

TITLE PAGE

Division: Worldwide Development

Information Type: Protocol Amendment

Title:	A phase III, 52 week, randomized, double-blind, 3-arm parallel group study, comparing the efficacy, safety and tolerability of the fixed dose triple combination FF/UMEC/VI with the fixed dose dual combinations of FF/VI and UMEC/VI, all administered once-daily in the morning via a dry powder inhaler in subjects with chronic obstructive pulmonary disease
---------------	--

Compound Number: GSK2834425

Development Phase: IIIB

Effective Date: 30-JUN-2016

Protocol Amendment Number: 05

Author(s): PPD

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2013N176913_00	2014-MAR-17	Original
2013N176913_01	2014-MAR-31	Amendment No. 1
To clarify approval status of products in the protocol, add additional wording concerning hematology collection and to correct minor errors in the time and Events Table.		
2013N176913_02	2014-APR-10	Amendment No. 2
Amendment 02 purpose was to add post-bronchodilator FEV1 to each visit and include this as an Other Efficacy Endpoint. A mortality endpoint was also added as an “Other Efficacy Endpoint”. Other changes included changing the predicted FEV1 reference values from NHANES III to the European Respiratory Society Global Lung Function Initiative and to correct minor errors in CAT, contraceptive methods, and ECG wording. In addition changes were made to correct minor errors and to clarify ambiguous wording.		
2013N176913_03	2014-DEC-05	Amendment No. 3 China ONLY
Amendment 03 purpose was to clarify that Serious AEs in China will be recorded from the time the consent form is signed until the 7-day safety follow-up visit/telephone contact has been completed, or until Visit 7(telephone contact) for subjects who have discontinued IP but continue in the study.		
2013N176913_04	2015-MAY-12	Amendment No. 4 China ONLY
Amendment 04 purpose was to clarify that no study centers in China will participate in genetic research in this study and the addition of a China-specific sub-study to collect the unit-cost data for healthcare utilization among subjects recruited in China		
2013N176913_05	2016-JUN-30	Amendment No. 5
Amendment 05 applies to all countries and study centers participating in the CTT116855 study. Amendment 05 purpose was to simplify the statistical hierarchy for the analysis of secondary endpoints. In addition there are minor changes to the definitions of the Analysis populations, changes in model terms that will be included in the primary efficacy endpoint analysis and clarification on the primary endpoint sensitivity analyses. For the safety analysis there were minor changes to clarify the analyses of Pneumonia Adverse events and MACE events.		



SPONSOR SIGNATORY

PPD



30 June 2016

David A. Lipson, M.D.

Date

Project Physician Leader;
Director Clinical Development;
Respiratory Therapy Area

PPD



INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol CTT116855

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

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

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

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

TABLE OF CONTENTS

	PAGE
LIST OF ABBREVIATIONS	9
PROTOCOL SUMMARY	11
1. INTRODUCTION.....	16
1.1. Background	16
1.2. Rationale	17
1.3. Benefit:Risk Assessment	18
1.3.1. Risk Assessment	19
1.3.2. Benefit Assessment	23
1.3.3. Overall Benefit: Risk Conclusion	24
2. OBJECTIVES.....	25
3. INVESTIGATIONAL PLAN	25
3.1. Study Design	25
3.2. Discussion of Design	27
4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA.....	28
4.1. Number of Subjects	28
4.2. Inclusion Criteria	28
4.3. Exclusion Criteria.....	30
4.4. Investigational Product (IP) Discontinuation Criteria	34
4.4.1. Protocol defined stopping IP criteria.....	34
4.4.2. Permanent Discontinuation of Investigational Product (IP).....	34
4.4.3. IP Discontinuation Study Assessments.....	35
4.4.4. Reasons for Permanent Discontinuation of IP.....	36
4.5. Study Withdrawal Criteria	36
4.5.1. Withdrawal from study	37
4.5.2. Study Withdrawal assessments	37
4.5.3. Lost to follow-up.....	37
4.5.4. Reasons for Study Withdrawal.....	38
4.6. Follow-up Contact.....	38
4.7. Pre-Screen Failures and Screening Failures.....	39
5. STUDY TREATMENTS	40
5.1. Investigational Product and Other Study Treatment.....	40
5.1.1. Storage.....	42
5.1.2. Investigational Product and albuterol/salbutamol Return.....	42
5.2. Treatment Assignment.....	42
5.3. Blinding.....	43
5.4. Product Accountability	44
5.5. Treatment Compliance.....	44
5.6. Concomitant Medications and Non-Drug Therapies.....	44
5.6.1. Permitted Medications and Non-Drug Therapies.....	44
5.6.2. Prohibited Medications and Non-Drug Therapies.....	46
5.7. Treatment after the End of the Study	47
5.8. Treatment of Study Treatment Overdose	47

6.	STUDY ASSESSMENTS AND PROCEDURES	48
6.1.	Critical Baseline Assessments	52
6.2.	Efficacy.....	53
6.2.1.	Co-Primary Efficacy Endpoints	53
6.2.2.	Secondary Efficacy Endpoints	53
6.2.3.	Other Efficacy endpoints.....	53
6.2.4.	COPD Exacerbations.....	54
6.2.4.1.	Guidelines for Identifying COPD Exacerbations.....	54
6.2.4.2.	COPD Exacerbation Severity	56
6.2.4.3.	Treatment of COPD Exacerbations	56
6.2.4.4.	Guidelines for Treatment with Corticosteroids	56
6.2.4.5.	Guidelines for Treatment with Antibiotics.....	57
6.2.4.6.	Onset and Resolution of COPD Exacerbations.....	57
6.2.4.7.	Guideline for assessing multiple mild exacerbations.....	57
6.2.4.8.	Guideline for assessing exacerbations that increase in severity.....	57
6.2.5.	Spirometry Testing.....	57
6.2.5.1.	Reversibility Testing	58
6.2.6.	SGRQ-C.....	58
6.2.7.	Diary Assessments	59
6.2.8.	Rescue Albuterol/Salbutamol Use	59
6.2.9.	Baseline Dyspnoea Index/Transitional Dyspnoea Index.....	59
6.2.10.	COPD Assessment Test (CAT).....	60
6.2.11.	Subject Global Rating of Activity Limitation and Subject Global Impression of Change in Activity Limitation.....	60
6.2.12.	Subject Global Rating Severity of COPD and Subject Global Impression of Change in COPD.....	60
6.3.	Safety	60
6.3.1.	Liver chemistry stopping and follow up criteria.....	61
6.3.2.	Adverse Events.....	64
6.3.2.1.	Definition of an AE.....	64
6.3.2.2.	Definition of an SAE	65
6.3.2.3.	Sentinel Events	66
6.3.3.	Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs.....	67
6.3.4.	Cardiovascular Events	67
6.3.5.	Death Events	67
6.3.6.	Disease-Related Outcomes Not Subject to Expedited Reporting to Regulatory Authorities	67
6.3.7.	Pregnancy	68
6.3.8.	Medical Devices.....	68
6.3.9.	Time Period and Frequency of Detecting AEs and SAEs.....	70
6.3.10.	Method of Detecting AEs and SAEs.....	70
6.3.11.	Prompt Reporting of Serious Adverse Events and Other Events to GSK.....	70
6.3.11.1.	Regulatory Reporting Requirements for SAEs.....	72
6.3.12.	Laboratory Assessments	73
6.3.13.	Vital Signs.....	74
6.3.14.	Medical Problems and Concomitant Medications.....	74
6.3.15.	ECG.....	74
6.3.16.	Pneumonia	74

6.3.17.	Radiography (Chest X-Rays)	75
6.3.18.	Oropharyngeal Examinations	76
6.3.19.	Pulse oximetry	76
6.4.	Health Outcomes	76
6.4.1.	EuroQol Questionnaire (EQ-5D-5L)	76
6.4.2.	Healthcare resource utilisation	77
6.5.	Pharmacokinetics	77
6.6.	Genetic Research	77
6.7.	Novel Biomarkers	77
7.	DATA MANAGEMENT	78
8.	DATA ANALYSIS AND STATISTICAL CONSIDERATIONS.....	78
8.1.	Hypotheses.....	78
8.2.	Study Design Considerations.....	79
8.2.1.	Sample Size Assumptions	79
8.2.2.	Sample Size Sensitivity.....	80
8.2.3.	Sample Size Re-estimation.....	80
8.3.	Data Analysis Considerations	81
8.3.1.	Analysis Populations.....	81
8.3.2.	Analysis Data Sets.....	81
8.3.3.	Treatment Comparisons	81
8.3.3.1.	Primary Comparisons of Interest	81
8.3.3.2.	Other Comparisons of Interest.....	82
8.3.4.	Interim Analysis	82
8.3.5.	Key Elements of Analysis Plan	83
8.3.5.1.	Efficacy Analyses	83
8.3.5.2.	Safety Analyses.....	84
8.3.5.3.	Health Outcomes Analyses	84
8.3.5.4.	Pharmacokinetic Analyses.....	85
8.3.5.5.	Genetic Analyses	85
8.3.5.6.	Novel Biomarker(s) Analyses	85
9.	STUDY CONDUCT CONSIDERATIONS	85
9.1.	Posting of Information on Publicly Available Clinical Trial Registers.....	85
9.2.	Regulatory and Ethical Considerations, Including the Informed Consent Process	85
9.3.	Quality Control (Study Monitoring)	86
9.4.	Quality Assurance.....	86
9.5.	Study and Site Closure	86
9.6.	Records Retention	87
9.7.	Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication	87
9.8.	Independent Data Monitoring Committee (IDMC)	88
9.9.	Adjudication Committee	88
10.	REFERENCES.....	89
11.	APPENDICES	92
11.1.	Appendix 1: Genetic research.....	92
11.2.	Appendix 2: Country Specific Requirements	95

11.2.1.	China-specific sub-study: Collection of unit-cost data for healthcare utilization among COPD subjects recruited to Study CTT116855 in China.....	95
11.2.1.1.	Introduction	95
11.2.1.2.	Objective	95
11.2.1.3.	Investigational Plan	95
11.2.1.4.	Subject Selection and Withdrawal Criteria	96
11.2.1.4.1.	Inclusion Criteria.....	96
11.2.1.4.2.	Exclusion Criteria.....	96
11.2.1.4.3.	Sub-study Withdrawal Criteria	97
11.3.	Appendix 3: Liver Chemistry Stopping and Follow-up Criteria.....	102
11.4.	Appendix 4: Laboratory Assessments.....	103
11.5.	Appendix 5: Protocol Changes.....	104
11.5.1.	Amendment 1	104
11.5.2.	Amendment 2	106
11.5.3.	Amendment 3	110
11.5.4.	Amendment 4	113
11.5.5.	Amendment 5	122

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
AV	Atrioventricular
BODE	Body mass index (B), the degree of airflow obstruction(O), and dyspnoea (D), and exercise capacity (E)
Bpm	Beats Per Minute
CAT	COPD Assessment Test
CI	Confidence Intervals
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatinine Phosphokinase
CPRD	Clinical Practice Research Database
CRF	Case Report Form
CT	Computed Tomography
CXR	Chest X-Ray
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol Questionnaire
FEV ₁	Forced Expiratory Volume in One Second
FF	Fluticasone Furoate
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma Glutamyl Transferase
GSK	GlaxoSmithKline
GSK573719	Umeclidinium (UMEC)
GW642444	Vilanterol Trifenatate (VI)
GW685698	Fluticasone Furoate (FF)
HRQoL	Health Related Quality of Life
IB	Investigator Brochure
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IND	Investigational New Drug
IRB	Independent Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine System
IVRS	Interactive Voice Recognition System
LABA	Long Acting Beta-Agonist
LAMA	Long-acting Muscarinic Receptor Antagonists
LDH	Lactate Dehydrogenase
LTOT	Long Term Oxygen Therapy

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

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ADVAIR
ELLIPTA
NEBULES
SERETIDE

Trademarks not owned by the GlaxoSmithKline group of companies
SAS

PROTOCOL SUMMARY

Rationale

COPD guidelines advocate the use of one or more long-acting bronchodilators (long-acting muscarinic receptor antagonists [LAMA]) or long-acting β 2-adrenergic receptor agonists [LABA]) in addition to inhaled corticosteroids (ICS) as second line therapy for the most advanced patients with significant symptoms and a high risk of exacerbations. Regular treatment with ICS has been reported to improve respiratory symptoms, lung function, health related quality of life (HRQoL) and reduce the frequency of COPD exacerbation in patients with a FEV₁<60% predicted. Additionally, withdrawal of ICS treatment has also lead to exacerbations in some patients [GOLD, 2013].

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

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

The benefit of adding a LAMA to ICS/LABA was demonstrated in the SPARK study which examined a LABA/LAMA (QVA149) vs. glycopyrronium vs. tiotropium. The dual therapy demonstrated a 12% reduction in COPD exacerbations over glycopyrronium and 10% reduction over tiotropium alone. In ICS users (~ 3/4 of subjects) there was a 16% and 12% decrease in exacerbations, respectively [Wedzicha, 2013]. A recently conducted retrospective cohort study conducted in a UK-based COPD cohort (National Health Service NHS Tayside Respiratory Disease Information System) assessed the impact of the addition of tiotropium (LAMA) to ICS/LABA [Short, 2012]. This study revealed that triple therapy may confer benefits in reducing all-cause mortality, hospital admissions and oral corticosteroid bursts compared to ICS/LABA alone. A further retrospective cohort study reported that tiotropium (LAMA) added to fluticasone propionate/salmeterol (ICS/LABA) was associated with significant reductions in the adjusted risks of a moderate exacerbation and any exacerbation over a follow-up period of up to 1 year, compared to tiotropium alone [Chatterjee, 2012].

GlaxoSmithKline (GSK) is currently developing a once-daily 'closed' triple therapy of a ICS/LAMA/LABA combination [Fluticasone furoate (FF)/Umeclidinium (UMEC)/Vilanterol (VI)] in a single device, with the aim of providing a new treatment option for the management of advanced (GOLD Group D) COPD which will reduce the exacerbation frequency, allow for a reduced burden of polypharmacy, convenience, and the potential for improvement in lung function, HRQoL and symptom control over established dual-/monotherapies.

Objective(s)

Primary Objective

- To evaluate the efficacy of FF/UMEC/VI to reduce the annual rate of moderate and severe exacerbations compared with dual therapy of FF/VI or UMEC/VI in subjects with COPD.

Secondary Objectives

- To evaluate the long term safety and other efficacy assessments of FF/UMEC/VI compared with dual therapy of FF/VI or UMEC/VI.
- To evaluate the efficacy of FF/UMEC/VI to reduce exacerbations compared with UMEC/VI in the subset of subjects with a blood eosinophil count ≥ 150 cells/ μ l

Other Objectives

- To evaluate the patient perspective of the efficacy of FF/UMEC/VI in subjects with COPD.
- To evaluate the population pharmacokinetic profiles of FF, UMEC and VI in subjects with COPD
- To collect blood samples for a genetics research study.

Study Design

This is a phase IIIa, randomized, double-blind, 3-arm parallel group, global multicenter study evaluating FF/UMEC/VI inhalation powder versus FF/VI inhalation powder and UMEC/VI inhalation powder, all given once daily in the morning. The target enrollment is 10,000 randomized subjects at approximately 1,200 study centers globally. The total duration of subject participation will be approximately 55 weeks, consisting of a 2-week run-in period, 52-week treatment period and a 1-week safety follow-up period. There will be a total of 7 to 8 clinic visits conducted on an outpatient basis. Clinic visits will occur at pre-screening/screening, Randomization (Day1), and after 4, 16, 28, 40, and 52 weeks of treatment. In addition, a safety follow-up telephone contact or clinic visit will be conducted 7 days after completing visit 7 or the discontinuation from IP visit.

Subjects will sign the informed consent form (ICF) at a pre-screen or screening visit and will be assigned a subject identifier. Subjects meeting all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will enter the 2-week run-in. Subjects will continue the use of their existing COPD medications during

the run-in and in addition will be provided with short acting albuterol/salbutamol to be used on an as-needed basis (rescue medication) throughout the study. Following the 2-week run-in period, eligible subjects will be randomized (2:2:1) to one of the following double-blind treatment groups:

- FF/UMEC/VI 100mcg/62.5mcg/25mcg QD
- FF/VI 100mcg/25mcg QD
- UMEC/VI 62.5mcg/25mcg QD

All treatments will be delivered by ELLIPTA™ dry powder inhaler (DPI). Each DPI will contain 30 doses of IP. Subjects will be instructed to administer medication once daily in the morning for the duration of the 52-week treatment period. Subjects will self-administer their first dose of IP in the clinic during Randomization (Day1) Visit 2. On the morning of each clinic study visit, subjects will refrain from taking their morning dose of IP until instructed to do so by clinic personnel. Subjects will take their last dose of IP in the clinic during Visit 7 (or IP Discontinuation Visit). A safety follow-up will be conducted either by phone call or clinic visit after successfully completing Visit 7 (or the IP Discontinuation visit).

Subjects will discontinue all COPD medications during the randomized treatment period but may continue their mucolytics and study-supplied rescue albuterol/salbutamol. Subjects will complete a daily electronic diary (eDiary) that captures symptoms of COPD, activity limitation and albuterol/salbutamol use. Subjects with increasing respiratory symptoms will automatically be notified through the eDiary to contact their investigator for further evaluation of their increasing symptoms. The real-time notification of increasing respiratory symptoms from the diary will assist the investigator in the identification of new COPD exacerbations.

A subject will be considered to have completed the study when they have completed all phases of the study including screening, run-in, randomization, the randomized treatment phase and safety follow-up.

Subjects that permanently stop IP are not required to withdraw from the study.

Subjects who wish to permanently discontinue from their IP should be encouraged to stay on their IP until they are able to return to complete the IP Discontinuation Visit. After completing the IP Discontinuation Visit and the safety follow-up visit, subjects will be encouraged to continue in the study by participating in telephone contacts in order to assess exacerbations, serious adverse events (SAEs) and concomitant medications post-treatment. Subjects will continue to be evaluated until they have completed all the remaining protocol specified study visits by telephone contact; up to and including Visit 7.

Subjects who have previously discontinued IP (and have completed their IP Discontinuation Visit and safety follow-up) and who no longer wish to participate in the study by telephone contacts 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.

Subjects who are currently 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 Visit and also to complete the safety follow-up visit. No further study visits or study-related telephone contacts can be conducted; however, if 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 Subject's planned 52 week participation.

Study Endpoints/Assessments

Co-Primary Efficacy Endpoints

- Annual rate of on-treatment moderate and severe exacerbations comparing FF/UMEC/VI with UMEC/VI
- Annual rate of on-treatment moderate and severe exacerbations comparing FF/UMEC/VI with FF/VI

Secondary Efficacy Endpoints

- Change from baseline trough FEV₁ at Week 52 comparing FF/UMEC/VI with FF/VI
- Change from baseline SGRQ Total Score at Week 52 comparing FF/UMEC/VI with FF/VI
- Time to first on-treatment moderate or severe exacerbation comparing FF/UMEC/VI with FF/VI and with UMEC/VI
- Annual rate of on-treatment moderate and severe exacerbations comparing FF/UMEC/VI with UMEC/VI in the subset of subjects with a blood eosinophil count ≥ 150 cells/ μ l
- Time to first on-treatment moderate or severe exacerbation comparing FF/UMEC/VI with UMEC/VI in the subset of subjects with a blood eosinophil count ≥ 150 cells/ μ l
- Annual rate of on-treatment severe exacerbations comparing FF/UMEC/VI with FF/VI and with UMEC/VI

Other Efficacy endpoints

- Change from baseline in post-bronchodilator FEV₁
- Time to death from any cause
- Responder rate based on the SGRQ Total Score
- Annual rate of all on-treatment exacerbations (mild, moderate, severe)
- Annual rate of on-treatment moderate exacerbations
- Time to first on-treatment COPD hospitalization and COPD re-hospitalization

- Annual rate of exacerbations requiring systemic/oral corticosteroids
- Annual rate of exacerbations requiring antibiotics
- Transitional Dyspnoea Index (TDI) focal score comparing FF/UMEC/VI with FF/VI
- Use of rescue albuterol/salbutamol
- Change from baseline trough FEV₁ at Week 52 comparing FF/UMEC/VI with UMEC/VI
- Change from baseline in SGRQ Total Score comparing FF/UMEC/VI with UMEC/VI
- COPD Assessment Test (CAT) score
- Subject Global Rating of Activity Limitation and Subject Global Impression of Change in Activity Limitation
- Subject Global Rating of severity of COPD and Change in COPD
- Annual rate of on-treatment severe exacerbations comparing FF/UMEC/VI with UMEC/VI in the subset of subjects with a blood eosinophil count ≥ 150 cells/ μ l

Safety endpoints

- Incidence of adverse events
- Incidence of pneumonia
- Incidence of cardiovascular events (including supraventricular arrhythmia and non-fatal myocardial infarction)
- ECG measurements
- Vital signs
- Hematological and clinical chemistry parameters
- Oropharyngeal examinations
- Incidence of bone fractures

Health outcome endpoints

- EQ-5D-5L score (standardized instrument for measuring health status)
- Health care utilization (all-cause and COPD related), including hospitalization, emergency department and physician office/clinic visits

Pharmacokinetic endpoint

- Population PK data from subset of subjects

1. INTRODUCTION

1.1. Background

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterised by increasing obstruction to airflow and the progressive development of respiratory symptoms including chronic cough, increased sputum production, dyspnea and wheezing.

In 2011, the Global Initiative for Chronic Obstructive Lung Disease ([GOLD](#), 2011) issued a guideline that outlined a new classification system for COPD aimed to more comprehensively assess disease severity and guide therapy choice, ultimately improving COPD management.

The [GOLD](#), 2011 classification system incorporates symptoms (measured by either the modified Medical Research Council (mMRC) dyspnea score or a health status measure such as the COPD Assessment Test [CAT] score), in addition to COPD exacerbation history and airflow limitation measured by forced expiratory volume in one second (FEV₁). This combined assessment results in the grouping of COPD patients into four categories ([Table 1](#)). A 2013 update to the 2011 strategy included an additional criterion to characterise patients that have had a hospitalised exacerbation as high risk, regardless of GOLD status [[GOLD](#), 2013].

Table 1 GOLD 2013 Classification

GOLD Classification	Risk Class Determinant*	Symptom Category Determinant**
A: Low risk, less symptoms	GOLD Grade 1-2 <i>AND</i> ≤1 exacerbation, prior year	mMRC < 2; CAT < 10
B: Low risk, more symptoms	GOLD Grade 1-2 <i>AND</i> ≤1 exacerbation, prior year	mMRC ≥ 2; CAT ≥ 10
C: High risk, less symptoms	GOLD Grade 3-4 <i>OR</i> ≥ 2 exacerbations, prior year <i>OR</i> COPD hospitalization, prior year	mMRC < 2; CAT < 10
D: High risk, more symptoms	GOLD Grade 3-4 <i>OR</i> ≥ 2 exacerbations, prior year <i>OR</i> COPD hospitalization, prior year	mMRC ≥ 2; CAT ≥ 10
* - GOLD Grade 1-2: FEV ₁ ≥ 50% of predicted normal; GOLD Grade 3-4: FEV ₁ < 50% of predicted normal.		
** - Symptomatic category determined by either instrument.		

Population-based studies have reported that between 38% and 60% of COPD patients meet the criteria for GOLD D (high symptoms and high risk), dependent on the use of mMRC or CAT to define symptom burden [[Han](#), 2013; [Augsti](#), 2013; [Mullerova](#), 2012]. Patients characterised as GOLD D consistently demonstrate higher BODE (body mass index (B), the degree of airflow obstruction(O), and dyspnoea (D), and exercise capacity (E)) scores on the BODE Index and higher rates of poor COPD outcomes, including

acute and hospitalised exacerbation episodes, FEV₁ decline, and mortality [Han, 2013; Augsti, 2013]. These data suggest that the GOLD D patient population is at the highest risk of future COPD exacerbations and represents a large proportion of all COPD patients.

The GOLD, 2011 guideline also outlined suggested management strategies for COPD based upon disease severity. For milder patients (GOLD Group A), the guidelines encourage active risk reduction (e.g., smoking cessation and influenza vaccination) with the addition of short-acting β_2 -adrenergic receptor agonists (SABAs) on an 'as needed' basis. However, as disease severity increases, the guidelines recommend an incremental approach to pharmacological treatment, involving the use of combinations of drug classes with different or complementary mechanisms of action [Celli, 2004; GOLD, 2011]. Long-acting bronchodilators (long-acting muscarinic receptor antagonists [LAMA] or long-acting β_2 -adrenergic receptor agonists [LABA]) have been shown to relieve symptoms, increase exercise capacity, improve health-related quality of life and reduce COPD exacerbations to a greater extent than SABAs. For advanced cases, or those with repeated exacerbations, the incorporation of inhaled corticosteroids (ICS) or triple therapy, is recommended.

1.2. Rationale

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

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

A number of studies have assessed the use of an 'open' triple therapy of fluticasone propionate/salmeterol or budesonide/formoterol (ICS/LABA) with tiotropium (LAMA) in moderate-severe COPD patients. These studies have reported greater improvements in lung function, HRQoL, hospitalization rates and rescue medication use, compared to dual (ICS/LABA) or LAMA alone, thus supporting the use of triple therapy in COPD [Aaron, 2007; Cazzola, 2007; Hanania, 2012; Jung, 2012; Welte, 2009]. These studies have also shown that the number and type of reported AEs were generally similar with

administration of dual or monotherapy doses for periods of up to one year, and were mostly related to their pharmacological mode of action.

The benefit of adding a LAMA to ICS/LABA was demonstrated in the SPARK study which examined a LABA/LAMA (QVA149) vs. glycopyrronium vs. tiotropium. The dual therapy demonstrated a 12% reduction in COPD exacerbations over glycopyrronium and 10% reduction over tiotropium alone. In ICS users (~ 3/4 of subjects) there was a 16% and 12% decrease in exacerbations, respectively [Wedzicha, 2013]. A recently conducted retrospective cohort study conducted in a UK-based COPD cohort (National Health Service NHS Tayside Respiratory Disease Information System) assessed the impact of the addition of tiotropium (LAMA) to ICS/LABA [Short, 2012]. This study revealed that triple therapy may confer benefits in reducing all-cause mortality, hospital admissions and oral corticosteroid bursts compared to ICS/LABA alone. A further retrospective cohort study reported that tiotropium (LAMA) added to fluticasone propionate/salmeterol (ICS/LABA) was associated with significant reductions in the adjusted risks of a moderate exacerbation and any exacerbation over a follow-up period of up to 1 year, compared to tiotropium alone [Chatterjee, 2012].

GlaxoSmithKline (GSK) is currently developing a once-daily ‘closed’ triple therapy of a ICS/LAMA/LABA combination [Fluticasone furoate (FF)/Umeclidinium (UMEC)/Vilanterol (VI)] in a single device, with the aim of providing a new treatment option for the management of advanced (GOLD Group D) COPD which will reduce the exacerbation frequency, allow for a reduced burden of polypharmacy, convenience, and the potential for improvement in lung function, HRQoL and symptom control over established dual-/monotherapies.

1.3. Benefit:Risk Assessment

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

1.3.1. Risk Assessment

Potential Risk of Clinical Significance		Mitigation Strategy
Pneumonia in patients with COPD	<p>Pneumonia is a class concern for any ICS-containing product for the treatment of COPD. In two replicate 12 month studies, 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 µg)/VI 25 µg combination than in those receiving VI 25 µg alone (3%). In some instances these pneumonia events were fatal (including one fatality on 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/m² and patients with an FEV₁<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/VI in COPD patients, hence a robust risk mitigation strategy is being proposed.</p>	<ul style="list-style-type: none"> - Exclusion criteria as specified in Section 4.3 of the protocol - Collection of information on previous history of pneumonia in past 12 months, including hospitalisation at baseline - Use of pneumonia electronic Case Report Form (eCRF) - All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable), as specified in Section 6.3.16 - Central CXR read required at baseline and whenever a patient has suspected pneumonia or mod/severe exacerbations during the study - Instream review of blinded data - IDMC review of unblinded data
Systemic effects of corticosteroids: bone disorders, bone mineral density decrease and associated fractures	<p>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.</p> <p>In two replicate 12 month studies, in the FF/VI 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 µg group (<1%). Although there were more fractures in the FF/VI groups compared</p>	<ul style="list-style-type: none"> - Evaluation of the potential for bone systemic corticosteroid effects will be conducted through assessment of reported bone adverse events - Use of bone fracture eCRF

Potential Risk of Clinical Significance		Mitigation Strategy
	<p>with the VI 25 µg group, fractures typically associated with corticosteroid use (<i>e.g.</i>, spinal compression/thoracolumbar vertebral fractures, hip and acetabular fractures) occurred in <1% of the FF/VI and VI treatment arms.</p> <p>As part of the FF/VI development program, a bone mineral density study with FF/VI is being conducted, and this will provide data relevant to FF/UMEC/VI.</p>	
Systemic effects of corticosteroids: cortisol suppression	<p>Although all steroids are likely to have some impact on the hypothalamic pituitary axis (HPA axis), the proposed dose of inhaled FF in this study is unlikely to lead to any clinically significant changes</p> <p>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 & FF/VI, no events of Adrenal Suppression were reported.</p>	- Review AE/SAE reports

Potential Risk of Clinical Significance		Mitigation Strategy
Systemic ocular effects of corticosteroids: glaucoma, cataract, raised intra-ocular pressure	<p>Systemic ocular effects (<i>e.g.</i> cataract and glaucoma) may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. However, these effects are much less likely to occur with inhaled corticosteroids compared with oral corticosteroids.</p> <p>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 opacification were observed on formal ophthalmic assessments in a study with FF/VI, FF and FP in subjects with asthma.</p>	<ul style="list-style-type: none"> - As per Section 4.3 of the protocol, patients with known narrow-angle glaucoma that, in the opinion of the Investigator contraindicates study participation or use of an inhaled anticholinergic, will be excluded from participating in this study. - Review AE/SAE reports
Cardiovascular effects of UMEC and VI	<p><u>UMEC</u> Cardiovascular effects are a potential class effect associated with anti-muscarinic therapies.</p> <p>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 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 (<1%) across all treatment groups, although small imbalances in exposure adjusted frequency were observed between UMEC- and VI containing treatment</p>	<p>Mitigation strategy for UMEC and VI:</p> <ul style="list-style-type: none"> - Exclusion criteria as specified in Section 4.3 of the protocol - Collection of cardiovascular risk factors and medical history at baseline - ECGs as per protocol - Vital sign assessments (heart rate and blood pressure) as per protocol - Cardiovascular eCRF for collection of AEs and SAEs (see Section 6.3.4) - Prospective independent SAE adjudication - Protocol defined stopping criteria as per Section 4.4.1 -Pre-specified Major Adverse Cardiac Event (MACE) analysis - Instream review of blinded data -IDMC review of

Potential Risk of Clinical Significance		Mitigation Strategy
	<p>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 µg daily dose of UMEC) and in Healthy Volunteers (in the Thorough QT study, UMEC 500 µg daily dose), no effect was observed on heart rate, blood pressure or QT.</p> <p><u>VI</u></p> <p>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 µg 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.</p> <p>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 125/25mcg or UMEC 500mcg and placebo. UMEC/VI 500/100mcg increased QTcF on average by 8.2msec (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 suprathreshold dose of FF/VI (800/100 mcg for 7 days), the largest mean time-matched difference from</p>	unblinded data

Potential Risk of Clinical Significance		Mitigation Strategy
	placebo was 9.6 msec (90% CI: 7.2, 12.0) at 30 min only.	
Anticholinergic effects (including constipation, nausea, dry mouth, glaucoma, raised intraocular pressure and blurred vision, urinary retention)	<p>In clinical studies in COPD, few anticholinergic effects were associated with UMEC; those observed included dry mouth, constipation and cough.</p> <p>ICS has a similar class risk of glaucoma and elevated IOP; however these effects occur by a different mechanism that is not expected to be synergistic or additive when FF is used in combination with UMEC.</p>	<p>- Patients with known narrow-angle glaucoma, prostatic hyperplasia or bladder outflow obstruction that in the opinion of the Investigator contraindicates study participation or use of an inhaled anticholinergic, will be excluded from participating in the study.</p> <p>- Review AE/SAE reports</p>
Hypersensitivity	<p>Although not associated with FF/VI during the clinical studies, isolated cases of hypersensitivity reactions have been observed, post marketing, with the licensed intranasal spray, AVAMYS. In addition, the FF inhaled formulation has had some reports of hypersensitivity-type reactions.</p> <p>FF/VI formulation contains lactose. There have been reports of serious allergic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose.</p>	<p>-As specified in Section 4.3 of the protocol, subjects with a history of allergy or hypersensitivity to lactose/milk protein or magnesium stearate, any corticosteroid, anticholinergic/muscarinic receptor antagonist, and/or beta2-agonist, that in the opinion of the investigator contraindicates study participation, would not be included in the study</p> <p>-Review AE/SAE reports</p>

*The narrow MACE definition refers to the preferred terms of “myocardial ischemia” and “acute myocardial infarction”.

1.3.2. Benefit Assessment

In a disease where polypharmacy is common, the ‘closed’ triple, once-daily combination of FF/UMEC/VI (100mcg/62.5mcg/25mcg), has the potential to optimise bronchodilator therapy, improve patient adherence to therapy and, as a result, improve overall disease management in COPD patients.

Published studies which assessed the use of an ‘open’ triple therapy (use of ICS/LAMA/LABA delivered via multiple inhalers) in moderate-severe COPD patients,

reported improvements in lung function, HRQoL, hospitalisation rates and rescue medication use, compared to dual therapy (ICS/LABA) or LAMA alone [Aaron, 2007; Cazzola, 2007; Hanania, 2012; Jung, 2012; Welte, 2009]. These studies have also shown that the number and type of reported AEs were generally similar with administration of dual or monotherapy doses for periods of up to one year, and were mostly related to their pharmacological mode of action.

A retrospective cohort study conducted in a UK-based COPD cohort (National Health Service NHS Tayside Respiratory Disease Information System) revealed that triple therapy (tiotropium added to ICS+LABA) may confer benefits in reducing all-cause mortality, hospital admissions and oral corticosteroid bursts compared to ICS+LABA alone [Short, 2012]. A further retrospective cohort study reported that tiotropium (LAMA) added to fluticasone/salmeterol (ICS/LABA) was associated with significant reductions in the adjusted risks of a moderate exacerbation and any exacerbation over a follow-up period of up to 1 year, compared to tiotropium alone [Chatterjee, 2012].

Additionally, the benefits of once-daily dosing and single-inhalers were observed in recently published studies. A retrospective database analysis of 8 million insured lives in the US found that COPD patients who initiated treatment with once-daily dosing had significantly higher adherence than other daily dosing frequencies, which yielded reductions in healthcare resource utilization and cost over 12 months follow-up period [Toy, 2011]. Similarly, a study of 11,747 matched pairs of COPD patients in the US Market Scan database demonstrated that multiple-inhaler users were less likely to be adherent than single-inhaler users. After adjusting for confounding factors, multiple-inhaler users experienced significantly more exacerbations, incurred significantly more inpatient hospitalizations, inpatient days, urgent care visits, outpatient visits and other medical service visits than single-inhaler users, resulting in significantly higher all-cause health care costs [Yu, 2011]. Improved patient outcomes might therefore be expected from the use of a single inhaler to deliver triple therapy due to improved adherence to therapy.

1.3.3. Overall Benefit: Risk Conclusion

Current risks that have been identified for the FF/UMEC/VI (100mcg/62.5 mcg/25mcg) combination are based on the known pharmacology of the individual components FF, UMEC and VI. These include key risks of pneumonia and bone disorders/fractures from ICS-containing combinations, and the risk of adverse cardiovascular effects from LAMA/LABA-containing combinations.

In the United States, the FF/VI combination is approved for the maintenance treatment of airflow obstruction and for reduction of exacerbations in COPD. The UMEC/VI combination is approved for maintenance treatment of airflow obstruction in COPD.

In the EU, the FF/VI combination is approved for the symptomatic treatment of adults with COPD with a FEV1 < 70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. The UMEC/VI combination has a CHMP Positive Opinion for the indication: maintenance treatment to relieve symptoms in adults with COPD.

A comprehensive safety monitoring strategy is being proposed for all the risks, including key risks (Section 1.3.1).

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

2. OBJECTIVES

Primary Objective

- To evaluate the efficacy of FF/UMEC/VI to reduce the annual rate of moderate and severe exacerbations compared with dual therapy of FF/VI or UMEC/VI in subjects with COPD.

Secondary Objectives

- To evaluate the long term safety and other efficacy assessments of FF/UMEC/VI compared with dual therapy of FF/VI or UMEC/VI.
- To evaluate the efficacy of FF/UMEC/VI to reduce exacerbations compared with UMEC/VI in the subset of subjects with a blood eosinophil count ≥ 150 cells/ μ l

Other Objectives

- To evaluate the patient perspective of the efficacy of FF/UMEC/VI in subjects with COPD.
- To evaluate the population pharmacokinetic profiles of FF, UMEC and VI in subjects with COPD
- To collect blood samples for a genetics research study.

3. INVESTIGATIONAL PLAN

3.1. Study Design

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

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.

This is a phase IIIa, randomized, double-blind, 3-arm parallel group, global multicenter study evaluating FF/UMEC/VI inhalation powder versus FF/VI inhalation powder and UMEC/VI inhalation powder, all given once daily in the morning. The target enrollment

is 10,000 randomized subjects at approximately 1,200 study centers globally. The total duration of subject participation will be approximately 55 weeks, consisting of a 2-week run-in period, 52-week treatment period and a 1-week safety follow-up period. There will be a total of 7 or 8 clinic visits conducted on an outpatient basis. Clinic visits will occur at pre-screening/screening, Randomization (Day1), and after 4, 16, 28, 40, and 52 weeks of treatment. In addition, a safety follow-up telephone contact or clinic visit will be conducted 7 days after completing visit 7 or the IP Discontinuation visit.

Subjects will sign an informed consent form (ICF) at a pre-screen or screening visit and will be assigned a subject identifier. Subjects meeting all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will enter the 2-week run-in. Subjects will continue the use of their existing COPD medications during the run-in and in addition will be provided with short acting albuterol/salbutamol to be used on an as-needed basis (rescue medication) throughout the study. Following the 2-week run-in period, eligible subjects will be randomized (2:2:1) to one of the following double-blind treatment groups:

- FF/UMEC/VI 100mcg/62.5mcg/25mcg QD
- FF/VI 100mcg/25mcg QD
- UMEC/VI 62.5mcg/25mcg QD

All treatments will be delivered by ELLIPTA™ dry powder inhaler (DPI). Each DPI will contain 30 doses of IP. Subjects will be instructed to administer medication once daily in the morning for the duration of the 52-week treatment period. Subjects will self-administer their first dose of IP in the clinic during Randomization (Day1) Visit 2. On the morning of each clinic study visit, subjects will refrain from taking their morning dose of IP until instructed to do so by clinic personnel. Subjects will take their last dose of IP in the clinic during Visit 7 (or the IP Discontinuation visit). A safety follow-up will be conducted either by phone call or clinic visit after successfully completing Visit 7 (or the IP Discontinuation Visit).

Subjects will discontinue all COPD medications during the randomized treatment period but may continue their mucolytics and study-supplied rescue albuterol/salbutamol. Subjects will complete a daily electronic diary (eDiary) that captures symptoms of COPD, activity limitation and albuterol/salbutamol use. Subjects with increasing respiratory symptoms will automatically be notified through the eDiary to contact their investigator for further evaluation of their increasing symptoms. The real-time notification of increasing respiratory symptoms from the diary will assist the investigator in the identification of new COPD exacerbations.

A subject will be considered to have completed the study when they have completed all phases of the study including screening, run-in, randomization, the randomized treatment phase and safety follow-up.

Subjects that permanently stop IP are not required to withdraw from the study.

Subjects who wish to permanently discontinue their IP should be encouraged to continue to take their IP until they are able to return to complete the IP Discontinuation Visit.

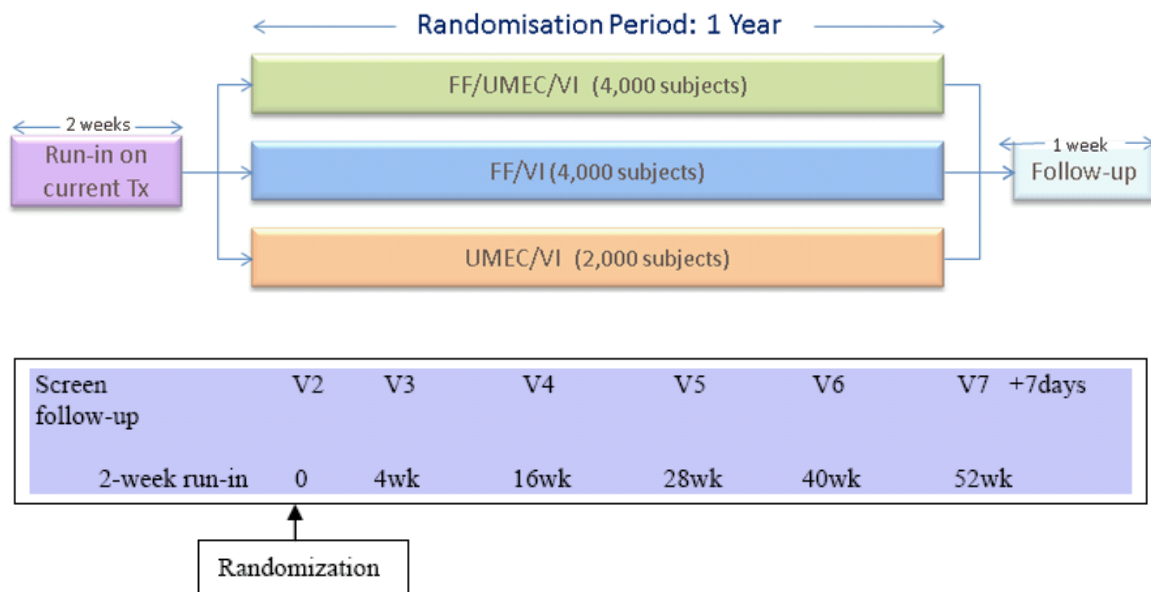
After completing the IP Discontinuation Visit and the safety follow-up visit, subjects will

be encouraged to continue in the study by participating in study-related telephone contacts in order to assess exacerbations, serious adverse events (SAEs) and concomitant medications post-treatment. Subjects will continue to be evaluated until they have completed all the remaining protocol specified study visits by telephone contact, up to and including Visit 7.

Subjects who are currently 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 Visit and also to complete the safety follow-up visit. No further study visits or study-related telephone contacts will 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 Subject's planned 52 week participation.

Subjects who have discontinued IP and are continuing in the study by completing study-related telephone contacts (after having completed their IP Discontinuation Visit and safety follow-up phone call/visit), 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.

Figure 1 Study Schematic



3.2. Discussion of Design

This study will use a multicenter, randomized, double-blind, parallel-group design. This is a well-established design to evaluate the efficacy and safety of an investigational drug. A placebo arm is not included because the comparisons of primary interest are FF/UMEC/VI versus FF/VI and versus UMEC/VI. In addition, it is not considered appropriate to include a placebo control arm for a duration of 1 year in patients with advanced COPD and a history of COPD exacerbations.

Eligible subjects must have been on daily maintenance COPD medications for at least 3 months and will continue these medications unchanged during the 2-week run-in period. The 2-week run-in period is necessary in order to assess subject compliance with the daily diary and to establish baseline diary symptoms and albuterol/salbutamol use.

Subjects who permanently discontinue IP before the end of the 52-week treatment period and agree to continue in the study will be followed by the Investigator until the end of the subjects' planned 52-week participation in order to capture important efficacy and safety assessments.

The FF/UMEC/VI dose was selected based on the doses that have been determined for the FF/VI and UMEC/VI dual combinations through extensive studies in the mono and dual therapy programs. The doses licensed and/or anticipated to be licensed by the FDA and the EMA for FF/VI and UMEC/VI are 100mcg/25mcg and 62.5mcg/25mcg (equivalent to 92mcg/22mcg and 55mcg/22mcg delivered dose); respectively.

While both the FF/VI and UMEC/VI programs allowed for a broader COPD population, there were still a large number of patients studied in those programs who would be considered as part of the target FF/UMEC/VI patient population. For the FF/VI phase III program, approximately 70% of patients from the COPD exacerbation studies and approximately half of the patients from the six-month studies would be considered 'high risk' (GOLD C or D according to respiratory guidelines). For the UMEC/VI phase III program, approximately half of the patients would be classified as GOLD D. The safety experience with FF/VI, UMEC/VI and their individual components, in previous clinical development, provides sufficient data to support the dose selection of 100/62.5/25 mcg for FF/UMEC/VI.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

Approximately 16,000 subjects will be screened in order to randomize approximately 10,000 subjects. All randomized subjects are considered evaluable. Approximately 1,200 centers globally will be required to recruit the study.

4.2. Inclusion Criteria

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

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

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

1. **Informed Consent:** A signed and dated written informed consent prior to study participation.

2. **Type of subject:** Outpatient.
3. **Age:** Subjects 40 years of age or older at Visit 1.
4. **Gender:** Male or female subjects.

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

Non-child bearing potential (*i.e.* physiologically incapable of becoming pregnant, including any female who is post-menopausal or surgically sterile). Surgically sterile females are defined as those with a documented hysterectomy and/or bilateral oophorectomy or tubal ligation. Post-menopausal females are defined as being amenorrhoeic for greater than 1 year with an appropriate clinical profile, *e.g.* age appropriate, > 45 years, in the absence of hormone replacement therapy.

OR

Child bearing potential, has a negative pregnancy test at screening, and agrees to one of the following acceptable contraceptive methods used consistently and correctly (*i.e.* in accordance with the approved product label and the instructions of the physician for the duration of the study – screening to safety follow-up contact):

- Abstinence
 - Oral Contraceptive, either combined or progestogen alone
 - Injectable progestogen
 - Implants of levonorgestrel
 - Estrogenic vaginal ring
 - Percutaneous contraceptive patches
 - Intrauterine device (IUD) or intrauterine system (IUS)
 - Male partner sterilization (vasectomy with documentation of azoospermia) prior to **the female subject's entry** into the study, and this male is the sole partner for that subject. 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.
 - Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository)
5. **COPD Diagnosis:** An established clinical history of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society [[Celli, 2004](#)].
 6. **Smoking History:** Current or former cigarette smokers with a history of cigarette smoking of ≥ 10 pack-years at screening (visit 1) [number of pack years = (number of cigarettes per day / 20) x number of years smoked (*e.g.*, 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)]. Previous smokers are defined as those

who have stopped smoking for at least 6 months prior to Visit 1. *Note: Pipe and/or cigar use cannot be used to calculate pack-year history*

7. **Severity of COPD symptoms:** A score of ≥ 10 on the COPD Assessment Test (CAT) at screening.
8. **Severity of COPD Disease:** A post-albuterol/salbutamol FEV₁/FVC ratio of < 0.70 at Screening.
9. **Existing COPD maintenance treatment:** Subject must be receiving daily maintenance treatment for their COPD for at least 3 months prior to Screening.
Note: Subjects receiving only PRN COPD medications are not eligible.
10. **History of Exacerbations:** Subjects must demonstrate:
a post-bronchodilator FEV₁ $< 50\%$ predicted normal and a documented history of ≥ 1 moderate or severe COPD exacerbation in the previous 12 months

OR

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

Note: *Percent predicted will be calculated using the European Respiratory Society Global Lung Function Initiative reference equations [Quanjer, 2012].*

Note: *A documented history of a COPD exacerbation (e.g., medical record verification) is a medical record of worsening COPD symptoms that required systemic/oral corticosteroids and/or antibiotics (for a moderate exacerbation) or hospitalization (for a severe exacerbation). Prior use of antibiotics alone does not qualify as an exacerbation history unless the use was associated with treatment of worsening symptoms of COPD, such as increased dyspnea, sputum volume, or sputum purulence (color). Subject verbal reports are not acceptable.*

11. **Liver function tests:**

- alanine aminotransferase (ALT) $< 2x$ upper limit of normal (ULN);
- alkaline phosphatase $\leq 1.5x$ ULN
- bilirubin $\leq 1.5x$ ULN (isolated bilirubin $> 1.5 x$ ULN is acceptable if bilirubin is fractionated and direct bilirubin $< 35\%$).

12. **French subjects:** In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

4.3. Exclusion Criteria

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

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

1. **Pregnancy:** Women who are pregnant or lactating or are planning on becoming pregnant during the study.
2. **Asthma:** Subjects with a current diagnosis of asthma. (Subjects with a prior history of asthma are eligible if they have a current diagnosis of COPD).
3. **α 1-antitrypsin deficiency:** Subjects with α 1-antitrypsin deficiency as the underlying cause of COPD.
4. **Other respiratory disorders:** Subjects with active tuberculosis, lung cancer, significant bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases.
5. **Lung resection:** Subjects with lung volume reduction surgery within the 12 months prior to Screening.
6. **Risk Factors for Pneumonia:** immune suppression (e.g. 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)

Patients at potentially high risk (e.g. very low BMI, severely malnourished, or very low FEV₁) will only be included at the discretion of the Investigator.
7. **Pneumonia and/or moderate or severe COPD exacerbation** that has not resolved at least 14 days prior to Screening and at least 30 days following the last dose of oral/systemic corticosteroids (if applicable). In addition, any subject that experiences pneumonia and/or moderate or severe COPD exacerbation during the run-in period will be excluded.
8. **Other Respiratory tract infections** that have not resolved at least 7 days prior to screening.
9. **Abnormal Chest x-ray:** Chest x-ray (posteroanterior and lateral) reveals evidence of pneumonia or a clinically significant abnormality not believed to be due to the presence of COPD, or another condition that would hinder the ability to detect an infiltrate on CXR (e.g. significant cardiomegaly, pleural effusion or scarring). All subjects will have a chest x-ray at Screening Visit 1 (or historical radiograph or CT scan obtained within 3 months prior to screening) that will be over-read by a central vendor. **Note:** *Subjects who have experienced pneumonia and/or moderate or severe COPD exacerbation within 3 months of screening must provide a post pneumonia/exacerbation chest x-ray to be over-read by the central vendor or have a chest x-ray conducted at screening.*

For sites in Germany: If a chest x-ray (or CT scan) within 3 months prior to Screening (Visit 1) is not available, approval to conduct a diagnostic chest x-ray will need to be obtained from the Federal Office for Radiation Protection (BfS).
10. **Other diseases/abnormalities:** Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, gastrointestinal, urogenital, nervous system, musculoskeletal, skin, sensory, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the subject at

risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.

11. **Unstable liver disease** as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices or persistent jaundice, cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). **Note:** *Chronic stable hepatitis B and C are acceptable if the subject otherwise meets entry criteria*
12. **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
13. **Abnormal and clinically significant 12-Lead ECG finding:** Investigators will be provided with ECG reviews conducted by a centralized independent cardiologist to assist in evaluation of subject eligibility. The PI 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 \geq 500 msec in patients with QRS <120 msec and QTcF \geq 530 msec in patients with QRS \geq 120 msec
14. **Contraindications:** A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate or a medical condition such as narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the Investigator contraindicates study participation.
15. **Cancer:** Subjects with carcinoma that has not been in complete remission for at least 5 years. Subjects who have had carcinoma *in situ* of the cervix, squamous cell carcinoma and basal cell carcinoma of the skin would not be excluded based on the 5 year waiting period if the subject has been considered cured by treatment.
16. **Oxygen therapy:** Use of long-term oxygen therapy (LTOT) described as resting oxygen therapy >3L/min (Oxygen use \leq 3L/min flow is not exclusionary.)

17. **Medication prior to spirometry:** Subjects who are medically unable to withhold their albuterol/salbutamol for the 4-hour period required prior to spirometry testing at each study visit.
18. **Pulmonary rehabilitation:** Subjects who have participated in the acute phase of a Pulmonary Rehabilitation Program within 4 weeks prior to Screening or subjects who plan to enter the acute phase of a Pulmonary Rehabilitation Program during the study. Subjects who are in the maintenance phase of a Pulmonary Rehabilitation Program are not excluded.
19. **Drug/alcohol abuse:** Subjects with a known or suspected history of alcohol or drug abuse within the last 2 years.
20. **Non-compliance:** Subjects at risk of non-compliance, or unable to comply with the study procedures. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits.
21. **Questionable validity of consent:** Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation or other conditions that will limit the validity of informed consent to participate in the study.
22. **Affiliation with investigator site:** Study investigators, sub-investigators, study coordinators, employees of a participating investigator or study site, or immediate family members of the aforementioned that is involved with this study.
23. **Inability to read:** In the opinion of the Investigator, any subject who is unable to read and/or would not be able to complete study related materials.
24. **Medication prior to screening:** Use of the following medications within the following time intervals prior to Screening (Visit 1) or during the study:

Table 2 Prohibited medications prior to Screening or during the study

Medication	No use within the following time intervals prior to Screening or during the study
Long term antibiotic therapy	Subjects receiving antibiotics for long term therapy are not eligible for the study. (Antibiotics are allowed for the short term treatment of an exacerbation or for short term treatment of other acute infections during the study)
Systemic, Oral, parenteral corticosteroids	30 days (Except during the study oral/systemic corticosteroids may be used to treat COPD exacerbations/pneumonia) Intra-articular injections are allowed
Any other investigational drug	30 days or 5 half lives whichever is longer.

4.4. Investigational Product (IP) Discontinuation Criteria

Subjects that permanently stop IP are not required to withdraw from the study. If for any reason a subject must permanently stop IP every effort should be made by the Investigator/staff to keep the subject in the study to collect important efficacy and safety data.

4.4.1. Protocol defined stopping IP criteria

A subject must be permanently discontinued from IP if any of the following stopping criteria are met:

- **Liver Chemistry:** Meets any of the protocol-defined liver chemistry stopping criteria as defined in Section 6.3.1.
- **Pregnancy:** Positive urine pregnancy test.
- **ECG:** An increase in QTcF by > 60msec from baseline 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 patient should be discontinued from the study.

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

4.4.2. Permanent Discontinuation of Investigational Product (IP)

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.

Subjects who have permanently discontinued IP are not required to withdraw from the study. Subjects who have permanently discontinued IP and have not withdrawn consent may continue in the study and will complete all remaining protocol specified visits by phone contact.

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. 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 capture the following:

- Exacerbations,
- SAEs,
- concomitant medications.

4.4.3. 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 Visit. The following evaluations and procedures as outlined in the Time and Events Table should be completed and recorded in the eCRF as required:

- Concurrent medication assessment
- Adverse event assessment
- COPD exacerbation assessment
- Smoking status
- Physical examination (source document only) including oropharyngeal examination
- Vital signs
- ECG
- Spirometry
- TDI
- EQ-5D-5L
- CAT
- SGRQ-C
- Subject Global Rating of Activity Limitation and Subject Global Impression of Change in Activity Limitation
- Subject Global Rating of Change in COPD
- Healthcare resource utilization
- Collect used IP and rescue albuterol/salbutamol
- Assess compliance with investigational product
- Urine pregnancy test for females of childbearing potential
- Hematology & Biochemistry

- Smoking cessation counseling
- Review and Collect eDiary
- Call IVRS (RAMOS) to record visit

A safety follow-up contact as described in Section 4.6 should be conducted 7 days following completion of Visit 7 or the IP Discontinuation Visit.

4.4.4. Reasons for Permanent Discontinuation of IP

The primary reason for permanent discontinuation of IP will be recorded in the electronic Case Report Form (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
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. Withdrew consent
 - subject relocated
 - frequency of visits
 - burden of procedures
 - other (specify)

4.5. Study Withdrawal Criteria

For this study there are no pre-determined protocol specific study withdrawal criteria (see Section 4.4.1 for protocol defined stopping IP criteria).

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.

4.5.1. 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 Visit and also 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 Subject's planned 52 week participation.

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.

4.5.2. 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 Visit assessments (Section 4.4.3) and to complete the safety follow-up contact 7 days later.

Subjects who have previously discontinued IP (and have already completed their IP Discontinuation 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.

4.5.3. Lost to follow-up

If a subject fails 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 they can appropriately be withdrawn from the study. These contact attempts should be documented in the subject's medical record. If the subject continues to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up". 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 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.

4.5.4. 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. Withdrew consent
 - subject relocated
 - frequency of visits
 - burden of procedures
 - other (specify)

4.6. Follow-up Contact

A safety follow-up contact will be conducted 7 days (-1/+4) following the completion of the randomized treatment period (Visit 7) or following the IP Discontinuation Visit.

The follow-up contact can be made by phone call or by site visit. The following procedures will be performed:

- Adverse event assessment
- Concurrent medication assessment
- COPD exacerbation assessment
- Call IVRS to report safety follow-up contact

Subjects who have successfully completed all on-treatment randomized visits (including Visit 7) will be discharged from the study upon completion of the safety follow-up contact.

Subjects who have discontinued IP will complete the IP Discontinuation Visit followed 7 days (-1/+4) later by the safety follow-up contact but then will continue in the study to

complete all remaining visits by telephone contact and will be discharged from the study once they complete the Visit 7 telephone contact.

Subjects who are on IP and wish to withdraw from further participation in the study will complete the IP Discontinuation Visit followed 7 days (-1/+4) later by the safety follow-up contact.

Subjects who have discontinued IP and are continuing in the study by completing study-related telephone contacts (after completing their IP Discontinuation Visit and safety follow-up phone call), but who now wish to withdraw from the study, should contact the site by phone to notify the site of their intention to withdraw; no additional safety follow-up visit is required.

4.7. Pre-Screen Failures and Screening 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 or any subject who completes Visit 1 and enters the run-in period, but is subsequently found to be ineligible for the study (e.g. ECG, spirometry, CXR, laboratory tests conducted) prior to randomization to the study treatment medication, is classified as a Screen Failure.

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

- Date of Pre-Screening Visit
- Subject number
- Date of ICF signature
- Demographic information including race, age and gender
- Details of COPD medications within 90 days of Visit 0 (For subjects that experience an SAE)
- Serious Adverse Events (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 GSK concomitant medication
- Investigator signature page
- IVRS-RAMOS will be contacted to report screen failures. In addition to the information above, the following information will be collected for screen failures:
 - Date of Screening Visit

- Reason for screen failure (screening failure and inclusion/exclusion criteria)

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

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

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 (IP) 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.

All treatments will be delivered by ELLIPTA dry powder inhaler (DPI). There are two double-foil laminate blister strips within each DPI, each containing 30 blisters. The DPI will provide a total of 30 doses (60 blisters) and will deliver, when actuated, the contents of both blisters simultaneously from each of the two blister strips.

Following the run-in period, eligible subjects will be randomized (2:2:1) to one of the following double-blind treatment groups:

- Fluticasone Furoate (FF)/Umeclidinium (UMEC)/Vilanterol (VI)
100mcg/62.5mcg/25mcg QD via DPI
- FF/VI 100mcg/25mcg QD via DPI
- UMEC/VI 62.5mcg/25mcg QD via DPI

Subjects will be instructed to administer IP once daily in the morning for the duration of the 52-week treatment period. Each subject should be advised to adhere to this dosing regimen throughout the study. In addition, each subject will be instructed on the proper use of the DPI. Subjects will self-administer their first dose of blinded IP in the clinic during Visit 2. On the morning of each clinic study visit, subjects will refrain from taking their morning dose of IP until instructed to do so by clinic personnel. Subjects will take their last dose of IP at the clinic at Visit 7 (or Discontinuation of IP visit).

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

Descriptions of the IPs administered via the DPI are provided in [Table 3](#).

Table 3 Description of IP Inhalation powder via ELLIPTA™ DPI

FF/UMEC/VI	First strip	Second strip
	GW685698 blended with lactose	GW642444 and GSK573719 blended with lactose and magnesium stearate
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	100mcg per blister	25 mcg per blister GW642444, 62.5 mcg per blister GSK573719
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	
FF/VI	First strip	Second strip
	GW685698 blended with lactose	GW642444 blended with lactose and magnesium stearate
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	100mcg per blister	25 mcg per blister
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	
UMEC/VI	First strip	Second strip
	GSK573719 blended with lactose and magnesium stearate	GW642444 blended with lactose and magnesium stearate
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	62.5 mcg per blister	25 mcg per blister
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	

Albuterol/salbutamol via metered-dose inhaler (MDI) with a spacer will be issued for reversibility testing at Visit 1. Albuterol/salbutamol MDI or NEBULES™ for as needed (prn) use throughout the study will be provided starting at Visit 1. Albuterol/salbutamol and spacers will be sourced from local commercial stock. If not available locally, GSK will source centrally.

5.1.1. Storage

All IP should be stored up to 25°C (77°F). Excursions permitted up to 30°C (86°F). Each DPI contains 30 doses and is packaged in a foil pouch with a desiccant sachet and stored in a carton. The inhaler should not be used for more than 30 days after opening the foil. The sites must maintain a daily temperature log for the storage of investigational product.

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

5.1.2. Investigational Product and albuterol/salbutamol Return

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

If any DPI fails to function properly, the subject should return to the clinic as soon as possible to obtain a new inhaler. The site will call IVRS to obtain a new treatment pack number for the subject and dispense a new IP kit from the site's investigational product supply as instructed by IVRS.

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

5.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomisation schedule. The randomization code will be generated by GSK using a validated computerized system. Subjects will be randomized using an Interactive Voice Response System (IVRS-RAMOS). The study will use site-based randomization to allocate treatments. Once a randomization number is assigned to a subject it cannot be reassigned to any other subject in the study.

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

- FF/UMEC/VI 100mcg/62.5mcg/25mcg QD via ELLIPTA DPI
- FF/VI 100mcg/25mcg QD via ELLIPTA DPI
- UMEC/VI 62.5mcg/25mcg QD via ELLIPTA DPI

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

The duration of treatment for each subject is 52 weeks. On the morning of each clinic study visit, subjects will refrain from taking their morning dose of IP until instructed to do so by clinic personnel. IP will be given at the clinic at approximately the same time of day as Day 1 (Visit 2). On the other days during the treatment period (*i.e.* “non-clinic days”), subjects will be instructed to take their IP each morning at approximately the same time of day. The IVRS will provide a means for site-based allocation of drug. Each investigator will be supplied with sufficient supplies to conduct the trial. Additional treatment packs will be supplied as needed to the sites. Details of how to use the IVRS to register and randomize subjects is provided in the SPM.

5.3. Blinding

Investigational product taken during the 52 week treatment period will be double-blinded and will be delivered by DPIs that are identical in appearance. Neither the subject nor the Investigator will know which IP the subject is receiving. Details of administration of study drug are provided in the SPM.

Subjects who have been unblinded by the investigator or treating physician must have their IP permanently discontinued, but may continue in the study to complete protocol assessments and visits. The primary reason for permanent discontinuation of IP (the event or condition that led to the unblinding) will be recorded in the eCRF.

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 after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be fully documented in the 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.

An IDMC will be utilised in this study to ensure external objective medical and/or statistical review of safety and/or efficacy data in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. In order to maintain blinding in communication with the IDMC, non-blinded persons separate from the study team (*e.g.* an unblinded statistician or data manager) will be appointed to provide required information to the IDMC.

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

Subjects' compliance with study treatment will be assessed at each study visit. Subjects who are non-compliant should be re-educated on the importance of treatment compliance. Every effort will be made to keep subjects in the study and to re-educate those subjects who continue to be non-compliant. Subjects who continue to be non-compliant after multiple visit assessments may be permanently discontinued from IP **after consultation with the GSK clinical team.**

5.6. Concomitant Medications and Non-Drug Therapies

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

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

Medications initiated after completion of the randomized treatment phase of the study (Visit 7) or started after withdrawal from the study must be recorded in the eCRF up to the safety follow-up Visit.

Subjects who have permanently discontinued IP and are continuing in the study will continue to collect and record concomitant medications up to Visit 7. Subjects that 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

The following **COPD medications** are permitted during the study while the subject is on IP:

- Study supplied albuterol/salbutamol MDI or Nebules (must be withheld for at least 4 hours prior to spirometry testing)
- Oral or injectable corticosteroids (short course ≤ 14 days) only for the short term treatment of COPD exacerbations and/or pneumonia

- Antibiotics (short course ≤ 14 days) for the short term treatment of COPD exacerbations and/or pneumonia
- Mucolytics such as acetylcysteine
- Long term oxygen therapy. (To be eligible to enter the study subjects who are on LTOT must be using at a flow rate of ≤ 3 liters/minute at rest. However, oxygen therapy may be adjusted as deemed medically necessary at any time during the study.) Oxygen therapy must be captured on the concomitant medication page of the eCRF. Supplemental oxygen is recommended for patients who exhibit oxyhemoglobin desaturation with rest or exertion (e.g. SaO₂ $\leq 88\%$)
- Maintenance phase of pulmonary rehabilitation treatment (subjects are not allowed to initiate treatment during the study)
- Any COPD medication deemed medically necessary for the short term treatment (≤ 14 days) of a moderate/severe COPD exacerbation or pneumonia
- The following Non-COPD medications are permitted during the study:
- Medications for rhinitis (e.g. intranasal corticosteroids, antihistamines, cromolyn, nedocromil, nasal decongestants)
- Topical and ophthalmic corticosteroids
- Localized corticosteroid injections (e.g. intra-articular and epidural)
- Vaccinations (Influenza vaccine, Pneumonia vaccine, Shingles vaccine, etc.) (Administration of influenza and pneumonia vaccines should be considered based on clinical discretion of the Investigator and local/national guidelines. Current influenza vaccines and pneumonia vaccines will be captured on the concomitant medication pages of the eCRF)
- Allergy immunotherapy
- Antibiotics for short-term treatment (≤ 14 days) of acute infections. (Long term treatment with antibiotics is not allowed)
- Systemic and ophthalmic beta-blockers. (Administer with caution as systemic beta-blockers block the pulmonary effect of beta-agonists, and may produce severe bronchospasm in patients with reversible obstructive airways disease. Cardioselective beta-blockers should be considered, although they also should be administered with caution).
- Smoking cessation treatments
- Cough suppressants
- Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). (Administer with extreme caution as they may potentiate the effects of beta-agonists on the cardiovascular system, including QTc prolongation.)
- Diuretics. (Caution is advised in the co-administration of beta-agonists with non-potassium sparing diuretics as this may result in ECG changes and/or hypokalemia.)

- Use of positive airway pressure for sleep apnea
- Oral muscarinic antagonists for the treatment of overactive bladder are permitted but should be used with caution as they may exacerbate medical conditions that are contraindicated for anticholinergics (e.g., narrow angle glaucoma and bladder outflow obstruction).
- CYP3A4 inhibitors (Caution should be exercised when considering the coadministration of long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur)

5.6.2. Prohibited Medications and Non-Drug Therapies

Medications prohibited at specific time intervals prior to Visit 1 (and at any time during the study) are identified in the Exclusion Criteria (Section 4.3).

NOTE: All COPD medications (except for rescue albuterol/salbutamol, mucolytics and oxygen) are prohibited during the randomized period of the study except during the treatment of a moderate/severe COPD exacerbation or pneumonia. In the event of an exacerbation or pneumonia, sites should attempt to follow protocol treatment guidelines (Section 6.2.4); however, treatment with any medication that the health care provider deems necessary is allowed. Caution is advised in using a LABA or LAMA to treat a subject currently taking IP as these additional medications may increase the risk of overdose. If necessary the PI or other health care personnel may stop the subjects IP temporarily in order to treat the COPD exacerbation. Subjects who require more than two consecutive 14 day courses of treatment (i.e. antibiotics or corticosteroids) should be evaluated for their continuation on IP by the PI in consultation with the GSK medical monitor.

Eligible subjects will be allowed to continue their usual COPD medications during screening and the 2-week run-in period. On the morning of the Screening Visit subjects will refrain from taking their morning dose of their usual COPD medications until instructed to do so by clinic personnel. During the run-in period subjects will continue to use their usual COPD medications.

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

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

- Inhaled and systemic corticosteroids (Except for the short term treatment [≤ 14 days] of a COPD exacerbation or pneumonia.) *Note: Topical and ophthalmic*

corticosteroids, and localized corticosteroid injections (intra-articular and epidural) are allowed.

- Long and short acting muscarinic antagonists
- Long and short acting β 2 -agonists
- PDE4 inhibitors (roflumilast)
- Theophylline preparations
- Cromoglycate and nedocromil inhalers
- Zafirlukast, montelukast, zileuton
- Acute phase of pulmonary rehabilitation (at any time during the study including run-in)
- Long term systemic antibiotic therapy (antibiotics used for ≤ 14 days for the acute infections or for exacerbations or pneumonia is allowed)

5.7. Treatment after the End of the Study

The Investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition.

GSK will not provide post-study treatment. There are no plans to provide IP for compassionate use following study completion.

At the end of the treatment period Visit 7, or after the IP Discontinuation Visit, or withdrawal from study, subjects can resume conventional COPD therapy as prescribed by the Investigator. Post-treatment concomitant medication should be entered into the eCRF until the safety follow-up visit for subjects that successfully complete Visit 7 on IP and for subjects that withdraw from the study. For subjects that discontinue IP, post-treatment concomitant medication should be entered into the eCRF until they complete telephone contact at the planned Visit 7 date.

5.8. Treatment of Study Treatment Overdose

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

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

6. STUDY ASSESSMENTS AND PROCEDURES

Table 4 Time and Events Table

Protocol Activity	Pre-Screen	Screen	Treatment						IP Discontinuation Visit	Follow Up
	Visit 0	Visit 1 Screen/run-in	Visit 2 Randomization	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7		Safety Follow-up Contact
Study Day		Week -2	Week 0	Week 4	Week 16	Week 28	Week 40	Week 52		1 week Fw-up
Window		-3/+8d		-4/+2d	-8/+6d	-8/+6d	-8/+6d	-8/+6d		-1/+4d
Procedures										
Written Informed Consent ^a	X	X								
Genetic Informed Consent ^b	X	X								
Demography ^c	X	X								
Medical History including cardiovascular history		X								
COPD and Exacerbation History		X								
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria		X	X							
Smoking History		X								
Smoking status		X				X		X	X	
Smoking Cessation Counseling		X						X	X	
Register Visit in RAMOS	X	X	X	X	X	X	X	X	X	X
Efficacy assessments										
Spirometry		X	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	
Reversibility Testing ^e		X								
Diary/device training and registration		X	X							
Diary Review			X	X	X	X	X	X	X	
Exacerbation Assessment		X	X	X	X	X	X	X	X	X

Protocol Activity	Pre-Screen	Screen	Treatment						IP Discontinuation Visit	Follow Up
	Visit 0	Visit 1 Screen/run-in	Visit 2 Randomization	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7		Safety Follow-up Contact
Study Day		Week -2	Week 0	Week 4	Week 16	Week 28	Week 40	Week 52		1 week Fw-up
Window		-3/+8d		-4/+2d	-8/+6d	-8/+6d	-8/+6d	-8/+6d		-1/+4d
Procedures										
SGRQ-C ^f			X	X		X		X	X	
BDI ^f			X							
TDI ^f				X		X		X	X	
CAT ^f		X	X	X		X		X	X	
EQ-5D-5L ^f			X			X		X	X	
Subject Global Rating of Activity Limitation ^f			X	X	X	X	X	X	X	
Subject Global Impression of Change in Activity Limitation ^f				X	X	X	X	X	X	
Subject Global rating of severity of COPD ^f			X							
Subject Global rating of Change in COPD ^f				X	X	X	X	X	X	
Healthcare Resource Utilisation				X	X	X	X	X	X	
eDiary close out ^g			X					X	X	
Safety Assessments										
Physical examination ^h		X				X		X	X	
Adverse Events Assessment [*]		X	X	X	X	X	X	X	X	X
Vital signs ⁱ		X		X		X		X	X	
ECG		X		X ^j		X		X	X	
Chest X-ray ^k		X								
Oropharyngeal examination		X	X	X	X	X	X	X	X	
Pulse oximetry ^l			X							
Laboratory Assessments										
Blood draw for PK					X ^m	X ⁿ				
Blood Draw for Genetics research ^o			X							
Hematology			X							

Protocol Activity	Pre-Screen	Screen	Treatment						IP Discontinuation Visit	Follow Up
	Visit 0	Visit 1 Screen/run-in	Visit 2 Randomization	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7		Safety Follow-up Contact
Study Day		Week -2	Week 0	Week 4	Week 16	Week 28	Week 40	Week 52		1 week Fw-up
Window		-3/+8d		-4/+2d	-8/+6d	-8/+6d	-8/+6d	-8/+6d		-1/+4d
Procedures										
Hematology/biochemistry ^p		X			X	X		X	X	
Urine Pregnancy Test ^q		X		X	X	X	X	X	X	
Hepatitis B and C tests		X								
Exploratory Lab Assessment										
Blood draw for fibrinogen					X					
Study Treatment										
Dispense IP			X	X	X	X	X			
Administer IP in clinic			X	X	X	X	X	X	X	
Assess IP compliance				X	X	X	X	X	X	
Collect IP				X	X	X	X	X	X	
Dispense albuterol/salbutamol		X	X	X	X	X	X			
Collect albuterol/salbutamol			X	X	X	X	X	X	X	

- Informed consent must be conducted at the Pre-screen visit prior to performing any study procedures including the changing or withholding of medications. The (IC) may be given at Screening Visit 1 if the subject does not take or has not taken any protocol excluded medications.
- Genetics research consent may be obtained at the same time as the study IC and must be obtained prior to obtaining a genetic blood sample. No study centers in China will participate in genetic research in this study.
- Demography may be captured at either the pre-screen visit or Screening visit (for subjects who do not have a pre-screen visit).
- At Visits 2-7 (and the IP discontinuation visit) both pre and post-bronchodilator spirometry will be conducted. Pre-bronchodilator spirometry will be performed prior to taking morning dose of IP, between 6am and 11am and after withholding rescue albuterol/salbutamol for ≥ 4 hours. Post-bronchodilator spirometry will be conducted (prior to taking morning dose of IP) approximately 10-30 minutes after administering 4 puffs of albuterol/salbutamol.
- Subjects are required to withhold their usual morning doses of their COPD meds including rescue albuterol/salbutamol for the protocol designated period prior to reversibility testing.
- Patient reported assessments should be conducted in the following order and before other study assessments: SGRQ-C, BDI/TDI, EQ-5D-5L, CAT, Subject Global Rating of Activity Limitation, Subject Global Impression of Change in Activity Limitation, Subject Global Rating of severity of COPD and Change in COPD. BDI/TDI will be conducted in a subset of subjects at selected sites.
- Close out eDiary for any subject who fails to randomize, discontinues IP, or completes visit 7.
- Physical examination may include height, weight, blood pressure, temperature, heart rate.
- Vital signs must be performed prior to spirometry and prior to taking morning dose of IP.

- j. ECG to be obtained 15 minutes to 45 minutes post-dose at treatment Visits 3, 5 and 7 and IP Discontinuation Visit (if applicable). In addition, at V3 (in a subset of subjects at selected sites) one additional ECG will be collected pre-dose.
- k. Chest X-ray is required at Screening (or historical x-ray obtained within 3 months prior to Screening) and at anytime there is a suspected pneumonia or a moderate/severe exacerbation.
- l. Pulse oximetry must be performed at V2 and anytime there is a suspected pneumonia or a moderate or severe exacerbation.
- m. In a subset of 300 subjects at selected sites, PK samples to be obtained at two timepoints at Visit 4: pre-dose and in the window 5 to 15 minutes post-dose.
- n. In a subset of 300 subjects at selected sites, PK samples to be obtained at two timepoints at Visit 5: 5 to 15 minutes post-dose and 45 to 90 minutes post-dose.
- o. Genetic consent must be obtained prior to obtaining a blood sample. No study centers in China will participate in genetic research in this study.
- p. Hematology and chemistry panels will include liver chemistry, and potassium and glucose levels.
- q. All female subjects of child bearing potential will have a urine pregnancy test at each visit except Visits 2 and follow-up.
- r. Subjects must withhold their morning dose of IP at each clinic visit and not take their IP dose until instructed to do so by study staff.

NOTE:

1. Subjects who have permanently discontinued IP (and have not withdrawn consent) will complete the discontinuation IP visit and the safety follow-up contact and then will continue in the study to complete all remaining per protocol scheduled visits by phone contact to collect Exacerbations, SAEs and Concomitant Medications.
2. * In China only, Serious AEs will be recorded from the time the consent form is signed until the 7-day safety follow-up visit/telephone contact has been completed, or until Visit 7(telephone contact) for subjects who have discontinued IP but continue in the study.

6.1. Critical Baseline Assessments

No study related procedures may be performed until the informed consent form has been signed by the subject. A pre-screening visit may be required in order to administer the informed consent before any changes are made to the subject's current medical regimen. Selection and modification of the subject's medications prior to study participation is based on the physician's judgment according to sound medical practice, principles, and each subject's needs. A subject's treatment must not be changed merely for the purpose of enabling the subject's participation in the study. The informed consent may be given at the Screening Visit (Visit 1) if the subject does not take or has not taken any protocol excluded medications. During the pre-screening visit (Visit 0) each subject will have the following information collected:

- Demographic history (including gender, ethnic origin, year of birth).
- Concomitant medication review.
- Register visit in RAMOS IVRS

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

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

In addition the following procedures must be completed at Visit 1:

- Smoking cessation counseling
- eDiary training
- Register visit in RAMOS
- Dispense albuterol/salbutamol

See Section 4.7 for specific data to be collected for screen failures.

6.2. Efficacy

6.2.1. Co-Primary Efficacy Endpoints

- Annual rate of on-treatment moderate and severe exacerbations comparing FF/UMEC/VI with UMEC/VI
- Annual rate of on-treatment moderate and severe exacerbations comparing FF/UMEC/VI with FF/VI

6.2.2. Secondary Efficacy Endpoints

- Change from baseline trough FEV₁ at Week 52 comparing FF/UMEC/VI with FF/VI
- Change from baseline SGRQ Total Score at Week 52 comparing FF/UMEC/VI with FF/VI
- Time to first on-treatment moderate or severe exacerbation comparing FF/UMEC/VI with FF/VI and with UMEC/VI
- Annual rate of on-treatment moderate and severe exacerbations comparing FF/UMEC/VI with UMEC/VI in the subset of subjects with a blood eosinophil count ≥ 150 cells/ μ l
- Time to first on-treatment moderate or severe exacerbation comparing FF/UMEC/VI with UMEC/VI in the subset of subjects with a blood eosinophil count ≥ 150 cells/ μ l
- Annual rate of on-treatment severe exacerbations comparing FF/UMEC/VI with FF/VI and with UMEC/VI

6.2.3. Other Efficacy endpoints

- Change from baseline in post-bronchodilator FEV₁
- Time to death from any cause
- Responder rate based on the SGRQ Total Score
- Annual rate of all on-treatment exacerbations (mild, moderate, severe)
- Annual rate of on-treatment moderate exacerbations

- Time to first on-treatment COPD hospitalization and COPD re-hospitalization
- Annual rate of exacerbations requiring systemic/oral corticosteroids
- Annual rate of exacerbations requiring antibiotics
- Transitional Dyspnoea Index (TDI) focal score comparing FF/UMEC/VI with FF/VI
- Use of rescue albuterol/salbutamol (percentage of rescue-free days and occasions/day)
- Change from baseline trough FEV₁ at Week 52 comparing FF/UMEC/VI with UMEC/VI
- Change from baseline in SGRQ Total Score comparing FF/UMEC/VI with UMEC/VI
- CAT score (change from baseline and responder rate)
- Subject Global Rating of Activity Limitation and Subject Global Impression of Change in Activity Limitation
- Subject Global Rating of Severity of COPD and Change in COPD
- Annual rate of on-treatment severe exacerbations comparing FF/UMEC/VI with UMEC/VI in the subset of subjects with a blood eosinophil count ≥ 150 cells/ μ l

6.2.4. COPD Exacerbations

Potential COPD exacerbations will be identified based on symptoms reported via the eDiary (triggering contact with the investigator for review via phone contact or at a clinic visit) and the Investigator's judgment.

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

- Chest X-ray
- Pulse oximetry

Refer to Section [6.3.17](#) for chest x-rays.

6.2.4.1. Guidelines for Identifying COPD Exacerbations

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

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

- Dyspnea
- Sputum volume
- Sputum purulence (color)

OR

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

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

Subjects who experience worsening COPD symptoms for greater than 24 hours should:

- Contact their study Investigator and/or research coordinator immediately, and report to the study clinic as required
- If the subject is unable to contact their study Investigator and/or research coordinator, they should contact their primary care physician (or other health care practitioner as required) and contact their study site as soon as possible
- Continue to record their symptoms and rescue albuterol/salbutamol usage in their daily eDiary
- If the subject seeks emergency/acute care for worsening respiratory symptoms, he/she should request the caring Health Care Provider (HCP) to contact the Investigator as soon as possible.

Subjects with worsening respiratory symptoms will be classified as having:

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

OR

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

Definitions for COPD exacerbations and pneumonia are given in Section 6.2.4.2 and in Section 6.3.16, respectively. If, based on these criteria, a subject's symptoms do not fulfill the diagnosis of an exacerbation and/or pneumonia, then the investigator should use their clinical judgment to assess the subject's symptoms (including increased volume of sputum production and/or change in the sputum color) for a diagnosis of LRTI (e.g. acute bronchitis), background variability of COPD, a non-respiratory related disease or other respiratory related disease. Investigator judgment should be used in deciding whether to report the signs and symptoms (and/or determined diagnosis) as recorded in the diary as an AE/SAE in the eCRF. Refer to Section 6.3.2.1 and Section 6.3.2.2 for definitions of AE and SAE, respectively.

6.2.4.2. COPD Exacerbation Severity

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

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

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

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

Every effort should be made to conduct a chest x-ray within 48 hours of identification of a moderate or severe exacerbation. All chest x-rays will be over-read centrally to determine if there are new radiographic findings compatible with pneumonia.

Details of an exacerbation should be recorded in the exacerbation page of the eCRF. However, exacerbations should not be recorded in the AE section of the eCRF unless they meet the definition of an SAE. (Pneumonia must be recorded in the AE or SAE section of the eCRF and on the Pneumonia page of the eCRF.)

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

6.2.4.3. Treatment of COPD Exacerbations

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

6.2.4.4. Guidelines for Treatment with Corticosteroids

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

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

6.2.4.5. Guidelines for Treatment with Antibiotics

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

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

Use of antibiotics for the treatment of upper or lower respiratory tract infections is not considered a COPD exacerbation unless the subject experiences worsening of symptoms of COPD as described in Section [6.2.4.1](#).

6.2.4.6. Onset and Resolution of COPD Exacerbations

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

The date of onset is the first day (of at least 2 consecutive days) of worsening symptoms of COPD as described in Section [6.2.4.1](#).

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

6.2.4.7. Guideline for assessing multiple mild exacerbations

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

6.2.4.8. Guideline for assessing exacerbations that increase in severity

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

6.2.5. Spirometry Testing

Spirometry measurements will be obtained using spirometry equipment that meets or exceeds the minimal performance recommendations of the ATS [[Miller, 2005](#)]. All subjects will have spirometry performed at Screening and each scheduled clinic visit during the treatment period. At the screening visit both pre- and post-albuterol/salbutamol spirometry measurements will be measured in order to assess eligibility and reversibility (see Section [6.2.5.1](#)). At Visits 2-7 (and discontinuation of IP

visit) both pre- and post-albuterol/salbutamol spirometry will be measured prior to the subject taking their morning dose of IP. For FEV₁ and FVC determinations, at least 3 acceptable spirometry efforts (with no more than 8) should be obtained. Acceptable spirometry efforts should have a satisfactory start of test and end of test (*e.g.* a plateau in the volume-time curve) and be free from artifacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons [Miller, 2005].

The largest FEV₁ and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort.

Spirometry must be performed as follows:

- Started approximately between 6:00AM and 11:00AM.
- If applicable, after completing the health outcomes assessments (SGRQ-C, BDI/TDI, EQ5D, CAT, Activity limitation, HRU, COPD assessment).
- After withholding albuterol/salbutamol for ≥ 4 hours.
- At screening, before the morning dose of their usual COPD medications.
- At randomization and all treatment visits, before the morning dose of IP.
- Subjects should refrain from smoking for 1 hour prior to each pulmonary function test.
- Subjects should abstain from drinking beverages with high levels of caffeine such as tea and coffee for 2 hours prior to each pulmonary function test.

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

6.2.5.1. Reversibility Testing

At Visit 1, both pre- and post-albuterol/salbutamol spirometry will be obtained. Post-albuterol/salbutamol FEV₁ and FEV₁/FVC findings will be used to determine subject eligibility.

Reversibility testing will be completed as follows: Following pre-albuterol/salbutamol spirometry (three acceptable spirometry efforts), the subject will self-administer 4 puffs of albuterol/salbutamol MDI using a spacer/valved-holding chamber. Three acceptable spirometry efforts will be obtained approximately 10 to 30 minutes after albuterol/salbutamol administration.

6.2.6. SGRQ-C

The St George's Respiratory Questionnaire -COPD specific (SGRQ-C) will be completed by subjects at Randomization, at Week 4, Week 28 and Week 52 (or at the IP Discontinuation Visit).

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

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

6.2.7. Diary Assessments

Subjects will complete a daily eDiary to provide the following information:

- Number of nighttime awakenings due to COPD symptoms
- Use of supplemental albuterol/salbutamol
- Major symptoms concerning the subject's dyspnea, sputum volume, sputum purulence (color)
- Minor symptoms of cough, wheezing, sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause
- Subjects will also be asked 'Did your respiratory symptoms stop you performing your usual activities in the last 24 hours?' with a Yes/No answer.

Subjects will be instructed to complete the daily eDiary in the morning, prior to taking any IP medication. Subjects will be instructed on how to use the eDiary to score each of these major and minor symptoms daily. COPD exacerbations will be identified based on eDiary review, and Investigator judgment. In addition, subjects will also capture their use of albuterol/salbutamol, the number of nighttime awakenings and if their activity level was affected by their respiratory symptoms.

Investigator judgment should be used in deciding whether to report the signs and symptoms (and/or determine diagnosis) as recorded in the diary as an AE/SAE in the eCRF. Refer to Section 6.3.2.1 and Section 6.3.2.2 for definitions of AE and SAE, respectively.

6.2.8. Rescue Albuterol/Salbutamol Use

Study supplied albuterol/salbutamol MDI and/or Nebules for use as rescue medication throughout the study will be sourced by GSK for centers in the United States of America; for all other centers it will be sourced locally where possible. Subjects will be instructed to record via daily eDiary the number of occasions rescue albuterol/salbutamol was used in the past 24 hours for the relief of COPD symptoms.

6.2.9. Baseline Dyspnoea Index/Transitional Dyspnoea Index

The BDI is used to measure the severity of dyspnoea in patients at baseline. The TDI measures changes in the patient's dyspnoea from baseline. The scores in both indexes depend on ratings for three different categories: functional impairment; magnitude of task; and magnitude of effort. The BDI will be measured at randomisation. TDI will be measured at Week 4, Week 28 and Week 52 (or IP Discontinuation Visit). Data will be collected in a subset of subjects at selected sites where translations are available.

6.2.10. COPD Assessment Test (CAT)

The CAT will be completed by subjects at screening, randomization, Week 4, Week 28 and Week 52 (or IP Discontinuation Visit).

The COPD Assessment Test (Jones, 2009; Jones, 2012) is a validated, short and simple patient completed questionnaire which has been developed for use in routine clinical practice to measure the health status of patients with COPD. The CAT is an 8-item questionnaire suitable for completion by all patients diagnosed with COPD. When completing the questionnaire, subjects rate their experience on a 6-point scale, ranging from 0 (no impairment) to 5 (maximum impairment) with a scoring range of 0-40. Higher scores indicate greater disease impact.

6.2.11. Subject Global Rating of Activity Limitation and Subject Global Impression of Change in Activity Limitation

Subjects will complete the Global Rating of Activity Limitation at randomisation and all subsequent visits including the final visit (or IP Discontinuation Visit). This single global question will ask subjects to rate their activity limitation on a four-point scale (not limited, slightly limited, limited, very limited).

Subjects will complete a Global Impression of Change in Activity Limitation question at all visits subsequent to randomisation including the final visit (or IP Discontinuation Visit). Response options will be on a 7 point Likert scale ranging from much better to much worse.

(Note: The above assessments are in addition to the subject's daily diary recording of activity level that was affected by their respiratory symptoms.)

6.2.12. Subject Global Rating Severity of COPD and Subject Global Impression of Change in COPD

Subjects will complete the Global rating severity of COPD at randomization. This single global question will ask subjects to rate their severity of COPD on a four point scale (mild, moderate, severe, very severe).

Subjects will complete a Global Rating of Change in COPD (overall disease) question at all visits subsequent to randomisation including the final visit (or IP Discontinuation Visit). Response options will be on a 7 point Likert scale ranging from much better to much worse. Asking at each visit allows for early detection of response as well as continued response.

6.3. Safety

See Section 9.8 and Section 9.9 for information on IDMC and adjudication of SAEs.

Safety endpoints and other assessments

- Incidence of adverse events

- Incidence of pneumonia
- Incidence of cardiovascular events (including supraventricular arrhythmia and non fatal myocardial infarction)
- ECG measurements
- Vital signs
- Hematological and clinical chemistry parameters
- Oropharyngeal examinations
- Incidence of bone fractures
- Radiography (CXR)
- Physical examinations
- Pulse oximetry
- Urine pregnancy test (for women of child-bearing potential)

6.3.1. Liver chemistry stopping and follow up criteria

Phase III-IV 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 III-IV liver chemistry stopping criteria 1-5 are defined below and are presented in a figure in [Appendix 3](#):

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

NOTE: if serum bilirubin fractionation is not immediately available, discontinue study drug for that subject if ALT \geq 3xULN and bilirubin \geq 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 \geq 8xULN.
3. ALT \geq 5xULN but <8 xULN persists for \geq 2 weeks
4. ALT \geq 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
5. ALT \geq 5xULN but <8 xULN and cannot be monitored weekly for \geq 2 weeks

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

- **Immediately** discontinue 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 \geq 3xULN **and** bilirubin \geq 2xULN (>35% direct) (or ALT \geq 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, discontinue IP for that subject if ALT \geq 3xULN **and** bilirubin \geq 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.
- Discontinue investigational product after completion of the liver chemistry monitoring as described below.
- Do not restart 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 \geq 5xULN and <8xULN which exhibit a decrease to ALT \geq 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 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 $\geq 2xULN$.
- 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 $\geq 3xULN$ and bilirubin $\geq 2xULN$ (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [[James, 2009](#)]). **NOTE: not required in China.**
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. **NOTE:** if hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [[Le Gal, 2005](#)].
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease.

6.3.2. 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. Subjects will be provided with a paper diary worksheet in which to record any medications they use or AEs they may have experienced. In addition, the worksheet will be used by the subject to record healthcare contacts between visits.

For the purposes of this study, all COPD exacerbations will be collected and recorded on the COPD exacerbation eCRF page. COPD exacerbations should not be recorded as an adverse event, unless they meet the definition of a Serious Adverse Event (see Section [6.3.2.2](#)). For COPD exacerbations that are considered serious, the SAE page of eCRF should be completed, in addition to the COPD eCRF page.

6.3.2.1. Definition of an AE

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

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

6.3.2.2. 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 ALT \geq 3xULN **and** bilirubin \geq 2xULN (>35% direct) (or ALT \geq 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin \geq 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

6.3.2.3. 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 necrosis

6.3.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

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

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

6.3.4. Cardiovascular Events

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

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

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

6.3.5. Death Events

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

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

6.3.6. Disease-Related Outcomes Not Subject to Expedited Reporting to Regulatory Authorities

The primary endpoint of this study is the annual rate of on-treatment moderate and severe COPD exacerbations.

COPD exacerbations should not be recorded as an adverse event, unless they meet the definition of a SAE (Section 6.3.2.2).

COPD exacerbation SAEs will not be subject to expedited reporting regardless of the “expectedness” or “relatedness” of the event.

6.3.7. 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.

6.3.8. Medical Devices

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

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

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

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

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

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

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

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

It is sufficient that

- An incident associated with a device happened and
- The incident was such that, if it occurred again, it might lead to death or serious deterioration in health

A serious deterioration in state of health can include:

- A life-threatening illness (a)
- Permanent impairment of body function or permanent damage to a body structure (b)
- A condition necessitating medical or surgical intervention to prevent (a) or (b)
- Any indirect harm as a consequence of an incorrect diagnostic or IVD test results when used within the manufacturer's instructions for use
- Fetal distress, fetal death or any congenital abnormality or birth defects

Incidents include, for example:

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

Incidents do not include for example:

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

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

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

6.3.9. 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 and SAEs will be collected from the time of Visit 2 (Randomization) until the 7-day safety follow-up visit/telephone contact has been completed or until Visit 7 for subjects who have discontinued IP but continue in the study. Additionally, 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, histopathological examinations, or consultation with other health care professionals.

COPD exacerbations will be collected from the time of Visit 2 (Randomization) until the 7-day safety follow-up visit/telephone contact has been completed or until Visit 7 for subjects who have discontinued IP but continue in the study. COPD Exacerbations will not be collected as AEs unless they meet the definition of an SAE.

NOTE: In China only, Serious AEs will be recorded from the time the consent form is signed until the 7-day safety follow-up visit/telephone contact has been completed, or until Visit 7(telephone contact) for subjects who have discontinued IP but continue in the study.

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?”

“Have you had any (other) medical problems since your last visit/contact?”

“Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

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

SAEs, pregnancies, medical device incidents, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in

the following table once the investigator determines that the event meets the protocol definition for that event.

Type of Event	Initial Reports		Follow-up Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Cardiovascular or death event	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Device Incident	24 hours	"Medical Device Incident Report Form"	24 hours	Updated "Medical Device Incident Report Form"
Pregnancy	2 weeks	"Pregnancy Notification Form"	2 weeks	"Pregnancy Follow-up Form"
Liver chemistry abnormalities for Phase I to IV:				
ALT \geq 3xULN and Bilirubin \geq 2xULN (>35% direct) (or ALT \geq 3xULN and INR>1.5, if INR measured) ¹	24 hours ²	"SAE" data collection tool. "Liver Event CRF" and "Liver Imaging" and/or "Liver Biopsy" CRFs, if applicable ³	24 hours	Updated "SAE" data collection tool/"Liver Event" Documents ³
Remaining liver chemistry abnormalities Phase III to IV:				
ALT \geq 8xULN; ALT \geq 3xULN with hepatitis or rash or \geq 3xULN and < 5xULN that persists \geq 4 weeks	24 hours ²	"Liver Event" Documents (defined above) ³	24 hours	Updated "Liver Event" Documents ³

Type of Event	Initial Reports		Follow-up Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
ALT \geq 5xULN plus bilirubin <2xULN	24 hours ²	“Liver Event” Documents (defined above) do not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks ³	24 hours	Updated “Liver Event” Documents, if applicable ³
ALT \geq 5xULN and bilirubin <2xULN that persists \geq 2 weeks	24 hours ²	“Liver Event” Documents (defined above) ³	24 hours	Updated “Liver Event” Documents ³
ALT \geq 3xULN and <5x ULN and bilirubin <2xULN	24 hours ²	“Liver Event” Documents (defined above) do not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks ³	24 hours	Updated “Liver Event” Documents, if applicable ³

1. INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants.
2. GSK must be contacted at onset of liver chemistry elevations to discuss subject safety
3. Liver Event Documents (i.e., “Liver Event CRF” and “Liver Imaging CRF” and/or “Liver Biopsy CRF”, as applicable) should be completed as soon as possible.

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

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

6.3.11.1. 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. Laboratory Assessments

Routine non-fasting clinical laboratory tests (hematology, chemistry), including serum glucose and serum potassium levels, will be performed at Screening (Visit 1) and at Week 16, Week 28, and Week 52 (or IP Discontinuation Visit). Hepatitis B and C will be collected as part of the Screening Visit blood draw. Hematology (alone) will be collected at Visit 2. The Week 16 hematology blood draw will also be used to assess fibrinogen as an exploratory biomarker of COPD.

All female subjects of child bearing potential will have urine pregnancy tests performed at the Screening (Visit 1) and at Weeks 4, Week 16, Week 28, Week 40, and Week 52 (or IP Discontinuation Visit).

At the discretion of the Investigator, additional samples may be taken for safety reasons.

All blood will be analyzed by a central laboratory. Full details regarding sample collection, processing and shipping are provided in the central laboratory manual.

Please see [Appendix 4](#) for a specific list of laboratory analytes to be tested.

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) 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.

6.3.13. 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 at Screening, Weeks 4, 28, and 52 (or IP Discontinuation Visit). Blood pressure (systolic and diastolic) and pulse rate will be measured in the sitting position after approximately 5 minutes rest. A single set of values will be collected and recorded in the source documentation and eCRF.

6.3.14. 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.

6.3.15. 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 spirometry. Recordings will be made at Screening (Visit 1) and approximately 15-45 minutes after dosing on treatment Week 4, Week 28, Week 52 (or IP Discontinuation Visit). In addition, in a subset of subjects, at selected sites one pre-dose measurement will also be assessed at Week 4. 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 QTc, protocol defined stopping criteria, triplicate ECGs (over a brief period of time) should be performed (see Section 4.4.1).

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, 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.

6.3.16. 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 patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD receiving fluticasone furoate/vilanterol include current smokers, patients with a history of prior pneumonia, patients with a body mass index < 25 kg/m² and patients with an FEV₁ < 50% predicted. 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.

6.3.17. Radiography (Chest X-Rays)

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

6.3.18. Oropharyngeal Examinations

Oropharyngeal examinations for clinical evidence of infection (*e.g.* *Candida albicans*) will be performed at each study visit as shown in the Time and Events Table. 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.

6.3.19. Pulse oximetry

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

6.4. Health Outcomes

All patient reported outcomes should be administered at the beginning of a study visit before any physical activity or spirometry. SGRQ-C should be administered first followed by BDI/TDI, EQ-5D-5L, CAT, Subject Global Rating of Activity Limitation and Subject Global Impression of Change in Activity Limitation and Subject Global Rating of COPD Severity and Subject Global Rating of Change in COPD. (See Section 6.2.6 for information on SGRQ-C, Section 6.2.9 for BDI/TDI, Section 6.2.10 for CAT, Section 6.2.11 for Activity limitation and change in activity limitation and Section 6.2.12 for COPD severity and change in COPD).

6.4.1. EuroQol Questionnaire (EQ-5D-5L)

The EQ-5D-5L questionnaire will be completed by subjects at randomization, at Week 28 and Week 52 (or IP Discontinuation Visit).

The EQ-5D-5L is a standardised instrument for use as a measure of health utility. It is designed for self-completion and is cognitively simple, taking only a few minutes to complete. The EQ-5D-5L is a two-part self-assessment questionnaire. The first part consists of five items covering five dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a five-point Likert scale (no problems, slight problems, moderate problems, severe problems, and extreme problems). Respondents are asked to choose one level that reflects their "own health state today" for each of the five dimensions. Respondents can be then classified into one of 243 distinct health states. The second part is a 20-cm visual analogue scale (EQ-VAS) that has endpoints labelled "best imaginable health state" and "worst imaginable health state" anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health by drawing a line from an anchor box to that point on the EQ-VAS which best represents their own health on that day. EQ-5D-5L health states are converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. The formula is based on the valuation of EQ-5D health states from general population samples.

6.4.2. Healthcare resource utilisation

All unscheduled visits to a physician office, visits to urgent care, visits to emergency department, and hospitalizations will be recorded in the eCRF. In addition visits and contacts that are due to a COPD exacerbation will be assessed and recorded. Patients will be provided with a paper worksheet diary to record any health care contacts between clinic visits. In addition, the paper worksheet diary will be used by subjects to record any medications they have taken or adverse events they have experienced.

6.5. Pharmacokinetics

Concentrations of FF, UMEC and VI in plasma will be determined using currently approved assay methodology under the control of GSK PTS-DMPK. A population pharmacokinetics approach will be employed in this study with samples collected in approximately 300 subjects (to achieve approximately 120 subjects treated with FF/UMEC/VI). At Visits 4 and 5, two 6mL blood samples will be collected from each of the 300 subject as follows:

Visit 4: Predose and in the window 5 to 15 minutes post-dose

Visit 5: In the windows 5 to 15 minutes and 45 to 90 minutes post-dose

Refer to the SPM for details of the sample collection, information to document and treatment, shipment and processing procedures. Raw data will be archived at the bioanalytical site (detailed in the SPM).

6.6. Genetic Research

Information regarding genetic research is included in [Appendix 1](#).

Note: No study centers in China will participate in genetic research in this study.

6.7. Novel Biomarkers

Plasma samples will be collected at Week 16 to analyze fibrinogen, a known inflammatory marker.

After completion of the clinical trial, an exploratory analysis will be conducted on the relationship of plasma fibrinogen with measures of response to each study treatment. The results gained may also be of application for future COPD trials.

7. DATA MANAGEMENT

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

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary. 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 objective of this study is to evaluate the efficacy of FF/UMEC/VI to reduce the annual rate of moderate and severe exacerbations compared with dual therapy of FF/VI or UMEC/VI in subjects with COPD over a 52 week period.

The aim of this study is to demonstrate the contribution of the ICS when used in combination with a fixed dose of a LABA/LAMA, and the contribution of the LAMA above the efficacy of an ICS/LABA combination, in reducing the rate of on-treatment moderate and severe exacerbations in patients with COPD. This is a superiority study.

The primary endpoint is the annual rate of on-treatment moderate and severe exacerbations (calculated as the number of moderate and severe exacerbations during the treatment period).

The primary analyses will be the pair-wise comparisons of FF/UMEC/VI against FF/VI and against UMEC/VI, with inferences adjusted for multiplicity as described in Section 8.3.3. The primary analyses will be based on a two-sided hypothesis testing approach. The hypotheses associated with the statistical test of the primary efficacy endpoint are $H_0: \lambda_T/\lambda_D=1$ versus $H_A: \lambda_T/\lambda_D \neq 1$ where λ_T is the annual rate for triple therapy (FF/UMEC/VI) and λ_D is the annual rate for the respective dual therapies (FF/VI and UMEC/VI).

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

Sample size calculations are based on the co-primary endpoints, the annual rate of on-treatment moderate and severe exacerbations for the comparison of FF/UMEC/VI with FF/VI and with UMEC/VI.

The treatment benefit for moderate and severe exacerbation rates when adding the ICS component to a LABA in studies with Advair™/Seretide™ [Ferguson, 2008] and with FF/VI [Dransfield, 2013] were approximately 20-30%, where all subjects were restricted from concomitant LAMA therapy. It will be assumed that the ICS effect will be largely maintained even on a background of dual bronchodilation (LABA/LAMA), therefore the study will target a treatment benefit of 15% for FF/UMEC/VI versus UMEC/VI.

As an estimate of dual bronchodilator effect, the SPARK study [Wedzicha, 2013] showed a benefit of a dual bronchodilator over LAMA monotherapy to be approximately 10-12%.

The annual rate of on-treatment moderate and severe exacerbations in the FF/VI treatment arm was 0.92 based on those subjects in the FF/VI arms from the FF/VI Phase IIIa program who can be classified as 'high risk' (unpublished data: studies HZC102871 and HZC102970) according to the most recent COPD guidelines [GOLD, 2013]. Based on these data, the exacerbation rate for FF/UMEC/VI in the current study is estimated to be 0.80 for purposes of sample size calculations, with the estimate for FF/VI being 12% higher (approximately 0.91) and the estimate for UMEC/VI being 15% higher (approximately 0.94). The co-primary endpoints will be controlled for multiplicity using the truncated Hochberg method [Dmitrienko, 2008]. In order to have 90% power to detect a 15% reduction in the annual rate of moderate and severe exacerbations in the FF/UMEC/VI arm compared with the UMEC/VI arm and a 12% reduction compared with the FF/VI arm, 4000 subjects will be randomized to each of the FF/UMEC/VI and FF/VI arms, along with 2000 subjects to the UMEC/VI arm. Calculations are based on a negative binomial regression and use a two-sided 1% significance level in order to satisfy regulatory requirements of substantial evidence of efficacy for a single study. For the multiplicity hierarchy, a 2-sided 5% risk associated with incorrectly rejecting the null hypothesis (significance level) is considered acceptable for this study. The estimate of the dispersion parameter for the negative binomial model is 0.75, which is similar to that seen with fluticasone propionate/salmeterol in the TORCH study [Calverley, 2007] and the dispersion in the FF/VI exacerbation program [Dransfield, 2013].

Subjects will be randomized in a 2:2:1 proportion to the FF/UMEC/VI, FF/VI and UMEC/VI arms, respectively. All randomized subjects (approximately 10,000 in total) are considered to be evaluable for the measurement of exacerbations, irrespective of whether they permanently discontinue from IP. Assuming a 38% screen failure rate, based on the FF/VI Phase III exacerbation program, it is estimated that approximately 16,000 subjects will be screened.

8.2.2. Sample Size Sensitivity

If the annual rate of moderate and severe exacerbations in the FF/UMEC/VI treatment arm is different from the 0.8 used in the sample size calculation, the power to detect the change in exacerbations rates will be affected.

Table 5 illustrates the power which would be obtained from various moderate and severe exacerbation rates and rate reductions for the FF/UMEC/VI treatment arm compared with the FF/VI treatment arm. The sample size, dispersion factor and two-sided significance threshold of 1% remain fixed.

Table 5 Power for varying FF/UMEC/VI exacerbation rates and treatment improvements versus FF/VI

FF/UMEC/VI rate	True Rate of Exacerbation Improvement, FF/UMEC/VI versus FF/VI		
	8% Reduction	10% reduction	12% reduction
0.90	51%	76%	92%
0.80	47%	72%	90%
0.70	43%	67%	87%
0.60	38%	62%	82%

Table 6 illustrates the power which would be obtained from various moderate and severe exacerbation rates and rate reductions for the FF/UMEC/VI treatment arm compared with the UMEC/VI treatment arm. The sample size, randomization ratio (2:1), dispersion factor and two-sided significance threshold of 1% remain fixed.

Table 6 Power for varying FF/UMEC/VI exacerbation rates and treatment improvements versus UMEC/VI

FF/UMEC/VI rate	True Rate of Exacerbation Improvement, FF/UMEC/VI versus UMEC/VI		
	10% reduction	12% reduction	15% reduction
0.90	53%	75%	94%
0.80	49%	71%	92%
0.70	45%	66%	89%
0.60	40%	60%	85%

8.2.3. Sample Size Re-estimation

Blinded evaluation of exacerbation rates is planned for this study. A blinded evaluation of exacerbation rates for the purpose of sample size re-estimation will be done after one year of enrolment, or when 5,000 subjects have been randomized, whichever is earlier. A subsequent evaluation will be done after approximately 18 months of enrolment, or when 7,500 subjects have been randomized, whichever is earlier.

If the exacerbation rates for the study are lower than planned, a sample size re-estimation may be conducted. Any subsequent change to the planned number of subjects randomized would be documented in a protocol amendment.

8.3. Data Analysis Considerations

8.3.1. Analysis Populations

- All Subjects Enrolled Population: This population includes all subjects for whom a record exists on the study database, including screened subjects and subjects who were not screened but signed an ICF. This population will be used for the summary of subject disposition and the listing of SAEs for non-randomised subjects.
- Intent-to-Treat (ITT) Population: The ITT Population will comprise all subjects randomised to treatment apart from those randomised in error. A subject who is recorded as a screen or run-in failure and also randomised, but did not receive a dose of study treatment, will be considered to be randomised in error. Any other subject who receives a randomisation number will be considered to have been randomised. The ITT Population is the primary analysis population of interest.
- Pharmacokinetic (PK) Population: The PK Population will comprise the subset of subjects in the ITT Population for whom a PK sample was obtained and analyzed. This population will be used for all concentration-time and PK parameter tables, listings and figures.

8.3.2. Analysis Data Sets

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 will be the pair-wise comparisons of FF/UMEC/VI against FF/VI and FF/UMEC/VI against UMEC/VI. The primary comparisons will be tested for the primary endpoint, the annual rate of on-treatment moderate and severe exacerbations.

The primary analysis will be based on a two-sided hypothesis testing approach. The hypotheses associated with the statistical test of the primary efficacy endpoint are $H_0: \lambda_T/\lambda_D=1$ versus $H_A: \lambda_T/\lambda_D \neq 1$ where λ_T is the annual rate for triple therapy (FF/UMEC/VI) and λ_D is the annual rate for the respective dual therapies (FF/VI and UMEC/VI).

Both primary comparisons will be tested using the ITT population. In order to account for multiplicity, the truncated Hochberg procedure [Dmitrienko, 2008] with a truncation parameter of $\gamma=0.6$ will be used to control overall Type I error at $\alpha=0.05$.

For the primary comparisons, both comparisons will be declared statistically significant if the p-value for both comparisons is significant at the 0.04 level. Should the largest p-value for the two comparisons be above 0.04, the other comparison will be declared

statistically significant if the smaller p-value is below 0.025. If at least one of the comparisons is significant, this will allow inference of secondary endpoints.

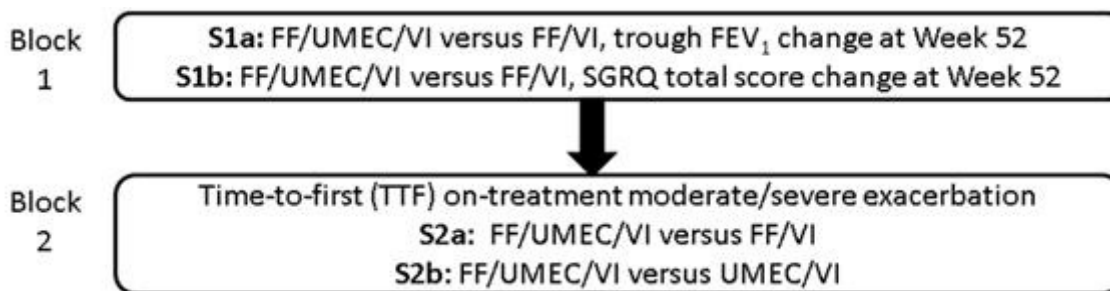
8.3.3.2. Other Comparisons of Interest

If one or both of the primary endpoints is considered statistically significant, inferences will be made from unadjusted p-values for treatment comparisons on secondary and other endpoints. If both co-primary treatment comparisons are statistically significant, these secondary and other treatment comparisons will be declared significant if the unadjusted p-value is <0.05 . If only one co-primary treatment comparison is statistically significant, these secondary and other treatment comparisons will be declared significant if the unadjusted p-value is <0.01 .

Where strong control of type I error is required for secondary endpoints, multiplicity will be controlled using a hierarchical, closed testing procedure. The secondary hypothesis tests will be grouped sequentially in two blocks of two comparisons each, grouped according to specific clinical concepts (lung function and symptoms, and time-to-first exacerbation event). Each block of comparisons will also be adjusted for multiplicity using the truncated Hochberg method as described for the primary endpoint analysis, with a truncation parameter of $\gamma=0.6$ for the first block and a truncation parameter of $\gamma=1$ for the second block.

Within each block, at least one endpoint must be considered statistically significant in order to make inferences in the subsequent block. For example, as shown in [Figure 2](#) at least one of endpoints S1a and S1b would need to be significant in order to make inferences for the S2a/S2b comparisons contained in the next block.

Figure 2 Secondary endpoint hierarchy



Methods for handling missing data for summaries of the secondary efficacy endpoints will be detailed in the RAP.

8.3.4. Interim Analysis

An Independent Data and Monitoring Committee (IDMC) will monitor progress of the study and ensure that it meets the highest standards of ethics and patient safety. Only the IDMC will be authorized to review unblinded interim safety analyses during the trial.

This committee will be formed specifically to oversee trial progression with regards to occurrence of adverse events. The committee, which will comprise a minimum of 3 people, will include an independent statistician and an independent respiratory clinician with experience in COPD and a cardiologist.

The unblinded periodic safety updates will be performed and delivered to the IDMC by an independent Statistical Data Analysis Centre (SDAC).

The IDMC will give a recommendation to the central study team as to whether the trial should be stopped prematurely following review of the interim results for safety. The central study team will decide whether to act on this recommendation.

In the event of early stopping, subjects will be brought to the investigational sites for a final visit, where possible. The final analysis will include all data collected up to and including the final visit.

Membership, functions and operating procedures of IDMC and other organisational groups for this study will be defined in a separate document. Operating procedures for the IDMC will be established before the first review of unblinded data.

8.3.5. Key Elements of Analysis Plan

8.3.5.1. Efficacy Analyses

The primary efficacy endpoint of the annual rate of on-treatment moderate and severe exacerbations will be analyzed using a generalized linear model assuming the negative binomial distribution, with the logarithm of time on treatment as an offset variable. The model will include terms for treatment group, gender, exacerbation history (one, two or more), smoking status at screening, baseline disease severity (as % predicted FEV₁) and geographical region. The adjusted mean annual rates, pair-wise treatment ratios and associated p-values and confidence limits will be presented. The fit of the negative binomial model will be examined using “Q-Q” plots of standardized residuals with simulated envelopes.

For the co-primary endpoints, sensitivity analyses will be performed where all available data collected until the time of study withdrawal will be used. For these sensitivity analyses, the total number of events and the total time in the study (both on-treatment and post-treatment) prior to study withdrawal will be used in the analysis model. Imputations made for the period following study withdrawal will be described in the RAP. Additional sensitivity analyses using multiple imputation methods will be described in the RAP.

The secondary endpoints of trough (pre-dose AM) FEV₁ and SGRQ total score will be analysed using mixed models repeated measures with covariates of treatment group, smoking status at screening, baseline, region, and visit, plus interaction terms for visit by baseline and visit by treatment group.

The secondary endpoints involving time to first moderate and/or severe exacerbation will compare the treatment groups using Cox's proportional hazards model, adjusting for treatment group, gender, exacerbation history (one, two or more), smoking status at screening, baseline disease severity (as % predicted FEV₁), and geographical region.

Secondary and other endpoints involving the annual rate of exacerbations will be analysed as described for the primary endpoint.

The additional endpoint of time to onset of multiple moderate and severe exacerbations will be analysed using an Anderson-Gill model for time to recurrent events.

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

8.3.5.2. Safety Analyses

The extent of exposure to study drug will be summarized by treatment group, using the statistics n, mean, SD, median, minimum and maximum.

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

Time to first event in the Pneumonia Adverse Event of Special Interest subgroup and time to first serious event in the Pneumonia Adverse Event of Special Interest subgroup will be analysed using Cox's proportional hazards model. Deaths due to pneumonia will be summarised and tabulated.

Incidence of bone fractures will be summarised. Full details will be given in the RAP.

Incidence of cardiovascular events (including supraventricular arrhythmia and non-fatal myocardial infarction) will be summarised.

All laboratory parameters will be summarised and tabulated.

A pre-specified MACE analysis (broad analysis and narrow analysis) will be performed using adjudicated cardiovascular deaths and other non-fatal SAEs. MACE events to be included in both the broad and narrow analysis would be defined *a priori*.

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

8.3.5.3. Health Outcomes Analyses

Details of the analysis of all health care utilization endpoints will be specified in the RAP.

8.3.5.4. Pharmacokinetic Analyses

The purpose of PK sampling in this study is for characterisation of patient population PK of FF, UMEC and VI. Plasma concentration-time data for FF, UMEC and VI will be subjected separately to nonlinear mixed effects modelling using the program NONMEM to develop a population PK models. Full details of the analyses for PK endpoints will be provided in the RAP.

8.3.5.5. Genetic Analyses

See [Appendix 1](#) for details about the Genetics Analysis Plan.

8.3.5.6. Novel Biomarker(s) Analyses

The results of these biomarker investigations will be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarised as appropriate to the data.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

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

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

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.

Subject informed consent.

Investigator reporting requirements.

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

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

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments *e.g.*, Genetics research 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) agrees to allow the monitor direct access to all relevant documents.

9.4. Quality Assurance

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

9.5. Study and Site Closure

The end of study is when the last subject completes the last visit.

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

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

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

9.6. Records Retention

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

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

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

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

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the

opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

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

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

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

9.8. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilised in this study to ensure external objective medical and/or statistical review of safety and/or efficacy data in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. In order to maintain blinding in communication with the IDMC, non-blinded persons separate from the study team (*e.g.* an unblinded statistician or data manager) will be appointed to provide required information to the IDMC. The analysis plan for IDMC review is described in the charter, which is available upon request.

9.9. Adjudication Committee

An adjudication committee will be established to independently review and categorize the cause of each Serious Adverse Event. The committee members will remain blinded to treatment. The adjudication plan is described in the charter, which is available upon request.

10. REFERENCES

Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, Balter M *et al.* (2007) Tiotropium in Combination with Placebo, Salmeterol, or Fluticasone–Salmeterol for Treatment of Chronic Obstructive Pulmonary Disease A Randomized Trial. *Ann Intern Med.* 146:545-555.

Augsti A, et al. Frequently asked questions (FAQs) about the GOLD 2011 assessment proposal of COPD. *ERJ Express*. Published on May 3, 2013 as doi: 10.1183/09031936.00036513

Calverley PM, Anderson, JA, Celli B. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *NEJM.* 2007;356:776-89.

Cazzola M *et al.* (2007) A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. *Pul. Pharm. & Therapeu.* 20:556–561.

Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932-946

Chatterjee A, Shah M, D’Souza AO, Bechtel B, Crater, G & Dalal, AA. (2012) Observational study on the impact of initiating tiotropium alone versus tiotropium with fluticasone propionate/salmeterol combination therapy on outcomes and costs in chronic obstructive pulmonary disease. *Respiratory Research* 2012, 13:15

Dmitrienko A, Tamhane A, Wiens B. (2008) General Multistage Gatekeeping Procedures. *Biometrical Journal* 50(5):667-677.

Dransfield, Mark T; Bourbeau, Jean; Jones, Paul W; Hanania, Nicola A; Mahler, Donald A.; Vestbo, Jorgen; Wachtel, Andrew; Martinez, Fernando; Barnhart, Frank; Sanford, Lisa; Lettis, Sally; Crim, Courtney; Calverley, Peter. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomized controlled trials. *DSc The Lancet Respiratory Medicine-1May 2013 (Vol.1, Issue 3, Pages 210-223)* DOI: 10.1016/S2213-2600(13)70040-7

Ferguson GT, Anzueto A, Fei A, Emmett A, Knobil K, Kalberg C. Effect of fluticasone propionate/salmeterol (250/50 µg) or salmeterol (50 µg) on COPD exacerbations. *Resp Med.* 2008;102:1099-1108.

Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013. Available from: <http://www.goldcopd.org/>.

GOLD. Global Initiative for Chronic Obstructive Lung Disease (Updated 2011). <http://www.copdgold.org>.

Han MK, Muellerova H, Currran-Everet D, et al. GOLD 2011 disease severity classification in COPDGene: a prospective cohort study. *The Lancet Res Med* 2013; *Mar 1(1):43-50* doi: 10.1016/S2213-2600 (12)70044-9. Epub 2012 Sep 3.

Hanania, HA *et al.* (2012) Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. *Resp. Med.* 106: 91-101.

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, P., Harding, G., Berry, P., Wiklund, I., Chen, W-H., Leidy, N. Development and first validation of the COPD Assessment Test (CAT) *Eur Respir J* (2009) 34: 648–654

Jones, PW., Harding, G., Wiklund, I., Berry, P., Tabberer, M., Yu, R., Leidy, N. ‘Tests of the Responsiveness of the Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT) Following Acute Exacerbation and Pulmonary Rehabilitation.’ *Chest* (2012) 142 134-140

Jung KS, *et al.* Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: A randomized controlled study. *Resp. Med.* (2012) 106: 382-389 doi:10.1016/j.rmed.2011.09.004.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. *J Clin Microbiol.* 2005;43(5):2363–2369.

Meguro M, Barley EA, Spencer S et al. Development and validation of an improved COPD-Specific Version of the St. George Respiratory Questionnaire. *Chest.* 2007;132:456-463

Miller MR, Hankinson J, Odencrantz J, Standardisation of spirometry. *Eur Respir J.* 2005;26:319-388.

Mullerova H, Locantore N, Jones P. GOLD assessment of COPD patients: impact of symptoms assessment choice.[abstract]. *Eur Respir J.* 2012;40(Suppl 56): 279s.

Quanjer, P., Stanojevic, S., Cole, T., Baur, X., Hall, G., Culver, B., Enright, P., Hankinson, J., Ip, M., Zheng, J., Stocks, J., & ERS Global Lung Function Initiative, (2012). Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. *European Respiratory Journal*, 40(6), 1324-1343.

Short, PM, Williamson, PA, Elder, DHJ & IW Samuel. (2012) The Impact of Tiotropium on Mortality and Exacerbations When Added to Inhaled Corticosteroids and Long-Acting b -Agonist Therapy in COPD. *Chest* 141:81–86.

Tashkin, DP. *et al* (2008) A 4-year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2008 359:1543-1554.

Toy, Edmond L.; Beaulieu, U., Nicolas, McHale, Joshua M.; Welland, Timothy R.; Plauschinat, Craig A.; Swensen, Andrine; Sheng Duh, Mei. Treatment of COPD: Relationships between daily dosing frequency, adherence, resource use, and costs *Respiratory Medicine* (2011) 105:435-441

Wedzicha, Jadwiga; Decramer, Marc; *et al*. Analysis of Chronic Obstructive Pulmonary disease exacerbations with the dual bronchodilator QVA 149 compared with glycopyrronium and tiotropium (SPARK): A randomized, double-blind, parallel-group study. *The Lancet Respiratory Medicine, Volume 1, Issue 3, pages 199-209, May 2013* doi:10. 1016/S2213-2600(13)70052-3

Welte, T *et al*. (2009) Efficacy and Tolerability of Budesonide/Formoterol Added to Tiotropium in Patients with Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* 180:741–750.

Wolters Kluwer's Source Lx Database (2012) Hierarchical Regimen Analysis (HRA) Application SLED Report With Filtering On Patients Aged 18+ With COPD Only. Data from February 2011 through January 2012.

Wurst KE, Bushnell G, Shukla A, Muellerova H, Davis KJ. Factors Associated with Time to Triple Therapy in Newly Diagnosed COPD Patients in the UK General Practice Research Database. (2013) *29th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Montreal, Canada. Abstract 62.*

Yu, Andrew P.; Guerin, Annie; Ponce de Leon, Diego; Ramakrishnan, Karthik; Wu, Eric Q.; Mocariski, Michelle; Blum, Steven I.; Setyawan, Juliana. Clinical and economic outcomes of multiple versus single long-acting inhalers in COPD *Respiratory Medicine* (2011) 105; 1861-1871

11. APPENDICES

11.1. Appendix 1: Genetic research

Genetic Research Objectives and Analyses

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

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

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

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

Study Population

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

Note: No study centers in China will participate in genetic research in this study.

Study Assessments and Procedures

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

- A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. Blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. If a subject initially declines to participate in genetic research and then changes their mind, a sample should be obtained at the earliest opportunity. Instructions for collection

and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The genetic sample is labelled (or “coded”) with the same study specific number as used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

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

Informed Consent

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

Subject Withdrawal from Study

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

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

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

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

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.

- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

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

Provision of Study Results and Confidentiality of Subject's Data

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

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

11.2. Appendix 2: Country Specific Requirements

In China only, Serious AEs will be recorded from the time the consent form is signed until the 7-day safety follow-up visit/telephone contact has been completed, or until Visit 7(telephone contact) for subjects who have discontinued IP but continue in the study.

No study centers in China will participate in genetic research in this study.

11.2.1. China-specific sub-study: Collection of unit-cost data for healthcare utilization among COPD subjects recruited to Study CTT116855 in China

11.2.1.1. Introduction

Globally, health economic (HE) evidence is becoming more and more critical to ensure that the value of new medicines is demonstrated and that patients with unmet need have access to these new medicines. In China, recent high-profile meetings, including Healthcare State Council meetings have highlighted the importance of generating HE evidence. In line with this, the first health technology assessment (HTA) center, to evaluate the cost-effectiveness of drugs, was established in Zhejiang Province in 2014. It is expected that more and more HTA centers will be established in many other areas of China in coming years.

This China-specific sub-study will collect the unit cost data for healthcare utilization among COPD subjects recruited to Study CTT116855 (called the Core Study throughout this document) in China; through the use of a “modified healthcare resource utilization” (“Modified HRU”) paper diary.

11.2.1.2. Objective

To collect unit cost data (direct and indirect) for healthcare utilization among COPD subjects recruited to Study CTT116855 in China

11.2.1.3. Investigational Plan

This is a China-specific sub-study to collect direct and indirect unit cost data for healthcare utilization in subjects who have consented and been randomized to study CTT116855 (Core Study), “A phase III, 52 week, randomized, double-blind, 3-arm parallel group study, comparing the efficacy, safety and tolerability of the fixed dose triple combination FF/UMEC/VI with the fixed dose dual combinations of FF/VI and UMEC/VI, all administered once-daily in the morning via a dry powder inhaler in subjects with chronic obstructive pulmonary disease”, in China.

Currently, subjects randomized to the Core Study complete a healthcare resource utilization (HRU) paper diary, when they have any contact with a health care provider. The current HRU paper diary, in the Core Study, does not require collection of the unit

cost (direct or indirect) for healthcare utilization. For the purpose of this China-specific sub-study, subjects who are consented and randomized to the Core Study in China will complete a “modified healthcare resource utilization” (“Modified HRU”) paper diary. This “Modified HRU” paper diary will collect data in response to five additional questions (see Supplement 1), two of which relate to the direct costs of healthcare services used by a subject and three of which relate to the indirect costs of the subject’s COPD. These questions are:

1. Cost paid by the subject for each healthcare contact due to any health problem¹
2. Cost covered by health insurance for each healthcare contact due to any health problem²
3. Days of work missed by the subject due to their COPD
4. Hours of paid caregiver services due to the subject’s COPD
5. Hours of work missed by family members/relatives due to the subject’s COPD

Subjects of this sub-study will be issued the “Modified HRU” paper diary at scheduled visits starting from Visit 2, and will be required to record their answers to these questions on the paper diary between scheduled visits.

All subjects who participate in this sub-study will be required to provide a separate consent to the use of the “Modified HRU” paper diary. Subjects who do not consent or withdraw consent from this sub-study will continue to use the HRU (unmodified and without the additional questions relating to direct and indirect costs) paper diary, as per the Core Study.

11.2.1.4. Subject Selection and Withdrawal Criteria

11.2.1.4.1. Inclusion Criteria

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

1. Subjects in China, who have provided written informed consent and have been randomized to study CTT116855 (Core Study).
2. Separate Informed Consent for China-specific sub-study: A signed and dated separate written informed consent to the sub-study, to assess direct and indirect unit cost data, prior to participation in the sub-study is required.

11.2.1.4.2. Exclusion Criteria

There are no exclusion criteria to this sub-study.

^{1, 2} Both of these are mutually exclusive and comprehensive. Therefore the sums of 1 and 2 should equate to the total unit cost of healthcare resource used

11.2.1.4.3. Sub-study Withdrawal Criteria

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

In the event that a subject withdraws consent from this sub-study, they will be encouraged to continue to use the HRU paper diary (unmodified and without the additional questions relating to direct and indirect costs) paper diary, as per the Core Study.

Discontinuation criteria from IP and withdrawal criteria from the Core Study will be dealt with as outlined in the Core Study protocol (CTT116855); Section 4.4. Investigational Product (IP) Discontinuation Criteria.

Supplement 1:

Modified Healthcare Resource Utilization Paper Diary (“Modified HRU”), page 1

Date of Healthcare Contact Day Month Year	Type of Healthcare Contact							Reason for Healthcare Contact	Cost paid by subject (Chinese Currency)	Cost paid by insurance (Chinese Currency)	Site validation of reason for contact* <i>(Site Use Only)</i>
	Home Visits		Physician Office/ Clinic Visits	Urgent Care/ Outpatient Clinic Visits	Accident and Emergency Room Visits	Inpatient Hospitalization					
	Day	Night				ICU	General Ward				
e.g., 15 MAR 14	√							Shortness of Breath	338.45	0	
e.g., 15 MAR 14							√	Shortness of Breath	1000.00	7755.87	
1.											
2.											
3.											
4.											
5.											
6.											
7.											
8.											
9.											
10.											
11.											
12.											
13.											
TOTAL <i>(Site use only)</i>											

UK:ENG (United Kingdom/English)

* 1=COPD exacerbation; 2=COPD not exacerbation; 3=Other healthcare contact; 4=Not a healthcare contact

Modified Healthcare Resource Utilization Paper Diary (“Modified HRU”) page 2

Since your last scheduled visit, if you are currently having paid employment and you have to skip work, due to your COPD (e.g., feel breathless or chest tightness, cough, or wake up at night because of these and related complaints), please fill in this paper diary with the date(s) when you miss work and the number of days of work you miss each time.

Date Day Month Year	Days of work you miss due to your COPD (Days)
e.g. 15 July 2015 – 18 July 2015	3.5
Total (Site use only)	

Modified Healthcare Resource Utilization Paper Diary (“Modified HRU”) page 3

Since your last scheduled visit, if you pay someone to take care of you, due to your COPD (e.g., feel breathless or chest tightness, cough, or wake up at night because of these and related complaints), please fill in this paper diary with the date(s) when this happens and the number of hours of using such service each time. If you hire two or more persons to take care of you at the same time, please list the date(s) and hours of using each hired service separately.

<p style="text-align: center;">Date Day Month Year</p>	<p style="text-align: center;"><u>Hours</u> using paid caregiver service due to your COPD (Hours)</p>
e.g. 17 July 2015 – 18 July 2015	6
Total (<i>Site use only</i>)	

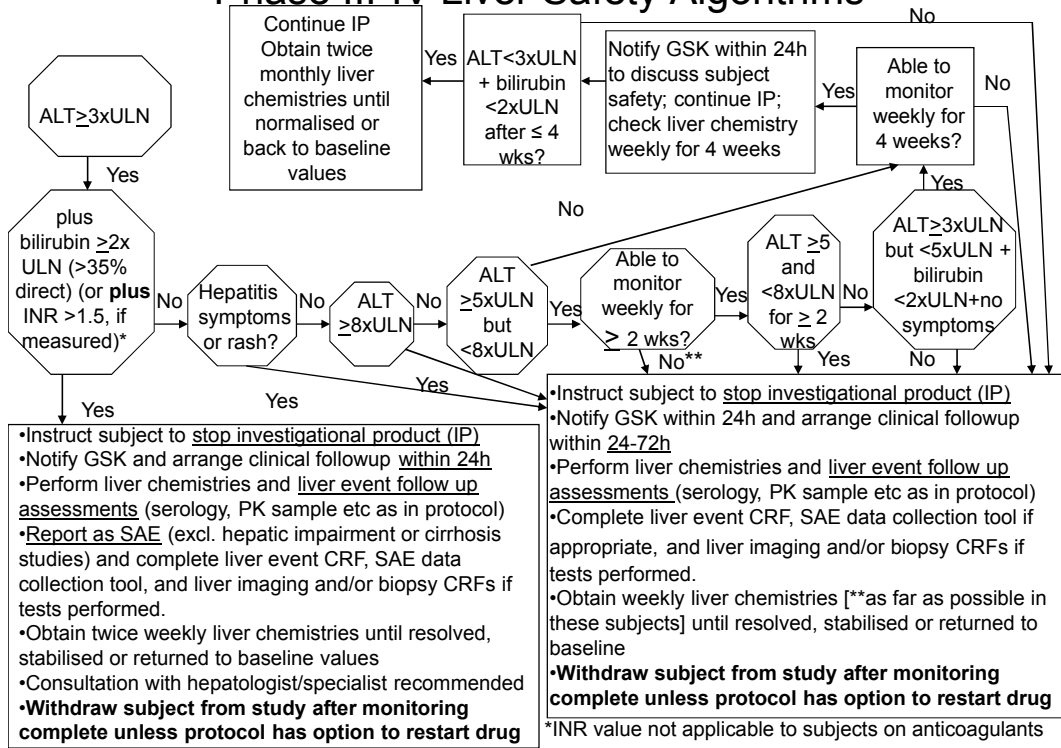
Modified Healthcare Resource Utilization Paper Diary (“Modified HRU”) page 4

Since your last scheduled visit, if your family members/relatives have to skip their work to take care of you, due to your COPD (e.g., feel breathless or chest tightness, cough, or wake up at night because of these and related complaints), please fill in this paper diary with the date(s) when this happens and the number of hours of work they miss each time. If two or more family members/relatives have to skip work to take care of you at the same time, please list the date(s) and hours of missed work by each individual separately.

<p style="text-align: center;">Date</p> <p style="text-align: center;">Day Month Year</p>	<p style="text-align: center;">Hours of work your family members/relatives miss when they take care of you due to your COPD</p> <p style="text-align: center;">(Hours)</p>
e.g. 19 July 2015	4
Total <i>(Site use only)</i>	

11.3. Appendix 3: Liver Chemistry Stopping and Follow-up Criteria

Phase III-IV Liver Safety Algorithms



11.4. Appendix 4: Laboratory Assessments

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

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

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

11.5. Appendix 5: Protocol Changes

Revision History

2013N176913_00	2014-MAR-17	Original
2013N176913_01	2014-MAR-31	Amendment No.: 01
2013N176913_02	2014-APR-10	Amendment No.:02
2013N176913_03	2014-DEC-05	Amendment NO.:03 (China Only)
2013N176913_04	2015-MAY-12	Amendment NO.:04 (China Only)
2013N176913_05	2016-JUN-30	Amendment No.:05

11.5.1. Amendment 1

Amendment 01 applies to all countries and study centers participating in the CTT116855 study. Amendment 01 purpose is to clarify verbiage pertaining to approval status of products in the protocol and to also clarify information concerning hematology collection and to correct minor errors in the Time and events table.

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

In Section 3.2 Discussion of design (4th paragraph) wording was changed to clarify approval status of UMEC/VI and to be consistent with Section 1.3.3. Overall Benefit:Risk.

*The FF/UMEC/VI dose was selected based on the doses that have been determined for the FF/VI and UMEC/VI dual combinations through extensive studies in the mono and dual therapy programs. The doses licensed **and/or anticipated to be licensed** by the FDA and ~~Europe~~ **the EMA** for FF/VI and UMEC/VI are 100mcg/25mcg and 62.5mcg/25mcg (equivalent to 92mcg/22mcg and 55mcg/22mcg delivered dose); respectively.*

In Section 6 Study Assessment and Procedures (Table 4 Time and Events Table) In the Safety Assessments section of the T&E table there is an error in the ECG row in the Visit 3 column. The visit 3 column mistakenly references the “i” table reference which provides additional information for vital signs. The “i” table reference has been changed to the “j” table reference which provides the correct information on ECG collection timings.

Safety Assessments	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	IP discount	Safety follow-up
ECG		X		i j		X		X	X	

In Section 6 Study Assessment and Procedures (Table 4 Time and Events Table) In the Study Treatment section of the T&E table there is an error in the Dispense albuterol/salbutamol row in the Visit 7 column. Albuterol/salbutamol is not dispensed at Visit 7 therefore the “X” has been deleted from Visit 7 column.

Study Treatments	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	IP discont	Safety follow-up
Dispense albuterol/salbutamol		X	X	X	X	X	X	✕		

In Section 6.3.12 Laboratory Assessments (first paragraph) hematology collection at visit 2 was inadvertently omitted. Additional wording was added to be consistent with the Time and Events Table.

*Routine non-fasting clinical laboratory tests (hematology, chemistry), including serum glucose and serum potassium levels, will be performed at Screening (Visit 1) and at Week 16, Week 28, and Week 52 (or IP Discontinuation Visit). Hepatitis B and C will be collected as part of the Screening Visit blood draw. **Hematology (alone) will be collected at Visit 2.** The Week 16 hematology blood draw will also be used to assess fibrinogen as an exploratory biomarker of COPD.*

In Section 11.4 Appendix 4: Laboratory Assessment (in the table) “**RBC count**” was inadvertently omitted. “**RBC count**” was added to the hematology column to correct the omission.

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

11.5.2. Amendment 2

Amendment 02 applies to all countries and study centers participating in the CTT116855 study. Amendment 02 purpose was to add post-bronchodilator FEV₁ to each visit and include this as an Other Efficacy Endpoint. A mortality endpoint was also added as an “Other Efficacy Endpoint”. Other changes included changing the predicted FEV₁ reference values from NHANES III to the European Respiratory Society Global Lung Function Initiative and to correct minor errors in CAT, contraceptive methods, and ECG wording. In addition changes were made to correct minor errors and to clarify ambiguous wording.

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

In the List of Abbreviations there was an error in the abbreviation for EuroQol Questionnaire.

eCRF	Electronic Case Report Form
EQ-5D- 5L	EuroQol Questionnaire
FEV ₁	Forced Expiratory Volume in One Second

In the Protocol Summary in the Study Design Section (second paragraph) wording was added to clarify that subjects usual COPD medications could only be used during the 2 week run-in period. This change was also made to Section 3.1 Study design (fourth paragraph).

Subjects will sign the informed consent form (ICF) at a pre-screen or screening visit and will be assigned a subject identifier. Subjects meeting all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will enter the 2-week run-in. Subjects will continue the use of their existing COPD medications during the run-in and in addition will be provided with short acting albuterol/salbutamol to be used on an as-needed basis (rescue medication) throughout the study.

In the Protocol Summary in the Study Design Section (sixth paragraph) wording was changed to clarify that subjects IP will be stopped at the IP Discontinuation visit. This change was also made to Section 3.1 Study design (eighth paragraph).

Subjects who wish to permanently discontinue from their IP should be encouraged to stay on their IP until they are able to return to complete the IP Discontinuation Visit. ~~and their safety follow-up visit 7 days later.~~ After completing the IP Discontinuation Visit and the safety follow-up visit, subjects will be encouraged to continue in the study by participating in telephone contacts in order to assess exacerbations, serious adverse events (SAEs) and concomitant medications post-treatment.

In the Protocol Summary, under Study Endpoints/Assessments, in the Other Efficacy Endpoints Section “Change from baseline in post-bronchodilator FEV₁” and “Time to

death from any cause” were added as other endpoints. These endpoints were also added to Section 6.2.3 “Other Efficacy endpoints”.

Other Efficacy endpoints

- **Change from baseline in post-bronchodilator FEV₁**
- **Time to death from any cause**
- Responder rate based on the SGRQ Total Score
- Annual rate of all on-treatment exacerbations (mild, moderate, severe)

In Section 1.3.3 Overall Benefit:Risk Conclusion (second paragraph) a missing word was added.

In the United States, the FF/VI combination is approved for the maintenance **treatment** of airflow obstruction and for reduction of exacerbations in COPD. The UMEC/VI combination is approved for maintenance treatment of airflow obstruction in COPD.

In Section 4.2 Inclusion Criteria (Inclusion criteria 4; Gender) under “Child Bearing potential” in the seventh bullet (intrauterine device) erroneous wording was deleted.

Child bearing potential, has a negative pregnancy test at screening, and agrees to one of the following acceptable contraceptive methods used consistently and correctly (*i.e.* in accordance with the approved product label and the instructions of the physician for the duration of the study – screening to safety follow-up contact):

- Abstinence
- Oral Contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of levonorgestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) ~~that meets the SOP effectiveness Criteria as stated in the product label.~~

In Section 4.2 Inclusion Criteria (Inclusion criteria 10; History of Exacerbations) the reference equations used for calculation of percent predicted were changed from *NHANES III* to the European Respiratory Society Global Lung Function Initiative.

History of Exacerbations: Subjects must demonstrate:

a post-bronchodilator FEV₁ < 50% predicted normal and a documented history of ≥ 1 moderate or severe COPD exacerbation in the previous 12 months

OR

a post-bronchodilator $50\% \leq FEV_1 < 80\%$ predicted normal and a documented history of ≥ 2 moderate exacerbations or a documented history of ≥ 1 severe COPD exacerbation (hospitalized) in the previous 12 months.

Note: *Percent predicted will be calculated using the European Respiratory Society Global Lung Function Initiative NHANES III-reference equations [Quanjer, 2012 Hankinson, 1999; Hankinson, 2010]*

In Section 6 Study Assessment and Procedures (Table 4 Time and Events Table) In the Efficacy Assessments section of the T&E table (in the spirometry row) in both the T&E table and in the table reference, new wording was added to clarify that both pre and post spirometry will be captured at Visits 2-7.

Efficacy Assessments	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	IP discontin	Safety follow-up
Spirometry ^d		X	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	
Reversibility Testing ^e		X								

- Informed consent must be conducted at the Pre-screen visit prior to performing any study procedures including the changing or withholding of medications. The (IC) may be given at Screening Visit 1 if the subject does not take or has not taken any protocol excluded medications.
- Genetics research consent may be obtained at the same time as the study IC and must be obtained prior to obtaining a genetic blood sample.
- Demography may be captured at either the pre-screen visit or Screening visit (for subjects who do not have a pre-screen visit).
- At Visits 2-7 (and the IP discontinuation visit) both pre and post-bronchodilator spirometry will be conducted. Pre-bronchodilator Spirometry to be performed prior to taking morning dose of IP, between 6am and 11am and after withholding rescue albuterol/salbutamol for ≥ 4 hours. Post-bronchodilator spirometry will be conducted (prior to taking morning dose of IP) approximately 10-30 minutes after administering 4 puffs of albuterol/salbutamol.**

In Section 6.2.5 Spirometry Testing, wording was added to clarify that both pre and post spirometry would be captured at Visit 2-7.

Spirometry measurements will be obtained using spirometry equipment that meets or exceeds the minimal performance recommendations of the ATS [Miller, 2005]. All subjects will have spirometry performed at Screening and each scheduled clinic visit during the treatment period. **At the screening visit both pre- and post-albuterol/salbutamol spirometry measurements will be measured in order to assess eligibility and reversibility (see Section 6.2.5.1). At Visits 2-7 (and discontinuation of IP visit) both pre- and post-albuterol/salbutamol spirometry will be measured prior to the subject taking their morning dose of IP.** For FEV₁ and FVC determinations, at least 3 acceptable spirometry efforts (with no more than 8) should be obtained.

In Section 6.2.10 COPD Assessment Test (CAT) wording was changed to correct a mistake in how the range was defined.

The COPD Assessment Test (Jones, 2009; Jones, 2012) is a validated, short and simple patient completed questionnaire which has been developed for use in routine clinical

practice to measure the health status of patients with COPD. The CAT is an 8-item questionnaire suitable for completion by all patients diagnosed with COPD. When completing the questionnaire, subjects rate their experience on a 6-point scale, ranging from 0 (**no impairment**~~maximum impairment~~) to 5 (**maximum impairment**~~no impairment~~) with a scoring range of 0-40. Higher scores indicate greater disease impact.

In Section 6.3.15 ECG wording was changed to correct the order of when an ECG was conducted in relation to vitals and spirometry.

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.

In Section 10 References, the *Hankinson* references were deleted and *Quanjer 2012* was added as the reference equations for calculation of percent predicted was changed from *NHANES III* to the *European Respiratory Society Global Lung Function Initiative*.

Hanania, HA *et al.* (2012) Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. *Resp. Med.* 106: 91-101.

~~Hankinson JL, Kawut SM, Shahar E, Smith LJ, MD, Hinekley Stukovsky K, and Barr RG. Performance of American Thoracic Society Recommended Spirometry Reference Values in a Multiethnic Sample of Adults: The Multi-ethnic Study of Atherosclerosis (MESA) Lung Study. *Chest*, 2010;137:138-45.~~

~~Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Resp Crit Care Med.* 1999;159:179-187.~~

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, P., Harding, G., Berry, P., Wiklund, I., Chen, W-H., Leidy, N. Development and first validation of the COPD Assessment Test (CAT) *Eur Respir J* (2009) 34: 648-654

Jones, PW., Harding, G., Wiklund, I., Berry, P., Tabberer, M., Yu, R., Leidy, N. 'Tests of the Responsiveness of the Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT) Following Acute Exacerbation and Pulmonary Rehabilitation.' *Chest* (2012) 142 134-140

Jung KS, *et al.* Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: A randomized controlled study. *Resp. Med.* (2012) 106: 382-389 doi:10.1016/j.rmed.2011.09.004.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. *J Clin Microbiol.* 2005;43(5):2363-2369.

Meguro M, Barley EA, Spencer S et al. Development and validation of an improved COPD-Specific Version of the St. George Respiratory Questionnaire. *Chest*. 2007;132:456-463

Miller MR, Hankinson J, Odencrantz J, Standardisation of spirometry. *Eur Respir J*. 2005;26:319-388.

Mullerova H, Locantore N, Jones P. GOLD assessment of COPD patients: impact of symptoms assessment choice.[abstract]. *Eur Respir J*. 2012;40(Suppl 56): 279s.

Quanjer, P., Stanojevic, S., Cole, T., Baur, X., Hall, G., Culver, B., Enright, P., Hankinson, J., Ip, M., Zheng, J., Stocks, J., & ERS Global Lung Function Initiative, (2012). Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. *European Respiratory Journal*, 40(6), 1324-1343.

Short, PM, Williamson, PA, Elder, DHJ & IW Samuel. (2012) The Impact of Tiotropium on Mortality and Exacerbations When Added to Inhaled Corticosteroids and Long-Acting b -Agonist Therapy in COPD. *Chest* 141:81–86.

11.5.3. Amendment 3

This country specific protocol amendment 03 applies to all study centers in China.

Reason for protocol amendment 03:

This amendment is written to meet the requirements of the China Good Clinical Practice (GCP) of Pharmaceutical Products. This amendment is specific to China that Serious AEs will be recorded from the time the consent form is signed until the 7-day safety follow-up visit/telephone contact has been completed, or until Visit 7(telephone contact) for subjects who have discontinued IP but continue in the study.

Section 6. STUDY ASSESSMENTS AND PROCEDURES, Table 4 Time and Events

An asterisk (*) was added to the row that contains “Adverse Events Assessment” and an additional note was added at the bottom of the T&E table to define the asterisk.

Original text:

NOTE: Subjects who have permanently discontinued IP (and have not withdrawn consent) will complete the discontinuation IP visit and the safety follow-up contact and then will continue in the study to complete all remaining per protocol scheduled visits by phone contact to collect Exacerbations, SAEs and Concomitant Medications.

Amended text:

NOTE:

1. Subjects who have permanently discontinued IP (and have not withdrawn consent) will complete the discontinuation IP visit and the safety follow-up contact and then will continue in the study to complete all remaining per protocol

scheduled visits by phone contact to collect Exacerbations, SAEs and Concomitant Medications.

2. * In China only, Serious AEs will be recorded from the time the consent form is signed until the 7-day safety follow-up visit/telephone contact has been completed, or until Visit 7(telephone contact) for subjects who have discontinued IP but continue in the study.

Reason for change:

This requirement is in accordance to new China GCP regulations, where the definition of SAE in the Chinese GCP regulations note: “A Serious Adverse Event includes inpatient hospitalization, prolongation of hospitalization, disability/incapacity, effect on work capability, life threatening, death, congenital anomaly etc., which occur during a clinical trial.”

Section 6.3.9. Time Period and Frequency of Detecting AEs and SAEsAdditional text:

NOTE: *In China only, Serious AEs will be recorded from the time the consent form is signed until the 7-day safety follow-up visit/telephone contact has been completed, or until Visit 7 (telephone contact) for subjects who have discontinued IP but continue in the study.*

Reason for change:

This requirement is in accordance to new China GCP regulations, where the definition of SAE in the Chinese GCP regulations note: “A Serious Adverse Event includes inpatient hospitalization, prolongation of hospitalization, disability/incapacity, effect on work capability, life threatening, death, congenital anomaly etc., which occur during a clinical trial.”

Section 11.2 Appendix 2: Country Specific RequirementsAdditional text:

In China only, Serious AEs will be recorded from the time the consent form is signed until the 7-day safety follow-up visit/telephone contact has been completed, or until Visit 7 (telephone contact) for subjects who have discontinued IP but continue in the study.

Reason for change:

This requirement is in accordance to new China GCP regulations, where the definition of SAE in the Chinese GCP regulations note: “A Serious Adverse Event includes inpatient hospitalization, prolongation of hospitalization, disability/incapacity, effect on work capability, life threatening, death, congenital anomaly etc., which occur during a clinical trial.”

11.5.4. Amendment 4

This country specific protocol amendment applies to all study centers in China.

Amendment 04 purpose was to:

Clarify that no study centers in China will participate in genetic research in this study. The reason for change is that due to a new interpretation of Chinese regulations, the main study cannot be initiated until the pharmacogenetic research portion obtained a permit from the Human Genetic Resource Administration of China (HGRAC). This would incur a substantial delay to the start of the study in China and prevent China from being able to recruit a sufficient number of subjects into the study. Therefore, China will not participate in the pharmacogenetic research portion of the study.

The addition of a China-specific sub-study to collect the unit-cost data for healthcare utilization among subjects recruited in China.

The specific areas where changes were made to the protocol are listed below.

Section 6. STUDY ASSESSMENTS AND PROCEDURES, Table 4 Time and EventsOriginal text:

- b Genetics research consent may be obtained at the same time as the study IC and must be obtained prior to obtaining a genetic blood sample.
- o. Genetic consent must be obtained prior to obtaining a blood sample.

Amended text:

- b Genetics research consent may be obtained at the same time as the study IC and must be obtained prior to obtaining a genetic blood sample. No study centers in China will participate in genetic research in this study.
- o. Genetic consent must be obtained prior to obtaining a blood sample. No study centers in China will participate in genetic research in this study.

Section 6. 6. Genetic ResearchOriginal text:

Information regarding genetic research is included in Appendix 1.

Amended text:

Information regarding genetic research is included in Appendix 1.

Note: No study centers in China will participate in genetic research in this study.

Section 11.1. Appendix 1: Genetic ResearchOriginal text:**Study Population**

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

Amended text:**Study Population**

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

Note: No study centers in China will participate in genetic research in this study.

Section 11.2 Appendix 2: Country Specific RequirementsOriginal text:

In China only, Serious AEs will be recorded from the time the consent form is signed until the 7-day safety follow-up visit/telephone contact has been completed, or until Visit 7(telephone contact) for subjects who have discontinued IP but continue in the study.

Amended text:

In China only, Serious AEs will be recorded from the time the consent form is signed until the 7-day safety follow-up visit/telephone contact has been completed, or until Visit 7(telephone contact) for subjects who have discontinued IP but continue in the study.

No study centers in China will participate in genetic research in this study.

11.2.1 China-specific sub-study: Collection of unit-cost data for healthcare utilization among COPD subjects recruited to Study CTT116855 in China

11.2.1.1 Introduction

Globally, health economic (HE) evidence is becoming more and more critical to ensure that the value of new medicines is demonstrated and that patients with unmet need have access to these new medicines. In China, recent high-profile meetings, including Healthcare State Council meetings have highlighted the importance of generating HE evidence. In line with this, the first health technology assessment (HTA) center, to evaluate the cost-effectiveness of drugs, was established in Zhejiang Province in 2014. It is expected that more and more HTA centers will be established in many other areas of China in coming years.

This China-specific sub-study will collect the unit cost data for healthcare utilization among COPD subjects recruited to Study CTT116855 (called the Core Study throughout this document) in China; through the use of a “modified healthcare resource utilization” (“Modified HRU”) paper diary.

11.2.1.2 Objective

To collect unit cost data (direct and indirect) for healthcare utilization among COPD subjects recruited to Study CTT116855 in China

11.2.1.3 Investigational Plan

This is a China-specific sub-study to collect direct and indirect unit cost data for healthcare utilization in subjects who have consented and been randomized to study CTT116855 (Core Study), “A phase III, 52 week, randomized, double-blind, 3-arm parallel group study, comparing the efficacy, safety and tolerability of the fixed dose triple combination FF/UMEC/VI with the fixed dose dual combinations of FF/VI and UMEC/VI, all administered once-daily in the morning via a dry powder inhaler in subjects with chronic obstructive pulmonary disease”, in China.

Currently, subjects randomized to the Core Study complete a healthcare resource utilization (HRU) paper diary, when they have any contact with a health care provider. The current HRU paper diary, in the Core Study, does not require collection of the unit cost (direct or indirect) for healthcare utilization. For the purpose of this China-specific sub-study, subjects who are consented and randomized to the Core Study in China will complete a “modified healthcare resource utilization” (“Modified HRU”) paper diary. This “Modified HRU” paper diary will collect data in response to five additional questions (see Supplement 1), two of which relate to the direct costs of healthcare services used by a subject and three of which relate to the indirect costs of the subject’s COPD. These questions are:

1. Cost paid by the subject for each healthcare contact due to any health problem¹
2. Cost covered by health insurance for each healthcare contact due to any health problem²
3. Days of work missed by the subject due to their COPD
4. Hours of paid caregiver services due to the subject's COPD
5. Hours of work missed by family members/relatives due to the subject's COPD

Subjects of this sub-study will be issued the "Modified HRU" paper diary at scheduled visits starting from Visit 2, and will be required to record their answers to these questions on the paper diary between scheduled visits.

All subjects who participate in this sub-study will be required to provide a separate consent to the use of the "Modified HRU" paper diary. Subjects who do not consent or withdraw consent from this sub-study will continue to use the HRU (unmodified and without the additional questions relating to direct and indirect costs) paper diary, as per the Core Study.

11.2.1.4 Subject Selection and Withdrawal Criteria

11.2.1.4.1 Inclusion Criteria

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

1. Subjects in China, who have provided written informed consent and have been randomized to study CTT116855 (Core Study).
2. Separate Informed Consent for China-specific sub-study: A signed and dated separate written informed consent to the sub-study, to assess direct and indirect unit cost data, prior to participation in the sub-study is required.

11.2.1.4.2 Exclusion Criteria

There are no exclusion criteria to this sub-study.

11.2.1.4.3 Sub-study Withdrawal Criteria

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

1, 2 Both of these are mutually exclusive and comprehensive. Therefore the sums of 1 and 2 should equate to the total unit cost of healthcare resource used

In the event that a subject withdraws consent from this sub-study, they will be encouraged to continue to use the HRU paper diary (unmodified and without the additional questions relating to direct and indirect costs) paper diary, as per the Core Study.

Discontinuation criteria from IP and withdrawal criteria from the Core Study will be dealt with as outlined in the Core Study protocol (CTT116855); Section 4.4. Investigational Product (IP) Discontinuation Criteria.

Supplement 1:

Modified Healthcare Resource Utilization Paper Diary (“Modified HRU”), page 1

Date of Healthcare Contact Day Month Year	Type of Healthcare Contact						Reason for Healthcare Contact	Cost paid by subject (Chinese Currency)	Cost paid by insurance (Chinese Currency)	Site validation of reason for contact* (Site Use Only)	
	Home Visits		Physician Office/ Clinic Visits	Urgent Care/ Outpatient Clinic Visits	Accident and Emergency Room Visits	Inpatient Hospitalization					
	Day	Night				ICU					General Ward
e.g., 15 MAR 14	√						Shortness of Breath	338.45	0		
e.g., 15 MAR 14						√	Shortness of Breath	1000.00	7755.87		
1.											
2.											
3.											
4.											
5.											
6.											
7.											
8.											
9.											
10.											
11.											
12.											
13.											
TOTAL (Site use only)											

UK:ENG (United Kingdom/English)

* 1=COPD exacerbation; 2=COPD not exacerbation; 3=Other healthcare contact; 4=Not a healthcare contact

Modified Healthcare Resource Utilization Paper Diary (“Modified HRU”) page 2

Since your last scheduled visit, if you are currently having paid employment and you have to skip work, due to your COPD (e.g., feel breathless or chest tightness, cough, or wake up at night because of these and related complaints), please fill in this paper diary with the date(s) when you miss work and the number of days of work you miss each time.

<p style="text-align: center;">Date Day Month Year</p>	<p style="text-align: center;"><u>Days</u> of work you miss due to your COPD (Days)</p>
e.g. 15 July 2015 – 18 July 2015	3.5
Total (<i>Site use only</i>)	

Modified Healthcare Resource Utilization Paper Diary (“Modified HRU”) page 3

Since your last scheduled visit, if you pay someone to take care of you, due to your COPD (e.g., feel breathless or chest tightness, cough, or wake up at night because of these and related complaints), please fill in this paper diary with the date(s) when this happens and the number of hours of using such service each time. If you hire two or more persons to take care of you at the same time, please list the date(s) and hours of using each hired service separately.

<p style="text-align: center;">Date Day Month Year</p>	<p style="text-align: center;"><u>Hours</u> using paid caregiver service due to your COPD (Hours)</p>
e.g. 17 July 2015 – 18 July 2015	6
Total (<i>Site use only</i>)	

Modified Healthcare Resource Utilization Paper Diary (“Modified HRU”) page 4

Since your last scheduled visit, if your family members/relatives have to skip their work to take care of you, due to your COPD (e.g., feel breathless or chest tightness, cough, or wake up at night because of these and related complaints), please fill in this paper diary with the date(s) when this happens and the number of hours of work they miss each time. If two or more family members/relatives have to skip work to take care of you at the same time, please list the date(s) and hours of missed work by each individual separately.

Date Day Month Year	<u>Hours</u> of work your family members/relatives miss when they take care of you due to your COPD (Hours)
e.g. 19 July 2015	4
Total (Site use only)	

11.5.5. Amendment 5

Amendment 05 applies to all countries and study centers participating in the CTT116855 study. Amendment 05 purpose was to simplify the statistical hierarchy for the analysis of secondary endpoints. In addition, there are minor changes to the definitions of the Analysis populations, changes in model terms that will be included in the primary efficacy endpoint analysis and clarification on the primary endpoint sensitivity analyses. For the safety analysis there were minor changes to clarify the analyses of Pneumonia Adverse events and MACE events.

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

In Section 8.3.1 Analysis Populations the All Subjects Screened Population was deleted and the ITT Population definition was clarified.

- All Subjects Enrolled Population: This population includes all subjects for whom a record exists on the study database, including screened subjects and subjects who were not screened but signed an ICF. This population will be used for the summary of subject disposition and the listing of SAEs for non-randomised subjects.
- ~~All Subjects Screened Population: This population contains all subjects screened and attending Visit 1. This population will be used for the summary of reasons for non-randomisation.~~
- Intent-to-Treat (ITT) Population: The ITT Population will comprise all subjects randomised to treatment **apart from those randomised in error. A subject who is recorded as a screen or run-in failure and also randomised, but did not receive a dose of study treatment, will be considered to be randomised in error. Any other subject who receives a randomisation number will be considered to have been randomised.** ~~and who have received at least one dose of double blind medication. Randomised subjects will be assumed to have received double blind medication unless definitive evidence to the contrary exists.~~ The ITT Population is the primary analysis population of interest.
- Pharmacokinetic (PK) Population: The PK Population will comprise the subset of subjects in the ITT Population for whom a PK sample was obtained and analyzed. This population will be used for all concentration-time and PK parameter tables, listings and figures.

In Section 8.3.3.1 Primary Comparisons of Interest the fifth paragraph on sensitivity analysis was deleted and was moved to Section 8.3.5.1 Efficacy Analysis.

The primary comparisons of interest will be the pair-wise comparisons of FF/UMEC/VI against FF/VI and FF/UMEC/VI against UMEC/VI. The primary comparisons will be tested for the primary endpoint, the annual rate of on-treatment moderate and severe exacerbations.

The primary analysis will be based on a two-sided hypothesis testing approach. The hypotheses associated with the statistical test of the primary efficacy endpoint are $H_0: \lambda_T/\lambda_D=1$ versus $H_A: \lambda_T/\lambda_D \neq 1$ where λ_T is the annual rate for triple therapy (FF/UMEC/VI) and λ_D is the annual rate for the respective dual therapies (FF/VI and UMEC/VI).

Both primary comparisons will be tested using the ITT population. In order to account for multiplicity, the truncated Hochberg procedure [Dmitrienko, 2008] with a truncation parameter of $\gamma=0.6$ will be used to control overall Type I error at $\alpha=0.05$.

For the primary comparisons, both comparisons will be declared statistically significant if the p-value for both comparisons is significant at the 0.04 level. Should the largest p-value for the two comparisons be above 0.04, the other comparison will be declared statistically significant if the smaller p-value is below 0.025. If at least one of the comparisons is significant, this will allow inference of secondary endpoints.

~~For the co-primary efficacy endpoints, sensitivity analyses will be performed where all available data collected until the time of study withdrawal will be used. For these sensitivity analyses, the total number of events and the total time in the study (both on-treatment and post-treatment) prior to study withdrawal will be used in the primary analysis model.~~

In Section 8.3.3.2 Other Comparisons of Interest the text was modified to amend how multiplicity will be controlled using a hierarchical closed testing procedure. The secondary hypothesis tests were amended from being grouped in four blocks to only two blocks of two comparisons, each grouped according to specific clinical concepts.

If one or both of the primary endpoints is considered statistically significant, inferences will be made ~~for secondary hypotheses from unadjusted p-values for treatment comparisons on secondary and other endpoints.~~ **If both co-primary treatment comparisons are statistically significant, these secondary and other treatment comparisons will be declared significant if the unadjusted p-value is <0.05. If only one co-primary treatment comparison is statistically significant, these secondary and other treatment comparisons will be declared significant if the unadjusted p-value is <0.01.** ~~The secondary hypothesis tests will be grouped sequentially in four blocks, with each block of comparisons also adjusted using the truncated Hochberg method as described for the primary endpoint analysis. Note that the significance level required for each block within the secondary hierarchy will depend on whether one or both comparisons were significant at the prior step.~~

~~The comparisons within each block have been grouped according to specific clinical concepts (lung function and symptoms, time to first exacerbation event, endpoints specific to the subgroup with raised eosinophils, COPD hospitalizations in all subjects).~~

Where strong control of type I error is required for secondary endpoints, multiplicity will be controlled using a hierarchical, closed testing procedure. The secondary hypothesis tests will be grouped sequentially in two blocks of two comparisons each, grouped according to specific clinical concepts (lung function and

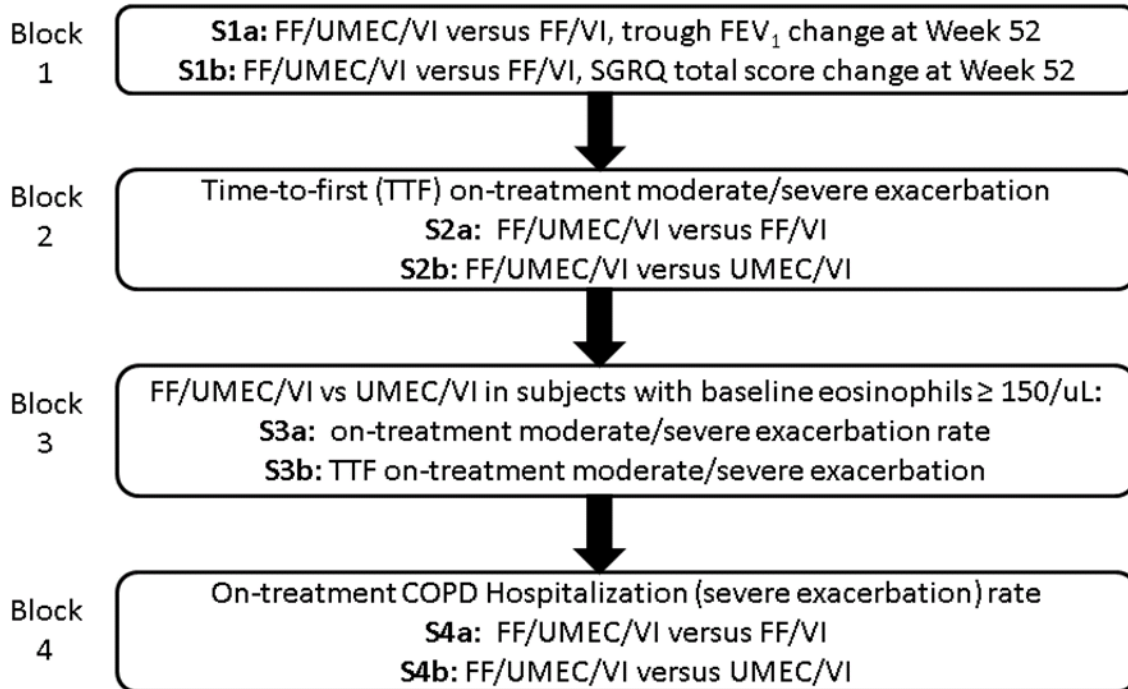
symptoms, and time-to-first exacerbation event). Each block of comparisons will also be adjusted for multiplicity using the truncated Hochberg method as described for the primary endpoint analysis, with a truncation parameter of $\gamma=0.6$ for the first block and a truncation parameter of $\gamma=1$ for the second block.

Within each block, at least one endpoint must be considered statistically significant in order to make inferences in the subsequent block. For example, as shown in Figure 2 at least one of endpoints S1a and S1b would need to be significant in order to make inferences for the S2a/S2b comparisons contained in the next block.

In Section 8.3.3.2 Other Comparisons of Interest Figure 2 Secondary endpoint hierarchy was modified by deleting block 3 and block 4 from the figure and deleting the paragraph directly below the figure.

Original Figure 2 and text:

Figure 2 Secondary endpoint hierarchy

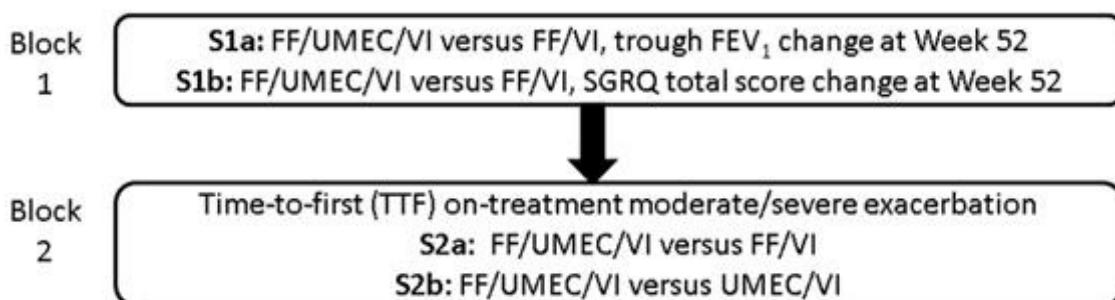


Should the gate-keeping fail at any step in the testing hierarchy, p-values for the remaining secondary endpoints will be provided for evaluation outside the context of multiplicity adjustment. Other efficacy endpoints not listed as part of the primary and secondary endpoint hierarchy will be evaluated without multiplicity adjustment.

Methods for handling missing data for summaries of the secondary efficacy endpoints will be detailed in the RAP.

Amended Figure 2 and text:

Figure 2 Secondary endpoint hierarchy



Should the gate-keeping fail at any step in the testing hierarchy, p-values for the remaining secondary endpoints will be provided for evaluation outside the context of multiplicity adjustment. Other efficacy endpoints not listed as part of the primary and secondary endpoint hierarchy will be evaluated without multiplicity adjustment.

Methods for handling missing data for summaries of the secondary efficacy endpoints will be detailed in the RAP.

In Section 8.3.5.1 Efficacy Analyses the text was modified to remove from the model the term “screening blood eosinophil levels” that was erroneously included in the proposed primary efficacy endpoint analysis and the secondary time to first moderate and /or severe exacerbation analysis. In addition, for the co-primary endpoints sensitivity analyses the text was modified to exclude a supporting analysis of the rate of exacerbations based on quarterly intervals.

The primary efficacy endpoint of the annual rate of on-treatment moderate and severe exacerbations will be analyzed using a generalized linear model assuming the negative binomial distribution, with the logarithm of time on treatment as an offset variable. The model will include terms for treatment group, gender, exacerbation history (one, two or more), smoking status at screening, baseline disease severity (as % predicted FEV₁), ~~screening blood eosinophil level~~ and geographical region. The adjusted mean annual rates, pair-wise treatment ratios and associated p-values and confidence limits will be presented. The fit of the negative binomial model will be examined using “Q-Q” plots of standardized residuals with simulated envelopes.

For the co-primary endpoints, sensitivity analyses will be performed where all available data collected until the time of study withdrawal will be used. For these sensitivity analyses, the total number of events and the total time in the study (both on- treatment and post-treatment) prior to study withdrawal will be used in the analysis model. Imputations made for the period following study withdrawal will be described in the RAP. Additional sensitivity analyses using multiple imputation methods will be described in the RAP.

~~For the purpose of analysis of the exacerbations, data will not be imputed. The method of analysis incorporates the length of time that each individual subject received treatment. However, for summaries of raw exacerbation rate data the number of exacerbations for subjects who withdraw prior to the end of treatment will be imputed to prevent unreasonably high values. Details of the imputation method will be described in the RAP.~~

~~In addition to the sensitivity analysis using any post-treatment data collected from subjects during the study, the pattern of missing data due to study withdrawals will be examined to determine if the missing data at random assumption for the analysis of exacerbation rate is met. To further examine any effect of study withdrawals, a supporting analysis of the rate of exacerbations will be performed on <1-year intervals (e.g. quarterly intervals), and study withdrawals will also be presented in graphical display (e.g., Kaplan-Meier plot of study withdrawals).~~

The secondary endpoints of trough (pre-dose AM) FEV₁ and SGRQ total score will be analysed using mixed models repeated measures with covariates of treatment group, smoking status at screening, baseline, region, and visit, plus interaction terms for visit by baseline and visit by treatment group.

The secondary endpoints involving time to first moderate and/or severe exacerbation will compare the treatment groups using Cox's proportional hazards model, adjusting for treatment group, gender, exacerbation history (one, two or more), smoking status at screening, baseline disease severity (as % predicted FEV₁), screening blood eosinophil level and geographical region.

Secondary and other endpoints involving the annual rate of exacerbations will be analysed as described for the primary endpoint.

The additional endpoint of time to onset of multiple moderate and severe exacerbations will be analysed using an Anderson-Gill model for time to recurrent events.

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

In Section 8.3.5.2 Safety Analyses the text was modified to clarify analysis of pneumonia events and MACE analysis.

The extent of exposure to study drug will be summarized by treatment group, using the statistics n, mean, SD, median, minimum and maximum.

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

Time to first **event in the pPneumonia Adverse Event of Special Interest subgroup** and time to first ~~hospitalisation for~~ **serious event in the pPneumonia Adverse Event of Special Interest subgroup** will be analysed using Cox's proportional hazards model. Deaths due to pneumonia will be summarised and tabulated.

Incidence of bone fractures will be summarised. Full details will be given in the RAP.

Incidence of cardiovascular events (including supraventricular arrhythmia and non-fatal myocardial infarction) will be summarised.

All laboratory parameters will be summarised and tabulated.

A pre-specified MACE analysis (broad analysis and narrow analysis) will be performed using ~~data from the~~ adjudicated **cardiovascular deaths and other non-fatal** SAEs. MACE events to be included in both the broad and narrow analysis would be defined *a priori*.

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