at Visits 1 through 8 between 6:00 and 11:00 electronically by spirometry. The highest of 3 technically acceptable measurements will be recorded at each visit.

Subjects must have a best post-bronchodilator FEV$_1$ of 50%-80% (inclusive) of their predicted normal value and both a pre- and post-bronchodilator FEV$_1$/FVC ratio of <0.7 to be eligible to take part in the study at Visit 1.

Subjects will always be required to withhold their albuterol/salbutamol for at least 4 hours before all clinic visits. Sustained-release bronchodilators (e.g., theophyllines) must also be withheld 48 hours prior to Visit 1. Since study drug will be administered at clinic visits, subjects must not take their study drug prior to coming to the clinic.

At Visits 4 through 8, FEV$_1$ should be measured approximately 24 hours after the subject’s last morning dose of investigational product and within ±1 hour of the time FEV$_1$ was measured at Visit 3 (baseline).

At Visit 5, after trough FEV$_1$ is measured, the subject will receive investigational product. After 3 hours, spirometry will be performed again, and then 2 puffs of albuterol/salbutamol will be administered. After 30 minutes, the subject will repeat the spirometry assessment.

Reversibility

The reversibility requirement for eligibility must be assessed at Visit 1. Subjects must demonstrate a ≥12% and ≥200 mL increase in FEV$_1$ to be eligible for the study.

At Visit 2, all subjects are required to perform reversibility testing in the morning. The results of the reversibility will be recorded and will determine eligibility for randomization.

Reversibility testing at Visit 1 and Visit 2 must be performed in the morning. FEV$_1$ will be measured pre-albuterol/salbutamol and within 20 to 60 minutes following 4 inhalations of albuterol/salbutamol. A spacer device may be used for testing, if required.
Percent reversibility will be calculated as follows:

\[
\frac{(\text{Post-bronchodilator FEV}_1 - \text{Pre-bronchodilator FEV}_1)}{\text{Pre-bronchodilator FEV}_1} \times 100\%
\]

**FEV\textsubscript{1} Stability Limit**

An FEV\textsubscript{1} Stability Limit will be calculated at Visit 3 using the following equation for all randomized subjects:

Best pre-salbutamol/albuterol FEV\textsubscript{1} at Visit 3 x 80%

The FEV\textsubscript{1} stability limit serves as a benchmark of the subject’s run-in COPD status and will be used for comparison during the treatment phase to assess subject safety.

### 6.2.5. Daily Diaries

#### 6.2.5.1. eDiary

Subjects will be issued a combination spirometer and eDiary for daily use throughout the study and will be instructed on how to use it. Subjects will record results for the following in the eDiary each day:

- Daily symptom assessment (EXACT-PRO, wheeze question)
- Number of inhalations of rescue albuterol/salbutamol inhalation aerosol used during the day and night.
- Global Impression of Disease Severity (Visit 3)
- Global Impression of Change Scale (Visit 5 or IP Discontinuation Visit)
- FSC medication (during the run-in period only)

The eDiary will also record daily values for morning and evening spirometry. Section 6.2.6 describes the assessments and questionnaires recorded on the eDiary device.

#### 6.2.5.2. Paper Diary

In addition, subjects will be issued a paper Medical Problems/Medications Taken diary to record any medical problems and non-study specific medications used during the study.

### 6.2.6. Morning and Evening Home Spirometry

An electronic home spirometer will be issued to subjects at Visit 1 for daily monitoring of their lung function. Subjects will conduct spirometry maneuvers each morning prior to study medication dosing and each evening. Three measurements for each session will be recorded by the subjects in the eDiary. Assessments will be performed prior to any rescue albuterol/salbutamol inhalation aerosol use.
6.2.6.1. PEF Stability Limit

For all randomized subjects, a PEF Stability Limit will be calculated from AM PEF measurements on the 7 days preceding Visit 3 as follows:

Mean AM PEF from the available 7 days preceding Visit 3 x 80%

The AM PEF measurement from the morning of randomization (Visit 3) is included in this calculation of the PEF stability limit.

The PEF stability limit serves as a benchmark of the subject’s run-in COPD status and will be used for comparison during the treatment phase to assess subject safety.

6.2.6.2. EXACT-PRO and EXACT-RS

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

EXACT-RS (Respiratory Symptoms) consists of 11 items from the 14 item EXACT-PRO instrument. EXACT-RS is intended to capture information related to the respiratory symptoms of COPD, i.e. breathlessness, cough, sputum production, chest congestion and chest tightness. The EXACT-RS has a scoring range of 0-40.

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

6.2.6.3. Wheeze Question

An additional question on Wheeze, a symptom of importance in COPD patients with an asthmatic component, will also be asked within the context of the daily diary. Subjects will be asked to respond to the question ‘Did you wheeze today?’ with response options of: Not at all, Rarely, Occasionally, Frequently, Almost constantly.

6.2.6.4. Rescue Albuterol (Salbutamol) Use

The number of puffs of albuterol (salbutamol) MDI used in the last 12 hours for relief of symptoms will be recorded morning and evening in the eDiary by the subject. Subjects should be instructed that study-provided albuterol (salbutamol) should be used on an “as
needed” basis only. Daily albuterol (salbutamol) use does not include planned use prior to exercise.

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

6.2.6.5. Global Patient Impression of Severity and Change Scales

Subjects will complete a Global Impression of Disease Severity question at randomisation. This single global question will ask subjects to rate their lung condition severity on a four-point scale (mild, moderate, severe, very severe).

Subjects will complete a Global Impression of Change in lung condition (overall disease) question at Visit 5 (or IP Discontinuation). Response options will be on a 7 point Likert scale ranging from much better to much worse.

6.2.7. St. George’s Respiratory Questionnaire (SGRQ)

The SGRQ will be administered as a paper questionnaire and will be completed by study subjects at Visits 3 and 5 and IP Discontinuation/Early Withdrawal.

The SGRQ [Jones, 1991] is a 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 used successfully in studies of COPD and asthma 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, and subjects should complete all the questions. The investigator will ask the subject to complete all questions as accurately as possible. If the subject requests help or clarification of any question in the SGRQ, he or she should be asked to reread the instructions and give the answer that best reflects how he/she feels. The subject should be reassured that there are no right or wrong answers. The investigator will not provide the subject with any answer or attempt to interpret any portion of a question. The form should be reviewed for completeness prior to the subject leaving the study site for the visit, and the subject should be encouraged to respond to any missing items.

6.2.8. Exploratory Markers to Predict Responses

Subjects will be phenotyped during screening and during the randomization visit to assess predictors of response. Phenotyping will include measurement of:

- Baseline lung function and reversibility
- Patient disease history (exposure to smoke, pets, and family history), baseline demographics, medication history, smoking history, atopic status, presence of co-morbid conditions, and exacerbation history
- Environmental exposures and triggers
- Blood (eosinophils, neutrophils, total IgE).

6.3. Safety

As indicated in the Time and Events Table (Table 12), initial safety assessments to determine subjects’ general health status will consist of obtaining medical history, clinical laboratory tests (chemistry/hematology), a 12-lead ECG, and a physical examination including oropharyngeal examination. COPD-specific assessments will include obtaining the subject’s respiratory history, COPD and asthma therapy history, and performing spirometry and reversibility testing (if historical reversibility is unavailable). Safety will continue to be assessed during the study via monitoring of AEs, SAEs, concomitant medications, and vital signs throughout the study.

6.3.1. Safety Endpoints

- Incidence of adverse events from the time of informed consent through the follow-up period
- Vital signs (pulse and systolic/diastolic blood pressure) pre-dose, assessed at all clinic visits
- Physical examination, including oropharyngeal examination
- Clinical chemistry and hematology in all subjects
- Liver function safety assessments
- 12-lead ECG at pre-dose and 10 minutes post dose

6.3.2. Liver chemistry stopping and follow up criteria

Phase II liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance).

Phase II liver chemistry stopping criteria 1-5 are defined below and are presented in Appendix 3:

1. Alanine transaminase (ALT) ≥3x the upper limit of normal (ULN) and bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT ≥3xULN and international normalized ratio [INR] ≥1.5, if INR measured).

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject 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 ≥ 5xULN.

3. 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 believed to be related to hypersensitivity (such as fever, rash or eosinophilia).

4. ALT ≥ 3xULN persists for ≥ 4 weeks

5. ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks

When any of the liver chemistry stopping criteria 1-5 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 case report form (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 bilirubin) (or ALT ≥ 3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects 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, withdraw study drug for that subject 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, stabilise, or return to baseline values as described below.
- Withdraw the subject from the study (unless further safety follow up is required) after completion of the liver chemistry monitoring as described below.
- Do not re-challenge with investigational product.

In addition, for criterion 1:

- Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, aspartate aminotransferase [AST], alkaline phosphatase, bilirubin) resolve, stabilise or return to within baseline values
For criteria 2, 3, 4 and 5:

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

Subjects with 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, stabilise 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 normalise or return to within baseline values.

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

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
  - Hepatitis C ribonucleic acid (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, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).
• Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B deoxyribonucleic acid (DNA) and hepatitis delta antibody.
• Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease.

6.3.3. Adverse Events

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

For the purposes of this study, all COPD or asthma exacerbations will be collected and recorded on the exacerbation eCRF page. Exacerbations should not be recorded as an adverse event, unless they meet the definition of a Serious Adverse Event (see Section 6.3.3.2). For exacerbations that are considered serious, the SAE page of eCRF should be completed, in addition to the exacerbation eCRF page.

6.3.3.1. Definition of an AE

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

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

Events meeting the definition of an AE include:
Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition

New conditions detected or diagnosed after 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.

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:

- 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

6.3.3.2. Definition of an SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation

NOTE: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria,
the event is serious. When in doubt as to whether “hospitalisation” occurred or was necessary, the AE should be considered serious.

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

d. Results in disability/incapacity, or

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

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as \( \text{ALT} \geq 3\times \text{ULN} \) and \( \text{bilirubin} \geq 2\times \text{ULN} \) (\( >35\% \) direct) (or \( \text{ALT} \geq 3\times \text{ULN} \) and \( \text{INR} >1.5 \), if INR measured) termed ‘Hy’s Law’ events (INR measurement is not required and the threshold value stated will not apply to subjects 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 \( \geq 2\times \text{ULN} \), then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

6.3.3.3. Sentinel Events

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

- Acquired Long QT Syndrome
- Agranulocytosis/Severe Neutropenia
- Anaphylaxis & Anaphylactoid Reactions
- Hepatotoxicity
- Acute Renal Failure
- Seizure
- Stevens Johnson syndrome/Toxic epidermal necrolysis

6.3.4. 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 judgment 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.

All events of pneumonia will be captured as adverse events. Chest x-rays must be performed to confirm the pneumonia diagnosis and subjects should be followed-up as appropriate by the investigator.

6.3.5. Cardiovascular Events

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

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

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

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

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

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

COPD and asthma 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 6.3.3.2. Exacerbation SAEs will not be subject to expedited reporting regardless of the “expectedness” or “relatedness” of the event. 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 or asthma exacerbation will be recorded in the exacerbation eCRF.

6.3.8. Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator’s attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to GSK as described above.

6.3.9. Time Period and Frequency of Detecting AEs and SAEs

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

AEs will be collected from the start of the run-in period 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 6.3.11.

All SAEs will be followed up until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the SAE eCRF page will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the SAE. This may include additional laboratory tests or investigations or investigations, histopathological examinations, or consultation with other health care professionals.

6.3.10. Method of Detecting AEs and SAEs

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

“How are you feeling?” or for paediatric studies, “How does your child seem to feel?”

“Have you had any (other) medical problems since your last visit/contact?” or for paediatric studies, “Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?”

“Have you taken any new medicines, other than those provided in this study, since your last visit/contact?” or for paediatric studies, ”Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?”

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

SAEs, non-serious AEs related to study treatment, pregnancies, medical device incidents, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in Table 13 once the investigator determines that the event meets the protocol definition for that event.
Table 13 Reporting Timelines

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Time Frame</th>
<th>Documents</th>
<th>Time Frame</th>
<th>Documents</th>
</tr>
</thead>
<tbody>
<tr>
<td>All SAEs</td>
<td>24 hours</td>
<td>“SAE” data collection tool</td>
<td>24 hours</td>
<td>Updated “SAE” data collection tool</td>
</tr>
<tr>
<td>Cardiovascular (CV) or death event</td>
<td>Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported</td>
<td>“CV events” and/or “death” data collection tool(s) if applicable</td>
<td>Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported</td>
<td>Updated “CV events” and/or “death” data collection tool(s) if applicable</td>
</tr>
<tr>
<td>Device Incident</td>
<td>24 hours</td>
<td>“Medical Device Incident Report Form”</td>
<td>24 hours</td>
<td>Updated “Medical Device Incident Report Form”</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>2 weeks</td>
<td>“Pregnancy Notification Form”</td>
<td>2 weeks</td>
<td>“Pregnancy Follow-up Form”</td>
</tr>
<tr>
<td>Non-serious adverse events related to study treatment</td>
<td>5 calendar days</td>
<td>“Adverse Reaction” data collection tool</td>
<td>2 weeks</td>
<td>Updated “Adverse Reaction” data collection tool</td>
</tr>
<tr>
<td>Drug-Related Event (DRE)</td>
<td>2 weeks4</td>
<td>DRE CRF</td>
<td>2 weeks4</td>
<td>Updated DRE CRF</td>
</tr>
<tr>
<td>ALT $\geq$ 3xULN and Bilirubin $\geq$ 2xULN (&gt;35% direct) (or ALT $\geq$ 3xULN and INR $&gt;1.5$, if INR measured)</td>
<td>24 hours$^2$</td>
<td>“SAE” data collection tool. “Liver Event CRF” and “Liver Imaging” and/or “Liver Biopsy” CRFs, if applicable$^3$</td>
<td>24 hours</td>
<td>Updated “SAE” data collection tool/“Liver Event” Documents$^3$</td>
</tr>
<tr>
<td>ALT $\geq$ 5xULN; ALT $\geq$ 3xULN with hepatitis or rash or 3xULN $\geq$ 4 weeks</td>
<td>24 hours$^2$</td>
<td>“Liver Event” Documents (defined above) $^3$</td>
<td>24 hours</td>
<td>Updated “Liver Event” Documents$^3$</td>
</tr>
<tr>
<td>ALT $\geq$ 3xULN and &lt;5xULN and bilirubin &lt;2xULN</td>
<td>24 hours$^2$</td>
<td>“Liver Event” Documents (defined above) do not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks$^3$</td>
<td>24 hours</td>
<td>Updated “Liver Event” Documents, if applicable$^3$</td>
</tr>
</tbody>
</table>

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

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.

6.3.11.1. Regulatory reporting requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

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

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

6.3.12. Other Safety Outcomes

6.3.12.1. COPD or Asthma Events

6.3.12.1.1. Exacerbations

A subject will be discontinued from IP due to lack of efficacy if he/she experiences a severe exacerbation.

An exacerbation is defined as an acute worsening of respiratory symptoms requiring the use of any treatment beyond study medication or rescue albuterol/salbutamol. This includes the use of systemic corticosteroids, antibiotics, and/or emergency treatment or hospitalization. All exacerbations will be recorded on the exacerbation page of the eCRF. Subjects who experience an exacerbation meeting specific severity criteria during the run-in period will not be randomized and will not be allowed to be re-screened. Subjects who experience a severe exacerbation during the treatment period will be withdrawn from investigational product.

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 6.3.3.2 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.

**Severe Exacerbations**

For the purposes of this study, a *severe exacerbation* is defined as either of the following:

- Deterioration of COPD or asthma requiring either the use of oral corticosteroids for at least 3 days or parenteral corticosteroids
- An in-patient hospitalization or emergency department visit due to COPD or asthma that required any oral or parenteral corticosteroids

Severe exacerbations should not be recorded as an AE unless they meet the definition of an SAE (Section 6.3.3.2). Severe exacerbations will be collected and recorded on the exacerbations log in the eCRF. The treatment details must also be recorded in the eCRF. The time period for collection of severe exacerbations will begin from the time of randomization (first receipt of investigational product) and will end after the 7 day follow-up period has been completed.

**6.3.12.2. Laboratory Assessments**

All protocol required laboratory assessments, as defined in Appendix 4, must be performed by the central laboratory, Quest Diagnostics. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by Quest Diagnostics. Reference ranges for all safety parameters will be provided to the site by Quest Diagnostics.

If additional non-protocol specified laboratory assessments are performed at the institution’s local laboratory and result in a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the subject’s CRF. Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All study-required laboratory assessments will be performed by a central laboratory, apart from:

- Urine pregnancy test. The results of each test must be entered into the study’s eCRF.
- Hematology*

* Local hematology results are only required in the event that the central hematology results are not available in time for either a treatment and/or response evaluation to be performed. If a local hematology sample is required it is important that the sample for central hematology analysis is obtained at the same time. Additionally if the local
hematology results are used to make either a treatment or response evaluation, the results must be entered into the study’s eCRF.

6.3.12.3. Vital Signs

Vital signs will be performed prior to taking the morning dose of IP and prior to conducting spirometry. Vital signs will be collected according to the Time and Events schedule (Table 12). Blood pressure (systolic and diastolic) and pulse rate will be measured in the sitting position after approximately 5 minutes rest. A single set of values will be collected and recorded in the source documentation and eCRF.

6.3.12.4. Medical Problems and Concomitant Medications

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

6.3.12.5. ECG

All sites will use standardized ECG equipment provided by a centralized external vendor. A single 12-lead ECG and rhythm strip will be recorded after measurement of vital signs and prior to spirometry. Recordings will be made at Screening (Visit 1) and approximately 10 minutes after dosing at Visit 3, Visit 5, Visit 7 and Visit 8 or IP Discontinuation/EW. In addition, 12-lead ECGs will be performed pre-dose at randomization and at the end of 4 weeks.

All ECG measurements will be made with the subject in a supine position having rested in this position for approximately 5 minutes before each reading.

For subjects who meet the protocol-defined stopping criteria for the QTc interval, triplicate ECGs (over a brief period of time) should be performed (see Section 4.3.1).

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

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

Details of the cardiac monitoring procedures will be provided by the centralized cardiology service provider.
6.3.12.6. Pneumonia

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

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

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

The investigators and site staff should remain vigilant for the possible development of pneumonia in subjects with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in subjects with COPD receiving fluticasone furoate/umeclidinium include current smokers, subjects with a history of prior pneumonia, and subjects with a body mass index <25 kg/m2. For all suspected cases of pneumonia, investigators are strongly encouraged to confirm the diagnosis (this includes obtaining a chest x-ray) and to initiate appropriate therapy as promptly as possible. All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable).

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

6.3.12.7. Radiography (Chest X-Rays)

Confirmation by chest x-ray (posteroanterior and lateral) should be performed as soon as possible and preferably within 48 hours of suspected pneumonia and severe exacerbation. Chest x-rays for moderate exacerbations should be performed if clinically appropriate. In all cases, the signs and symptoms that were used to identify the pneumonia must be documented in the source documents and eCRF. Diagnoses of pneumonia must be recorded as adverse events in the eCRF.

6.3.12.8. Oropharyngeal Examinations

Oropharyngeal examinations for clinical evidence of infection (i.e., Candida albicans) will be performed at Visit 1, 5 and 8 as part of the physical exam as shown in the Time and Events table (Table 12). If there is evidence of infection, appropriate therapy should be instituted at the discretion of the investigator. Subjects may continue in the study on
appropriate anti-infective treatment at the discretion of the investigator. The results of these assessments, and any resulting pharmacotherapy, will be recorded in the subject’s clinic notes and in the eCRF. All suspected cases of candidiasis must be reported as adverse events.

6.4. Health Outcomes

In addition to examining the impact of treatment on PRO, the PRO data will be used to address the following objectives:

- To explore the relationship of PROs with patient characteristics such as level of reversibility and obstruction, diagnosis and other measures of disease severity
- To explore the responsiveness of PRO measures to response on other outcomes and determine potential responder definitions

Further details of this analysis will be presented in the RAP.

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

The PROs are described in Section 6.2.6.2 and Section 6.2.6.3. The analyses of these endpoints will be defined in the reporting and analysis plan (RAP).

6.5. Pharmacogenetic (PGx) Research

Information regarding PGx research is included in Appendix 1.

7. DATA MANAGEMENT

For this study subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDurg. 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 primary efficacy endpoint is the change from baseline in clinic trough FEV$_1$ at the end of Treatment Phase A (Visit 6). Though the primary objective of the study is to model the dose response, comparisons among the treatments will also be carried out. The primary comparisons of interest are between each of the FF/UMEC doses and FF. Demonstration of the efficacy of each of the doses of FF/UMEC relative to FF will be based on a hypothesis testing approach whereby the null hypothesis is that the effect of each of the doses of FF/UMEC and FF on change from baseline in clinic trough FEV$_1$ is identical:

$H_0$: $\tau_i - \tau_j = 0$

where $i$= FF/UMEC 15.6mcg once daily, FF/UMEC 62.5mcg once daily, FF/UMEC 125mcg once daily, FF/UMEC 250mcg once daily, and $j$=FF.

The alternative hypothesis is that the effect of each dose of FF/UMEC and FF has different effects on change from baseline in clinic trough FEV$_1$:

$H_a$: $\tau_i - \tau_j \neq 0$.

Similar hypotheses will be tested for the comparison between FF/VI and FF.

Comparisons of selected doses of FF/UMEC versus FF/VI may also be conducted, if appropriate.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

Justification of Sample Size

The following questions are of interest:

1. Which is the appropriate set of doses of FF/UMEC to include: FF/UMEC 15.6, FF/UMEC 62.5, FF/UMEC 125, and FF/UMEC 250 or FF/UMEC 31.25, FF/UMEC 62.5, FF/UMEC 125, and FF/UMEC 250?

2. What is the probability that at least 150 mL difference is observed between each dose of FF/UMEC and FF?

3. What is the probability that at least 50 mL difference is observed between each dose of FF/UMEC and the next lower dose?

4. What is the probability that at least 50 mL difference is observed between each dose of FF/UMEC and FF/VI?

5. What is the required $n$?
In order to address these questions, simulations were carried out based on the effect sizes observed in ILA115938. Note that study ILA115938 was a three-period, incomplete block crossover study that included five doses of FF/UMEC, FF/VI, and FF100. Each simulation assumed that the standard deviation of change in trough FEV$_1$ was 350 mL, six treatment arms were included in the study (FF100, FF/UMEC 15.6 or FF/UMEC 31.25, FF/UMEC 62.5, FF/UMEC 125, FF/UMEC 250, and FF/VI), and the number randomized to each treatment arm was varied with twice as many assigned to the FF/UMEC 250 and FF/VI arms. A total of 10000 simulations were run for a variety of scenarios.

Three scenarios for the effect sizes were used to generate simulated trough FEV$_1$ data and are plotted in Figure 2 (includes the unadjusted changes from Period 1 in the subjects with persistent airflow obstruction) below:

- **Scenario 1**: Emax model for change from baseline in trough FEV$_1$ with $E0=101$ mL, $ED50=14.30$ mcg, and $Emax=283$ mL and form $E0 + \frac{E_{max} \times dose}{ED50 + dose}$; includes FF100, FF/UMEC 15.6, FF/UMEC 62.5, FF/UMEC 125, FF/UMEC 250, and FF/VI treatment arms;
- **Scenario 2**: Emax model and treatments as in Scenario 1 but the effects of UMEC reduced by half; and
- **Scenario 3**: Linear log dose model for change from baseline in trough FEV$_1$ with $\beta_0=106$ mL and $\beta_1=51.3$ mL and form $\beta_0 + \beta_1 \times \log(dose + 1)$; includes FF100, FF/UMEC 31.25, FF/UMEC 62.5, FF/UMEC 125, FF/UMEC 250, and FF/VI treatment arms.

Scenario 1 is the Emax model that was fit to the data obtained during Period 1 from subjects with persistent airflow obstruction, Scenario 2 has the effects of Scenario 1 reduced by half, and Scenario 3 is the log-dose linear model fit to the data obtained during Period 1 from subjects with persistent airflow obstruction. In each case, covariance between the effect estimates has been included in the data generation.
The number of subjects per simulated treatment arm ranged from 40 to 200 in each scenario.

For each set of simulated data, an analysis of variance model was fit and pairwise comparisons were constructed to estimate the effect of each FF/UMEC dose versus FF100, each FF/UMEC dose versus FF/VI, and each FF/UMEC dose versus the next lower dose of FF/UMEC and associated confidence intervals. The estimated treatment effect was the median effect size of the 10000 simulations and confidence intervals were constructed from the 2.5 and 97.5 percentiles. The probabilities of exceeding 150 mL or 50 mL were calculated as the proportion of simulations (out of 10000) in which the effect estimate was greater than 150 mL or 50 mL, respectively.

In order to determine which set of doses would be most appropriate, the mean width of the confidence intervals across the treatment comparisons was calculated for Scenario 1 and Scenario 2. The Emax model with doses FF/UMEC 15.6, FF/UMEC 62.5, FF/UMEC 125, and FF/UMEC 250 resulted in smaller confidence intervals than the log-dose linear model with doses FF/UMEC 31.25, FF/UMEC 62.5, FF/UMEC 125, and FF/UMEC 250. A summary is given in Figure 3 below.
The probability of observing at least 150 mL difference from FF 100 was calculated for each dose of FF/UMEC under each scenario. Similar probabilities were observed for Scenarios 1 and 3. A reduction in the expected treatment effect (Scenario 2) yielded smaller probabilities for identification of differences between FF/UMEC and FF100. The probabilities for the FF/UMEC 62.5 dose results appear in Figure 4 below.

**Figure 4** Summary of Probabilities (≥150 mL) for FF/UMEC 62.5 versus FF100
The probability of observing at least 50 mL difference from the next lower dose of FF/UMEC was calculated for each dose of FF/UMEC under each scenario. The probabilities for the FF/UMEC 62.5 dose results appear in Figure 5 below. Note that in Scenarios 1 and 2 the next lower dose is FF/UMEC 15.6 and in Scenario 3 the next lower dose is FF/UMEC 31.25.

**Figure 5** Summary of Probabilities (≥50mL) for FF/UMEC 62.5 versus Next Lower Dose

The probability of observing at least 50mL difference from FF/VI was calculated for each dose of FF/UMEC under each scenario. Probabilities were similar for Scenarios 1 and 3. The probabilities for the FF/UMEC 62.5 dose results appear in Figure 6 below.
If the true treatment effect is represented by Scenario 1 or Scenario 3, it is likely that at least one of the FF/UMEC dose combinations will show an effect greater than 150 mL versus FF100 when the number of subjects randomized to each treatment at least 40. Increasing sample sizes increase precision associated with the treatment comparisons and increase the probabilities of observing the differences of interest, but these increases appear to be small. Higher doses of FF/UMEC have higher probabilities of at least 150 mL versus FF100 and of at least 50 mL versus FF/VI.

Additionally, modeling the dose response curve will increase the power of the study as it uses the full data to estimate the effect of each dose. Randomization will be stratified by smoking history (as measured by pack years) and age when first treated with an inhaler in order to ensure adequate coverage of the population. It is planned that at least 70% of subjects will have <10 pack years smoking history (this includes non-smokers, former smokers and current smokers).

8.2.2. Sample Size Sensitivity

If the standard deviation observed in the study is different from value assumed in Section 8.2.1, the power to detect the planned difference in clinic trough FEV$_1$ will be affected. An increase in the between subject standard deviation would result in lower power for the comparisons of interest. Decreases in the between subject standard deviation would result in higher power for these comparisons under constant sample size.

8.2.3. Sample Size Re-estimation

No sample size re-estimation is planned.
8.3. Data Analysis Considerations

8.3.1. Analysis Populations

The following subject populations will be identified:

Total Population: This population will comprise all subjects screened and for whom a record exists on the study database and will be used for the tabulation and listing of reasons for withdrawal before randomization and listings of AEs and SAEs for non-randomized subjects.

Intent-to-Treat (ITT) Population: This population will comprise all subjects randomized to treatment and who received at least one dose of study medication. Randomized subjects will be assumed to have received study medication unless definitive evidence to the contrary exists. This will constitute the primary population for all analyses of efficacy measures and safety measures. Outcomes will be reported according to the randomized treatment allocation. Subjects will be included in the summary/analysis of a particular outcome if they provide at least one on-treatment assessment of that outcome.

Phase B Population: This population will comprise all ITT subjects who completed Phase A according the protocol and received at least one dose of Phase B study treatment. This will constitute the primary population for all analyses of efficacy measures and safety measures during Phase B. Outcomes will be reported according to the randomized treatment allocation.

Phase C Population: This population will comprise all ITT subjects who completed Phase A and Phase B according the protocol and received at least one dose of Phase C study treatment. This will constitute the primary population for all analyses of efficacy measures and safety measures during Phase C. Outcomes will be reported according to the randomized treatment allocation.

8.3.2. Analysis Data Sets

The analysis datasets will be Clinical Data Interchange Standards Consortium (CDISC)-compliant. Both Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets will be created and used for reporting. More details of the analysis datasets to be created will be given in the RAP.

8.3.3. Treatment Comparisons

8.3.3.1. Primary Comparisons of Interest

The primary comparisons of interest are between each of the four doses of FF/UMEC and FF alone for the primary endpoint of change from baseline in clinic trough FEV1 at the end of Treatment Phase A (Visit 6) for the ITT Population.

A 2-sided 5% risk associated with incorrectly rejecting any of the null hypotheses for these comparisons (significance level) is considered acceptable for this study.
8.3.3.2. Other Comparisons of Interest

Comparison of the primary endpoint between selected doses of FF/UMEC and FF/VI may be performed.

Comparisons of each active treatment (FF/UMEC or FF/VI) and FF will be performed for the secondary and other efficacy endpoints as well as for safety endpoints.

Though the study is powered on change from baseline in clinic trough FEV\(_1\), other efficacy measures may be used to further assess the doses of FF/UMEC.

8.3.4. 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 for each treatment phase will be a baseline evaluation and at least one on-treatment evaluation. Baselines for each treatment phase will be calculated from data collected in a previous phase or from data collected during the Run-in Period.

It is anticipated that approximately 60 centres will participate in the study.

8.3.4.1. Efficacy Analyses

All efficacy data will be summarized by treatment using means, standard deviations, medians, and ranges for continuous variables and frequencies and percentages for categorical variables. Individual subject data listings will be prepared for the raw data and any derived efficacy endpoints. Plots of raw data and endpoints will also be provided where warranted.

8.3.4.1.1. Primary Endpoint Analyses

Phase A

The primary endpoint for this study is change from baseline in clinic trough FEV\(_1\). FEV\(_1\) will be collected at each study visit prior to dosing. Change from baseline in trough FEV\(_1\) is defined as the difference in the value obtained at Visit 6 (24 hours post-dose) and the last acceptable/borderline acceptable value obtained prior to randomization (from Visit 2 pre-bronchodilator or Visit 3 pre-dose).

The primary planned analysis is modelling the dose-response curve of change from baseline in clinic trough FEV\(_1\). The shape of the dose response curve for change from baseline in clinic trough FEV\(_1\) at the end of Treatment Phase A (Visit 6) will be investigated. Several models including a linear model, a log linear model, and an Emax model will be used to characterize the dose response of UMEC. FF/VI data will be included in the model via a separate term. The model that appears to most accurately model the dose response will be used to predict the change from baseline in trough FEV\(_1\) (adjusted for FF) across the dose range of UMEC using-SAS procedure for nonlinear
mixed effect models or simulations if needed. Expected covariates in the model are baseline FEV₁ and treatment. Other covariates, such as age and sex, may also be included. Standard model checking and evaluation of the assumptions will be conducted to assess validity.

Plots will be produced to aid in the interpretation of results.

**8.3.4.1.2. Secondary Endpoint Analyses**

*Phase A*

As a supporting analysis, the change from baseline in clinic trough FEV₁ at the end of Treatment Phase A (Visit 6) will be analyzed using an ANCOVA model including study site, baseline FEV₁ and treatment as terms. This analysis also allows for comparisons of interest between FF/VI and FF and comparisons of interest between FF/UMEC and FF/VI. Adjusted means, the difference in adjusted means, and 95% confidence intervals for the differences will be presented for each treatment comparison of interest.

The analyses of change from baseline in rescue medication use and change from baseline in EXACT-RS score will be carried out in a manner similar to that specified above for change from baseline in clinic trough FEV₁. Changes will be based on the differences between the mean over the last 7 days of treatment and the mean over the last 7 days of the Run-in Period for each endpoint.

The change from baseline in daily AM PEF (measured at home) averaged over the last 21 days of treatment during Treatment Phase A will be analyzed using ANCOVA including baseline and treatment as covariates. Baseline will be derived from the last 7 days of data collected during the Run-in Period. The change from trough FEV₁ at 3 hours post-dose at Visit 5 will be analyzed using an ANCOVA model with covariates of trough FEV₁ and treatment. Trough FEV₁ is the FEV₁ value collected at Visit 5 prior to dosing. The change in clinic FEV₁ following 2 puffs of albuterol/salbutamol at Visit 5 will be analyzed using an ANCOVA model with covariates of treatment and baseline. Baseline is defined as the 3 hours post-dose FEV₁ obtained at Visit 5.

**8.3.4.1.3. Exploratory Endpoint Analyses**

*Phase A*

Clinic trough FEV₁ during Treatment Phase A will be analyzed via a random coefficients model with study site, baseline FEV₁, and treatment as covariates, if appropriate.

The change from baseline in wheeze score over the last 7 days of treatment during Treatment Phase A will be analyzed using ANCOVA including baseline and treatment as covariates. Baseline will be derived from the last 7 days of data collected during the Run-in Period. Additionally, random coefficients models with similar covariates will be constructed for home trough FEV₁, if appropriate.

The changes from baseline in home trough FEV₁ at the end of Treatment Phase A, over 1, 2, 3, and 4 weeks of Treatment Phase A, and averaged over Treatment Phase A will be analyzed using ANCOVA models including baseline home FEV₁ and treatment as covariates. The baselines for each measure will be derived from data collected during the Run-in Period.
The changes from baseline in each EXACT-RS subscale (breathlessness, cough and sputum, and chest symptoms) at the end of Treatment Phase A will be analyzed using ANCOVA models including baseline and treatment as covariates. Changes will be based on the differences between the mean over the last 7 days of treatment and the mean over the last 7 days of the Run-in Period for each subscale.

The number of exacerbations and the incidence of symptom-defined events (defined as an increase in EXACT score $\geq 9$ points above baseline for 3 days or $\geq 12$ points above baseline for 2 days) during Treatment Phase A will be summarized by treatment and compared via chi-square tests.

The number (percentage) of subjects with an improvement of $\geq 4$ points from baseline in SGRQ Total Score and each of the domains (Symptoms, Activity, and Impacts) at the end of Treatment Phase A will be summarized by treatment and compared via chi-square tests.

To determine differential responses and their phenotypic characteristics, exploratory and subgroup analyses will be performed for the primary endpoint. Subjects will be phenotyped during the screening and randomization visits to assess possible predictors of response. The predictors of particular interest will be detailed in the RAP.

**Phase B**

The change from baseline in clinic trough FEV$_1$ at the end of Treatment Phase B (Visit 7) will be analyzed using an ANCOVA model including study site, baseline FEV$_1$ and treatment as covariates. An additional covariate of end of Treatment Phase A FEV$_1$ may also be included. Baseline FEV$_1$ is the last acceptable/borderline acceptable value obtained prior to randomization (from Visit 2 pre-bronchodilator or Visit 3 pre-dose).

**Phase C**

The change from baseline in clinic trough FEV$_1$ at the end of Treatment Phase C (Visit 8) will be analyzed using an ANCOVA model including study site, baseline FEV$_1$ and treatment as covariates. An additional covariate of end of Treatment Phase A FEV$_1$ may also be included. Baseline FEV$_1$ is the last value obtained prior to dosing at Visit 7, if available.

Home trough FEV$_1$ during Treatment Phase C will be analyzed via a random coefficients model with study site, home trough FEV$_1$ at end of Treatment Phase B, and treatment as covariates, if appropriate.

The change from baseline in clinic trough FEV$_1$ at the end of Treatment Phase C (Visit 8) for the subset of subjects who have taken FF/UME or FF/UME/VI for two weeks over Phase B and Phase C, will be analyzed using an ANCOVA model including study site, baseline FEV$_1$ and treatment as covariates. The clinic trough FEV$_1$ at end of Treatment Phase A may also be included. Baseline is defined as the pre-dose clinic trough FEV$_1$ at the Visit 6.

Further details of these and any other planned analyses will be included in the RAP.
8.3.4.2. Safety Analyses

All safety data will be listed and summarized by treatment for each of the treatment phases.

Formal statistical analyses will be performed on changes from baseline in pulse rate and systolic and diastolic blood pressure via ANCOVA models that include baseline and treatment as covariates. Baselines will be derived from the vital signs data collected at Visit 3.

Further details will be given in the RAP.

8.3.4.3. Health Outcomes Analyses

The responsiveness of each questionnaire in the population under study will also be compared. The inclusion of these patient reported outcomes and the comparative analysis are to inform the Phase III program. Analyses will be carried out to address the exploratory objectives:

- To explore the relationship of PROs with patient characteristics such as level of reversibility and obstruction, diagnosis and other measures of disease severity
- To explore the responsiveness of PRO measures to response on other outcomes and determine potential responder definitions

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 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:

- IRB/ 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.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., PGx assessments described in Appendix 1, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

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) agree 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 randomization 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.

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


James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Protein Adducts in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37(8): 1779-1784.


Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. Eur Respir J 2002;19:398-404


11. APPENDICES

11.1. Appendix 1: Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx associations with safety/adverse events include:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease</th>
<th>Gene Variant</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>HIV</td>
<td>HLA-B* 57:01 (Human Leukocyte Antigen B)</td>
<td>Carriage of the HLA-B<em>57:01 variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective HLA-B</em>57:01 screening and exclusion of HLA-B<em>57:01 positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective HLA-B</em>57:01 screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. HLA-B*57:01 screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Seizure, Bipolar disorders &amp; Analgesia</td>
<td>HLA-B*15:02</td>
<td>Independent studies indicated that patients of East Asian ancestry who carry HLA-B<em>57:02 are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of HLA-B</em>57:02 prior to initiating treatment with carbamazepine.</td>
</tr>
<tr>
<td>Drug</td>
<td>Disease</td>
<td>Gene Variant</td>
<td>Outcome</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>--------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Cancer</td>
<td>UGT1A1*28</td>
<td>Variations in the UGT1A1 gene can influence a patient’s ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular UGT1A1 gene variation might be too high for another patient without this variation, raising the risk of certain side-effects that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the UGT1A1*28 variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.</td>
</tr>
</tbody>
</table>

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

For example, PGX research recently led to the identification of an association between genetic variants in the gene GLCCI1 and response to glucocorticoid therapy in asthma [Tantisira, 2011].

Collection of whole blood samples, even when no a priori hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to fluticasone furoate (FF), fluticasone furoate/umeclidinium bromide (FF/UMEC), fluticasone furoate/vilanterol (FF/VI), or fluticasone propionate/salmeterol (FSC).

**Pharmacogenetic Research Objectives**

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to FF, FF/UMEC, FF/VI, or FSC. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with FF, FF/UMEC, FF/VI, or FSC, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Safety and/or tolerability
- Efficacy

**Study Population**

Any subject who is enrolled in the clinical study, can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.
Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

**Study Assessments and Procedures**

Blood samples can be taken for Deoxyribonucleic acid (DNA) extraction and used in PGx assessments.

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

- The PGx sample is labelled (or “coded”) with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or a set of studies) of FF, FF/UMEC, FF/VI, or FSC has been completed and the clinical study data reviewed. In some cases, the samples may not be studied, e.g., no questions are raised about how people respond to FF, FF/UMEC, FF/VI, or FSC.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

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

**Subject Withdrawal from Study**

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

- Continue to participate in the PGx research with the PGx sample retained for analysis
- Withdraw from the PGx research and destroy the PGx sample
If a subject withdraws consent for PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. The investigator should forward the Pharmacogenetic Sample Destruction Request Form to GSK as directed on the form. This can be done at any time when a subject wishes to withdraw from the PGx research or have their sample destroyed whether during the study or during the retention period following close of the main study.

**Screen and Baseline Failures**

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

**Pharmacogenetics Analyses**

Pharmacogenetics Analyses

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.  

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to FF, FF/UMEC, FF/VI, or FSC. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarised as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study RAP or in a separate pharmacogenetics RAP, as appropriate.
Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research.

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

GSK may summarise the PGx research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject’s medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.
References


11.2. Appendix 2: Country Specific Requirements

No country-specific requirements exist.
11.3. Appendix 3: Liver Chemistry Stopping and Follow-up Criteria

Phase II Liver Safety Algorithms

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

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

1. ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT ≥ 3xULN and INR > 1.5, if INR measured).

NOTE: If serum bilirubin fractionation is not immediately available, withdraw study drug for that subject 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 ≥ 5xULN.

3. 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 believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. ALT ≥ 3xULN persists for ≥4 weeks
5. ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks

When any of the liver chemistry stopping criteria 1-5 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 bilirubin) (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, withdraw study drug for that subject 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, stabilise, or return to baseline values as described below.
- Withdraw the subject from the study (unless further safety follow up is required) after completion of the liver chemistry monitoring as described below.
- Do not re-challenge with investigational product.

In addition, for criterion 1:

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

For criteria 2, 3, 4 and 5:

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

Subjects with 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, stabilise 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 normalise or return to within baseline values.

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

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Cytomegalovirus IgM antibody;
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
  - Hepatitis E IgM antibody
- 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, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).
- 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.
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Protein Adducts in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37(8): 1779-1784.
11.4. Appendix 4: Important Study Assessment Details & Study Specific Equipment

Subjects do not have to fast prior to collection of blood samples.

Refer to the Time and Events Table (Table 12) for information regarding the timing of laboratory tests.

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Hematology</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>Hemoglobin</td>
<td>Hepatitis B surface antigen(^1)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Hematocrit</td>
<td>Hepatitis C virus antibody(^1)</td>
</tr>
<tr>
<td>Alanine amino-transferase</td>
<td>Platelet count</td>
<td>hCG qualitative (serum pregnancy)(^2)</td>
</tr>
<tr>
<td>(ALAT or SGPT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate amino-transferase</td>
<td>WBC count</td>
<td>Urine pregnancy test (in clinic/home test)(^2)</td>
</tr>
<tr>
<td>(ASAT or SGOT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, direct</td>
<td>Neutrophils, absolute</td>
<td>Total Serum IgE</td>
</tr>
<tr>
<td>Bilirubin, indirect</td>
<td>Neutrophils, segs (%)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin, total</td>
<td>Neutrophils, bands (%)</td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>Basophils (%)</td>
<td></td>
</tr>
<tr>
<td>CO2 content/Bicarbonate</td>
<td>Eosinophils (%)</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>Eosinophils, absolute</td>
<td></td>
</tr>
<tr>
<td>Creatine phosphokinase (CPK)</td>
<td>Lymphocytes (%)</td>
<td></td>
</tr>
<tr>
<td>Gamma glutamyl transferase</td>
<td>Monocytes (%)</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein, total serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea nitrogen (BUN)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Assessed at Visit 1 (Screening) only
\(^2\) Only females of child-bearing potential; refer to Time and Events Table for specific visit information
11.5. Appendix 5: Protocol Changes

Protocol Amendment 01

This amendment applies to all study centers participating in study 200699.

Description

This amendment was implemented in order to modify the treatment duration of Phase B and visit windows of Phase B and Phase C. Updates were also made to clarify procedures, update inclusion/exclusion criteria, ensure consistency in the definition of severe exacerbation, and ensure the EXACT endpoint definition was consistent with the EXACT manual. Minor adjustments in wording were made to exploratory endpoints and statistical testing methods.

Method of Amendment

Original and amended text is presented together below with the text removed being struck through and the new text being bolded in the order of occurrence.

Amendment Details

Protocol Summary/Study Endpoints/Assessment/Exploratory Endpoints (bullet 9)

This edit clarifies the endpoint to match the EXACT manual created by Evidera.

REVISED TEXT:

- Number Incidence of symptom-defined events: Acute, sustained symptomatic worsening of COPD, defined as an increase in EXACT score $\geq 9$ points for 3 days or $\geq 12$ points for 2 days, above baseline during Treatment Phase A

Section 4.2.1 Inclusion Criteria

This edit removes the reference to ethnicity as it is not part of the ERS Global Lung Function Initiative predicted normal equation.

2. **Diagnosis:** At the point of screening subjects, have sufficient medical history (e.g., signs and symptoms) to diagnose the subject as having COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society (Celli, 2004), AND evidence of an asthmatic component as demonstrated by spirometry, reversibility and current therapy at Visit 1 as follows:

A. Spirometry:

   1. A best post-bronchodilator morning (AM) $FEV_1 \geq 50\%$ and $\leq 80\%$ of the predicted normal value at Visit 1. Predicted values will be based upon the ERS Global Lung Function Initiative [Quanjer, 2012]. If a subject is recorded as having Hispanic or Latino ethnicity, then the Caucasian equations will be used (irrespective of race).
If a subject is recorded as being of African heritage/African-American race, then the African-American equations will be used.

AND

2. Pre- and post-bronchodilator FEV$_1$/FVC ratio <0.7 at Visit 1.

Section 4.2.2 Exclusion Criteria

This edit clarifies the severe exacerbation definition used in this study and creates consistency with this definition throughout the protocol.

3. **Severe Exacerbation:** A subject must not have had an exacerbation prior to Visit 1 meeting either of the following severity criteria:
   
   - Deterioration of COPD or asthma requiring either the use of oral corticosteroids for at least 3 days or parenteral corticosteroids in the previous 3 months.
   - An in-patient hospitalization or emergency department visit due to COPD or asthma that required any oral or parenteral corticosteroids in the previous 6 months

   For consistency, courses of corticosteroids separated by 1 week or more should be treated as separate exacerbations.

Section 4.2.2 Exclusion Criterion 11

This edit allows for use of beta-blockers at the investigator’s discretion and clarifies the time for withholding LABA prior to Visits1, 2, and 3.

11. **Concomitant Medication:** Administration of prescription or over-the-counter medication that would significantly affect the course of COPD or asthma, or interact with study drug, such as:
   
   - Beta-adrenergic blocking medications, including beta-blocker eye drops (e.g., timolol, betaxolol)
   - Anticholinergic medications, with the exception of those used for gastrointestinal or genitourinary conditions such as overactive bladder or those which have minimal systemic effects
   - Potent Cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, clarithromycin)
   - Anticonvulsants (barbiturates, hydantoins, carbamazepine)
   - Polycyclic antidepressants
   - Phenothiazines

Monoamine oxidase (MAO) inhibitors
Table 3  Concomitant Respiratory Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>No use within the following time interval before visit 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous, intramuscular (including depot), intra-articular, or oral</td>
<td>12 weeks</td>
</tr>
<tr>
<td>corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Inhaled short-acting anticholinergics</td>
<td>6 hours</td>
</tr>
<tr>
<td>Inhaled short-acting anticholinergics+ Short-acting beta agonist combination</td>
<td>6 hours</td>
</tr>
<tr>
<td>Inhaled long-acting anticholinergics</td>
<td>7 days</td>
</tr>
<tr>
<td>Anti-IgE (e.g., Xolair)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Immunosuppressive medications including immunomodulators</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Allergen immunotherapy for the treatment of allergies</td>
<td>Allowed during the study provided it was initiated at least 4 weeks prior to Visit 1 and the subject remains in the maintenance phase throughout the study</td>
</tr>
<tr>
<td>Inhaled long-acting beta\textsubscript{2}-agonists (e.g., salmeterol, formoterol) or combination products containing inhaled long-acting beta\textsubscript{2}-agonists (e.g., Seretide, Symbicort)</td>
<td>Must be withheld after the morning dose on the day before the visit (for Visits 1, 2, and 3) 12 hours</td>
</tr>
<tr>
<td>Inhaled very long-acting beta2-agonists, (Vilanterol, Indacaterol, Olodaterol)</td>
<td>10 days for Vilanterol, Indacaterol and Olodaterol component</td>
</tr>
<tr>
<td>Oral long-acting beta\textsubscript{2}-agonists (e.g., bambuterol)</td>
<td></td>
</tr>
<tr>
<td>Inhaled short-acting beta\textsubscript{2}-agonist (rescue albuterol/salbutamol is permitted during the study)</td>
<td>4 hours (including all study visits)</td>
</tr>
<tr>
<td>Theophyllines, anti-leukotrienes, slow-release bronchodilators, ketotifen, nedocromil sodium, sodium cromoglycate, roflumilast</td>
<td>48 hours</td>
</tr>
<tr>
<td>Any other investigational drug</td>
<td>30 days or within 5 drug half-lives of the investigational drug (whichever is longer)</td>
</tr>
</tbody>
</table>

Section 4.2.4 Randomization Exclusion Criteria (#5)

This edit clarifies the severe exacerbation definition used in this study and creates consistency with this definition throughout the protocol.

5. **Evidence of an Severe Exacerbation:** A subject must not have had an exacerbation between Visit 1 and Visit 3 meeting either of the following severity criteria:
   - Deterioration of COPD or asthma requiring the use of oral corticosteroids for at least 3 days or parenteral corticosteroids
   - An in-patient hospitalization or emergency department visit due to COPD or asthma that required any oral or parenteral corticosteroids

For consistency, courses of corticosteroids separated by 1 week or more should be treated as separate exacerbations.
Section 4.3.1 Protocol-Defined IP Discontinuation Criteria #1

This edit clarifies the severe exacerbation definition used in this study and creates consistency with this definition throughout the protocol.

1. **Severe Exacerbation** defined as either of the following: deteriorate of COPD or asthma requiring the use of oral corticosteroids for at least 3 days or requiring parenteral corticosteroids.
   - Deterioration of COPD or asthma requiring either the use of oral corticosteroids for at least 3 days or parenteral corticosteroids
   - An in-patient hospitalization or emergency department visit due to COPD or asthma that required any oral or parenteral

Section 4.4 Withdrawal Criteria

This edit clarifies that all patients who discontinue IP or withdraw from the study will, at a minimum, have vital status recorded.

For this study there are no pre-determined protocol specific study withdrawal criteria (see Section 4.3.1 for protocol defined stopping IP criteria).

If a subject meets IP discontinuation criteria, at a minimum, the subject’s vital status will be tracked for the duration of the study via either telephone contact or a Follow-Up visit.

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

Section 4.4.4 Reasons for Study Withdrawal

The section was updated to include investigator discretion as a reason for study withdrawal.

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

The primary reason for study withdrawal will be categorized as:

1. Adverse event
2. Study closed/terminated
3. Lost to follow-up
4. Withdrew consent Investigator Discretion
   - Subject relocated
   - Frequency of visits
5. Withdrew consent

- Subject relocated
- Frequency of visits
- Burden of procedures
- Other (specify)

Section 5.1 Investigational Product and Other Study Treatment Paragraphs 4 and 5

This section was updated to correctly reflect the inactive ingredients in the placebo containing devices.

For Treatment Phase B the FF/UMEC/VI treatments will be provided in two inhalers, one device containing FF and UMEC as described above and the other device containing VI (blended with lactose and magnesium stearate in a dual strip) (one strip containing VI blended with lactose and magnesium stearate and one strip containing lactose). The FF/UMEC treatments in Treatment Phase B will also have two devices; one device with FF/UMEC as described above and the other a dual-strip placebo device.

Treatments in Treatment Phase C will also be delivered in two devices to retain the blind. The FF/UMEC/VI treatment will consist of one device containing FF and UMEC as described above and the other device containing VI (blended with lactose and magnesium stearate in a dual strip) (one strip containing VI blended with lactose and magnesium stearate and one strip containing lactose). The FF/UMEC, FF/VI and FF treatments will be delivered in a device as described at the beginning of this section and one dual-strip placebo device.

Section 5.1 Table 8 and 9

These tables were updated to correctly reflect the inactive ingredients in the placebo containing devices.

Table 8 Description of VI Inhalation Powder DPI

<table>
<thead>
<tr>
<th>Formulation</th>
<th>First strip</th>
<th>Second strip</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VI blended with lactose and magnesium stearate</td>
<td>Lactose and magnesium stearate</td>
</tr>
<tr>
<td>Dosage Form</td>
<td>DPI with 30 doses (2 strips with 30 blisters)</td>
<td></td>
</tr>
<tr>
<td>Unit Dose Strengths</td>
<td>25 mcg per blister</td>
<td>0 mcg per blister N/A</td>
</tr>
<tr>
<td>Physical description</td>
<td>Dry white powder</td>
<td>Dry white powder</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Inhaled</td>
<td></td>
</tr>
</tbody>
</table>
Table 9 Description of Placebo Inhalation Powder DPI

<table>
<thead>
<tr>
<th>Formulation</th>
<th>First strip</th>
<th>Second strip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose and magnesium stearate</td>
<td>Lactose and magnesium stearate</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>DPI with 30 doses (2 strips with 30 blisters)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Unit Dose Strengths</th>
<th>0 mcg per blister</th>
<th>N/A</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Physical description</th>
<th>Dry white powder</th>
<th>Dry white powder</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Inhaled</th>
</tr>
</thead>
</table>

Section 5.2 Treatment Assignment

The edit creates clarity of the subject stratification groups for randomization.

Subjects will be assigned to study treatment in accordance with the randomization schedule. The randomization code will be generated by GSK using a validated computerized system, RandAll. Subjects will be randomized using an IVRS.

Following the completion of the run-in period, eligible subjects will be stratified by smoking status and age when first treated with an inhaler and randomized to 1 of 24 treatment sequences. The strata are as follows:

<table>
<thead>
<tr>
<th>Stratum Code</th>
<th>Stratum Description</th>
<th>Stratum definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Never/Light Smoker Early Treatment</td>
<td>&lt;10 pack years and &lt;30 years of age when first treated with an inhaler</td>
</tr>
<tr>
<td>2</td>
<td>Never/Light Smoker Late Treatment</td>
<td>&lt;10 pack years and ≥30 years of age when first treated with an inhaler</td>
</tr>
<tr>
<td>3</td>
<td>Heavy Smoker Early Treatment</td>
<td>≥10 pack years and &lt;30 years of age when first treated with an inhaler</td>
</tr>
<tr>
<td>4</td>
<td>Heavy Smoker Late Treatment</td>
<td>≥10 pack years and ≥30 years of age when first treated with an inhaler</td>
</tr>
</tbody>
</table>

Section 5.6.1.1 Permitted COPD and Asthma Medications (bullets 4 and 5)

These edits clarify the time for withholding LABA prior to Visits 1, 2, and 3.

- Note: If the subject is on an ICS/LABA for at least 4 weeks prior to Visit 1, then after signing informed consent the subject must discontinue LABA therapy at least 12 hours after the morning dose on the day before starting the study (prior to Screening/Visit1) and, at the investigator’s discretion, continue appropriate therapy (i.e., the same or equivalent ICS dose as monotherapy).

- Study-provided FSC will be started at Visit 1 if the subject meets screening eligibility. This medication will be used throughout the run-in period, but it must be withheld at least 12 hours after the morning dose on the day before Visits 2 and 3.
for lung function testing. FSC will be returned at the end of the run-in period to avoid confusion with study medication.

**Section 5.6.1.2 Permitted Non-COPD and Non-Asthma Medications**

This edit allows for the use of beta-blockers at the investigator’s discretion.

The following medications are permitted during this study:

- Medications for rhinitis (e.g., intranasal corticosteroids, antihistamines [including ocular and intranasal], cromolyn, nedocromil, nasal decongestants)
  
  Note: Information on the use of these medications should be captured prior to ECG measurements.

- Antibiotics for short term treatment of acute infections other than respiratory

- Decongestants: Subjects may take decongestants during the study, but these are disallowed for 24 hours prior to ECG measurements.

- Immunotherapy: Immunotherapy for the treatment of allergies is allowed during the study provided it was initiated 4 weeks prior to Visit 1 and subjects remain in the maintenance phase for the duration of the study.

- Topical corticosteroids: Subjects may use topical corticosteroids (≤1% hydrocortisone cream) for dermatological diseases. Non-corticosteroid containing creams are permitted.

- **Systemic and ophthalmic beta-blockers**: Administer with caution as systemic beta-blockers block the pulmonary effect of beta-agonists and may produce severe bronchospasm in patients with reversible obstructive airways disease. Cardioselective beta-blockers should be considered, although they also should be administered with caution.

- Flu vaccine

- Pneumonia vaccine

**Section 5.6.2 Prohibited Medications and Non-Drug Therapies**

These edits removes beta blockers from prohibited medications, allowing their use at the investigator’s discretion and clarify the time for withholding LABA before Visits 1, 2, and 3.

**Table 11 Concomitant Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>No use within the following time interval before Visit 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous, intramuscular (including depot), intra-articular, or oral corticosteroids</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Inhaled short-acting anticholinergics</td>
<td>6 hours</td>
</tr>
<tr>
<td>Inhaled short-acting anticholinergics + Short-acting beta agonist combination</td>
<td>6 hours</td>
</tr>
<tr>
<td>Inhaled long-acting anticholinergics</td>
<td>7 days</td>
</tr>
<tr>
<td>Anti-IgE (e.g., Xolair)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Medication</td>
<td>No use within the following time interval before Visit 1</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>Immunosuppressive medications including immunomodulators</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Allergen immunotherapy for the treatment of allergies</td>
<td>Allowed during the study provided it was initiated at least 4 weeks prior to Visit 1 and the subject remains in the maintenance phase throughout the study</td>
</tr>
<tr>
<td>Inhaled long-acting beta(_2)-agonists (e.g., salmeterol, formoterol) or combination products containing inhaled long-acting beta(_2)-agonists (e.g., Seretide, Symbicort) Inhaled very long-acting beta2-agonists, (Vilanterol, Indacaterol, Olodaterol) Oral long-acting beta(_2)-agonists (e.g., bambuterol)</td>
<td><strong>Must be withheld after the morning dose on the day before the visit (for Visits 1, 2, and 3)</strong> 42 hours 10 days for Vilanterol, Indacaterol and Olodaterol component 10 days</td>
</tr>
<tr>
<td>Inhaled short-acting beta(_2)-agonist (rescue albuterol/salbutamol is permitted during the study)</td>
<td>4 hours (including all study visits)</td>
</tr>
<tr>
<td>Theophyllines, anti-leukotrienes, slow-release bronchodilators, ketotifen, nedocromil sodium, sodium cromoglycate, roflumilast</td>
<td>48 hours</td>
</tr>
<tr>
<td>Any other investigational drug</td>
<td>30 days or within 5 drug half-lives of the investigational drug (whichever is longer)</td>
</tr>
</tbody>
</table>

A subject may not concurrently use any other prescription or over-the-counter medication which may affect the course of COPD or asthma or interact with study drug, such as:

- Beta-adrenergic blocking medications, including beta-blocker eye drops (e.g., timolol, betaxolol)
- Anticholinergic medications, with the exception of those used for gastrointestinal or genitourinary conditions such as overactive bladder or those which have minimal systemic effects
- Potent Cytochrome P450 3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole)
- Anticonvulsants (barbiturates, hydantoins, carbamazepine)
- Polycyclic antidepressants
- Phenothiazines
- MAO inhibitors

**Section 6 Study Assessments and Procedures**

This edit updates the Time and Events table to provide clarity on procedures to be performed, consistency of the procedures between the protocol text and the table, and provides additional detail to procedures in the footnotes of the table.
## Table 14  Time and Events

<table>
<thead>
<tr>
<th>Protocol Activity</th>
<th>Pre-Screen</th>
<th>Screen / Run-In</th>
<th>Run-In</th>
<th>Phase A: Dose-Ranging</th>
<th>Phase B: Benefit of LABA</th>
<th>Phase C: Carryover</th>
<th>IP Discontinuation/Early Withdrawal</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 0(^a)</td>
<td>Visit 1(^b)</td>
<td>Visit 2</td>
<td>Visit 3</td>
<td>Visit 4</td>
<td>Visit 5(^c)</td>
<td>Visit 6</td>
<td>Visit 7</td>
</tr>
<tr>
<td>Study Day</td>
<td>-28</td>
<td>-7</td>
<td>1</td>
<td>1415</td>
<td>28</td>
<td>29</td>
<td>35</td>
<td>Visit 6 +7d</td>
</tr>
<tr>
<td>Window</td>
<td></td>
<td>-/+2d</td>
<td>-/+2d</td>
<td>-/+2d</td>
<td>-/+2d</td>
<td>-/+2d +3d</td>
<td>-/+2d +3d</td>
<td>+2d</td>
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<tr>
<td>Informed Consent Process</td>
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<td></td>
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<td></td>
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<tr>
<td>Subject Demography</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Medical/Disease History(^d)</td>
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<td></td>
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<td>MMRC Dyspnea Scale</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
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<td></td>
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<td>Randomization</td>
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</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>X(^e)</td>
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<td></td>
</tr>
<tr>
<td>IP Discontinuation Phone Call Follow-up(^f)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

### Efficacy Assessments

<p>| Spirometry(^g) | X | X | X | X | X | X | X | X | X | X | X |
| Reversibility(^h) | X | X | X | X | X | X | X | X | X | X | X |
| Spirometry(^i) | X | X | X | X | X | X | X | X | X | X | X |
| Peak Pre-/Post-Bronchodilator Spirometry | X | X | X | X | X | X | X | X | X | X | X |
| Subject-initiated Spirometry(^j) | X | X | X | X | X | X | X | X | X | X | X |
| St. George's Respiratory Questionnaire | X | X | X | X | X | X | X | X | X | X | X |</p>
<table>
<thead>
<tr>
<th>Protocol Activity</th>
<th>Pre-Screen</th>
<th>Screen / Run-In</th>
<th>Run-In</th>
<th>Phase A: Dose-Ranging</th>
<th>Phase B: Benefit of LABA</th>
<th>Phase C: Carryover</th>
<th>IP Discontinuation/Early Withdrawal</th>
<th>Follow Up</th>
<th>Telephone Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 0⁺</td>
<td>Visit 1⁻</td>
<td>Visit 2</td>
<td>Visit 3</td>
<td>Visit 4</td>
<td>Visit 5⁻</td>
<td>Visit 6</td>
<td>Visit 7</td>
<td>Visit 8</td>
</tr>
<tr>
<td><strong>Study Day</strong></td>
<td></td>
<td>-28</td>
<td>-7</td>
<td>1</td>
<td>4415</td>
<td>28</td>
<td>29</td>
<td>35 Visit 6 +7d</td>
<td>42-Visit 7+7d</td>
</tr>
<tr>
<td><strong>Window</strong></td>
<td></td>
<td>-/+2d</td>
<td>-/+2d</td>
<td>-/+2d</td>
<td>-/+2d</td>
<td>-/+2d +3d</td>
<td>-/+2d +3d</td>
<td>+2d</td>
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</tr>
<tr>
<td>Patient Global Impression of Disease Severity</td>
<td>X</td>
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<td>Patient Global Impression of Change</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>COPD or Asthma Exacerbation Assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Dispense Medical Problems/Medications Taken Diary</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of Medical Problems/Medications Taken Diary</td>
<td>X</td>
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<td></td>
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<td>Dispense AM3/eDiary*</td>
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<tr>
<td>Collection of AM3/eDiary</td>
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<tr>
<td>Review Diaries</td>
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<td>X</td>
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<td>X</td>
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<tr>
<td><strong>Safety Assessments</strong></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant Medications†</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Physical Exam*</td>
<td>X</td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Vital Signs</td>
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<td>X</td>
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<td>X</td>
<td>X</td>
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<td></td>
</tr>
<tr>
<td>12-Lead ECG</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Adverse Events Assessment / SAEs</td>
<td>X</td>
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*IP Disc/EW
**IP Disc or Visit 8 +7d
†Follow Up
‡Patient Global Impression of Disease Severity
§Patient Global Impression of Change
‖COPD or Asthma Exacerbation Assessment
¶Dispense Medical Problems/Medications Taken Diary
**Dispense AM3/eDiary
***Collection of Medical Problems/Medications Taken Diary
****Dispense AM3/eDiary
*****Collection of AM3/eDiary
******Review Diaries
††Safety Assessments
‡‡Concomitant Medications
§§Physical Exam
‖‖Vital Signs
****12-Lead ECG
*****Adverse Events Assessment / SAEs
******Laboratory Assessments
*******Chemistry

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<th>Phase B: Benefit of LABA</th>
<th>Phase C: Carryover</th>
<th>IP Discontinuation/Early Withdrawal</th>
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Visit 0 and Visit 1 can be combined if no washout of medications is required.

Note: All clinical visits will occur between 6 and 11 in the morning except for the pre-screen visit.

The procedures in Visit 5 could take up to 6 hours to complete. Subjects and investigational sites should plan accordingly.

Includes detailed smoking, respiratory, and cardiovascular history.

Reversibility demonstrated by ≥12% and ≥200 mL reversibility of FEV₁ within 20-60 minutes following 4 inhalations of albuterol/salbutamol inhalation aerosol (or equivalent nebulised treatment with albuterol/salbutamol solution) at Screening and Visit 2. Spirometry including reversibility at Visit 2 determines eligibility for randomization at Visit 3.

Subjects who complete the IP Discontinuation /Early Withdrawal Visit for permanent discontinuation of IP, should continue to have telephone contacts according to the visit schedule to assess exacerbations, adverse events, and concomitant medications.

Spirometry measurements for this study will be conducted pre-bronchodilator and pre-dose at each visit. Starting after the randomization visit and throughout the treatment duration, subjects will be required to inform the site staff of the time of the dose prior to the visit and perform trough FEV₁ measurements approximately 24 hours post-dose.

Spirometry measurements will be conducted at home by the subject in the morning and evening each day from Visit 1 through Visit 8.

To be conducted at IP Disc/EW if this visit takes place after Visit 3 and before Visit 5.

Chest x-rays should be performed if pneumonia is suspected.

Includes EXACT and wheeze questionnaires and rescue medication use diary.

All current concomitant medications are to be collected, and COPD and asthma medications taken during the 30 days prior to Visit 0 also are to be collected.

Including oropharyngeal examination.

12-lead ECGs will be performed pre-dose and 10 minutes post-dose at randomization and at the end of 4 weeks.

Informed consent for optional pharmacogenetics (PGx) research should be obtained before collecting a sample. The sample can be obtained any time after randomization.

A pregnancy test is required for all females of child bearing potential.

Albuterol will be dispensed at clinic visits on an individual as-needed basis.
Section 6.1 Critical Screening Assessments

The purpose of this edit is to create transparency around the data collected in this study being combined with data from other studies to further characterize the asthma-COPD overlap syndrome.

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

- Demographic history (including gender, ethnic origin, date of birth)

*Visit 0 and Visit 1 can be combined if the subject does not require wash-out from prohibited medications. See Table 3 for required wash-out periods.*

The following critical screening assessments will be conducted at Visit 1:

- Height and weight
- COPD and/or asthma diagnosis history (including duration of disease)
- Smoking history
- Exacerbation history
- COPD, asthma, and other concurrent medications
- Medical History including previous and/or concurrent medical conditions, pneumonia, and pneumonia vaccine status
- Reason for screen failure (if applicable)
- Lung function
- Vital signs
- Pre-and post-albuterol/salbutamol lung function (reversibility)
- Inclusion/Exclusion criteria assessment
- Physical examination including oropharyngeal exam
- 12-lead ECG
- Clinical laboratory tests (including hematology, chemistry, Hepatitis B antigen and Hepatitis C antibody testing, urinalysis and pregnancy test)
- SAE assessment

*Information collected during this study regarding spirometry and medical and respiratory history will be combined with data from other respiratory studies to further characterize the asthma-COPD overlap syndrome.*

See Section 4.5 for any specific data to be collected for screen failures.
Section 6.2.3 Other Efficacy / Exploratory (bullet 9)

This edit clarifies the endpoint to match the EXACT manual created by Evidera.

- **Number Incidence** of symptom-defined events: Acute, sustained symptomatic worsening of COPD, defined as an increase in EXACT score ≥9 points for 3 days or ≥12 points for 2 days, above baseline during Treatment Phase A.

Section 6.2.6.5 Global Impression of Change Scale

The purpose of this change is to accurately reflect both the two Global Impression scales that are utilized in the study by updating the title of this section to Global Patient Impression of Severity and Change Scales.

6.2.6.5 Global Impression of Severity and Change Scales

Section 6.2.7 St. George's Respiratory Questionnaire (SGRQ) (paragraph 3)

The purpose of the change is to the site staff to verify the completeness of the SGRQ before the subject leaves the clinical.

The SGRQ is self-completed by subjects, taking on average 20 minutes, and subjects should complete all the questions. The investigator will ask the subject to complete all questions as accurately as possible. If the subject requests help or clarification of any question in the SGRQ, he or she should be asked to reread the instructions and give the answer that best reflects how he/she feels. The subject should be reassured that there are no right or wrong answers. The investigator will not provide the subject with any answer or attempt to interpret any portion of a question. The form should be reviewed for completeness prior to the subject leaving the study site for the visit, and the subject should be encouraged to respond to any missing items.

Section 6.3.12.1.1 Exacerbations

Since the protocol states there are pre-defined study withdraw criteria, this edit clarifies that patients should be discontinued from IP in the event of a severe exacerbation. The definition of a severe exacerbation has been modified for clarity and to be consistent with other sections of the protocol.

A subject will be withdrawn **discontinued from IP** due to lack of efficacy if he/she experiences a severe exacerbation.

An exacerbation is defined as an acute worsening of respiratory symptoms requiring the use of any treatment beyond study medication or rescue albuterol/salbutamol. This includes the use of systemic corticosteroids, antibiotics, and/or emergency treatment or hospitalization. All exacerbations will be recorded on the exacerbation page of the eCRF. Subjects who experience an exacerbation meeting specific severity criteria during the run-in period will not be randomized and will not be allowed to be re-screened. Subjects who experience a severe exacerbation during the treatment period will be withdrawn from investigational product.
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 6.3.3.2 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.

Severe Exacerbations

For the purposes of this study, a **severe exacerbation** is defined as either of the following: deterioration of COPD or asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an in-patient hospitalization or emergency department visit due to COPD or asthma that required systemic corticosteroids.

- Deterioration of COPD or asthma requiring either the use of oral corticosteroids for at least 3 days or parenteral corticosteroids
- An in-patient hospitalization or emergency department visit due to COPD or asthma that required any oral or parenteral corticosteroids

Severe exacerbations should not be recorded as an AE unless they meet the definition of an SAE (Section 6.3.3.2). Severe exacerbations will be collected and recorded on the exacerbations log in the eCRF. The treatment details must also be recorded in the eCRF. The time period for collection of severe exacerbations will begin from the time of randomization (first receipt of investigational product) and will end after the 7 day follow-up period has been completed.

Section 8.3.4.1.1 Primary Endpoint Analyses (paragraph 2)

This section has been updated to provide clarification.

The primary planned analysis is modelling the dose-response curve of change from baseline in clinic trough FEV$_1$. The shape of the dose response curve for change from baseline in clinic trough FEV$_1$ at the end of Treatment Phase A (Visit 6) will be investigated. Several models including a linear model, a log linear model, and an Emax model will be used to characterize the dose response of UMEC. FF/VI data will be included in the model via a separate term. The model that appears to most accurately model the dose response will be used to predict the change from baseline in trough FEV$_1$ (adjusted for FF) across the dose range of UMEC using simulations **SAS procedure for nonlinear mixed effect models or simulations if needed**. Expected covariates in the model are baseline FEV$_1$ and treatment. Other covariates, such as age and sex, may also be included. Standard model checking and evaluation of the assumptions will be conducted to assess validity.

Section 8.3.4.1.3 Exploratory Endpoint Analyses (paragraph 5)

This edit clarifies the endpoint to match the EXACT manual created by Evidera.

The number of exacerbations and the number incidence of symptom-defined events (defined as an increase in EXACT score $\geq$ 9 points above baseline for 3 days or $\geq$ 12 points above baseline for 2 days) during Treatment Phase A will be summarized by treatment and compared via chi-square tests.