TITLE PAGE

Protocol Title: A Phase IV, 12-week, randomised, double-blind, triple dummy study to compare single inhaler triple therapy, fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) with multiple inhaler therapy (budesonide/formoterol plus tiotropium) based on lung function and symptoms in participants with chronic obstructive pulmonary disease

Protocol Number: 207608/01

Short Title: A randomised study, comparing FF/UMEC/VI single inhaler triple therapy, versus multiple inhaler therapy (budesonide/formoterol plus tiotropium) in participants with chronic obstructive pulmonary disease

Compound Number: GSK573719+GW642444+GW685698 (GSK2834425)

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SPONSOR SIGNATORY:

PPD

17 July 2018

PPD

David A. Lip... M.D.
Project Physician Leader

Date

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Protocol Amendment 1	*17-Jul-2018*
Original Protocol	*11-Oct-2017*

Amendment 1 [17-JUL-2018]

Overall Rationale for the Amendment: This amendment is required to update the QTc stopping criteria to that which was used in the Phase III Trelegy registration studies. In addition, a section describing Smoking Cessation Counselling has been added as does a corresponding assessment at the end of study (Visit 4). Clarified that it is preferable to have the participants stay at the clinic or approved facilty during the serial spirometry assessments. The physical form of Symbicort and matching placebo was reported as a solution for inhalation, which is incorrect, and should be corrected to a suspension for inhalation. An additional footnote has been added to the Schedule of Activities (SoA), to provide clarity on the collection of trough forced expiratory volume in 1 second (FEV_1) spirometry on Day 28. Clarified that run-in treatment will be collected at Visit 2. Correction made (reference section) regarding prohibited medications within a specified time interval during pre-screening and prior to Visit 1. Also, wording regarding suggested order for assessments and procedures has been added to the end of the Schedule of Activities section. Removed reference to Fridericia formula in calculation of QTc. Clarification regarding collecting the CAT assessment questionnaire prior to the SGRQ-C has also been provided along with clarification that vital signs should be collected before the ECG and prior to spirometry. Corrected reporting time regarding pregnancy. Routine urinalysis assessment has been deleted as this will not be collected during the study. Finally, added wording to Genetics Appendix 9 regarding withdraw process and sample destruction process.

Section # and Name	Description of Change	Brief Rationale
Table of Contents	Added Smoking Cessation Counselling Section (9.10)	Explained the reasoning for the Smoking Cessation Counselling and to clarify the visits when this counselling will be provided
Synopsis and Section 5.1 Overall Design Randomization/treatment	Corrected wording regarding participants stay in the clinic during serial spirometry assessments: Participants will remain available, preferably at the clinic or approved facility, for at least 24 hours for serial spirometry assessments	Clarified, with added flexibility, that it is preferred that the participants remain available at the clinic or approved facility during 24 hour serial spirometry instead of will remain at the clinic for at least 24 hours, for serial spirometry assessments as previously written
Section 2 Schedule of Activities	Added Smoking Cessation Counselling to Visit 4	Clarified that Smoking Cessation Counselling will also be collected at Visit 4
	Added collecting run-in treatment at Visit 2	Clarified that run-in medication will be collected at Visit 2
	Added footnote (o) regarding trough FEV_1	Explained that trough FEV_1 will be performed pre-dose at 30 mins and 5 mins prior to taking the morning dose of study treatment
	Added wording regarding order for assessments and procedures (CAT, SGRQ-C, Vitals, ECG, Spirometry, Clinical Lab Assessments)	Clarified the requested order of assessments and procedures at visits (1 and 2 in particular) when a number of assessments and procedures are collected and performed
Section 5.1 Pre-screening	Updated reference section regarding medications that are prohibited within a specified time interval during the pre-screening visit and prior to Visit 1	Deleted reference Section 7.7 and corrected to Section. 6.2.24 regarding pre-screening and medications that are prohibited within a specific time interval prior to Visit 1

Section # and Name	Description of Change	Brief Rationale
Section 6.2 Exclusion Criteria 13	Removed reference to Fridericia formula in calculation of QTc	Fridericia and Bazett formulas provide equal safety in calculation of Qtc and either may be used if done consistently throughout the study
Section 7.1 Table 4 Description of Symbicort MDI	Updated physical form of Symbicort and matching placebo	Explained that the physical form of Symbicort and matching placebo was updated to "suspension" instead of "solution" based upon additional documentation since the original protocol detailing the physical form of both the Symbicort and the matching placebo
Section 8.1.1 QTc Stopping Criteria	Updated QTc stopping criteria to: • an increase in QTc by > 60 msec from baseline or • development of a QTc > 530 msec (based on an average of triplicate ECGs) NOTE: These criteria should be based on the average of QTc 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 QTc value of the three ECGs will be used to determine whether the patient should be discontinued from the study	Adapted the QTc stopping criteria to be in line with stopping criteria from the registration Phase III Trelegy Studies
Section 9.1.1 Spirometry	Corrected: If applicable, after completing the health outcomes assessments (CAT should be administered first followed by SGRQ-C)	CAT is a shorter assessment questionnaire to complete and the participant will already have experience completing this at Screening Visit 1

Section # and Name	Description of Change	Brief Rationale
Section 9.1.2 SGRQ-C	Added wording regarding CAT should be collected prior to SGRQ-C	CAT is a shorter assessment questionnaire to complete and the participant will already have experience completing this at Screening Visit 1
Section 9.1.3 CAT	Added wording regarding CAT should be collected prior to SGRQ-C	CAT is a shorter assessment questionnaire to complete and the participant will already have experience completing this at Screening Visit 1
Section 9.2.9 Pregnancy	Corrected to match Appendix 3: If a pregnancy is reported, the Investigator should inform GSK within 24 hours of learning fo the pregnancy and should follow the procedures outlined in Appendix 3	Clarified that the reporting period for pregnancy should be within 24 hours of learning of the pregnancy and not 2 weeks as previously written
Section 9.4.3 Electrocardiograms	Corrected: A single 12-lead ECG and rhythm strip will be recorded after measurement of vital signs and prior to spirometry	Clarified that the ECG should be collected after the vital signs and prior to spirometry
Section 9.10 Smoking Cessation Counselling	Added Section 9.10 Smoking Cessation Counselling	Explained the reasoning and expectations for the Smoking Cessation Counselling
Section 12.6 Appendix 6 Adverse Events	Removed reference to urinalysis as part of safety assessments	Confirmed routine urinalysis isn't required or being collected in the study
Section 12.8 Appendix 8 and Table 8 Laboratory Assessments	Deleted routine urinalysis from Appendix 8 and the Table 8	Confirmed routine urinalysis isn't required or being collected in the study
Section 12.9 Appendix 9 Genetics	Added wording for both withdraw process and destruction process	Explained what should be done if a participant withdraws consent along with the destruction of samples after the storage period or on withdrawal of consent

TABLE OF CONTENTS

PAGE

1. SYNOPSIS

Protocol Title: A Phase IV, 12-week, randomised, double-blind, triple dummy study to compare single inhaler triple therapy, fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) with multiple inhaler therapy (budesonide/formoterol plus tiotropium) based on lung function and symptoms in participants with chronic obstructive pulmonary disease

Short Title: A randomised study, comparing FF/UMEC/VI single inhaler triple therapy, versus multiple inhaler therapy (budesonide/formoterol plus tiotropium) in participants with chronic obstructive pulmonary disease

Rationale: Chronic obstructive pulmonary disease (COPD) guidelines advocate the use of long-acting muscarinic receptor antagonists (LAMA) added to the combination of inhaled corticosteroids plus a long-acting β_2-adrenergic receptor agonist (LABA) as second line therapy for the most advanced patients with significant symptoms and a high risk of exacerbations. Regular treatment with ICS containing regimens 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 forced expiratory flow in 1 second (FEV_1) <60% predicted.

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 United States (US) 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. A study in the United Kingdom (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. In the four-year long term safety study conducted with tiotropium, 46% of patients were receiving a concurrent fixed combination of ICS/LABA in addition to tiotropium.

A number of studies have assessed the use of an 'open' triple therapy of fluticasone propionate/salmeterol or budesonide/formoterol (ICS/LABA) with 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. These studies have also shown that the number and type of reported adverse events (AE) 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.

GlaxoSmithKline (GSK) is currently developing a once-daily 'closed' triple therapy of a ICS/LAMA/LABA combination [fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) (100/62.5/25 mcg)] in a single inhaler, with the aim of providing a new treatment option for the management of symptomatic COPD patients at risk of exacerbations which will reduce the exacerbation frequency, allow for a reduced burden

of polypharmacy, convenience, and increase the potential for improvement in lung function, HRQoL and symptom control over established dual/monotherapies.

GSK conducted a Phase III study comparing once-daily FF/UMEC/VI to twice-daily Symbicort MDI (budesonide/formoterol) 400/12 mcg in COPD participants that were symptomatic and at risk of an exacerbation despite receiving maintenance therapy (CTT116853). FF/UMEC/VI demonstrated statistically significant improvements in trough FEV_1, a statistically significant reduction in the annual rate of moderate or severe COPD exacerbations, and a statistically significant reduction of COPD symptoms (using Exacerbations and Chronic Pulmonary Disease – Respiratory Symptoms [E-RS]) when compared to budesonide/formoterol. Additionally, clinically meaningful improvements from baseline in St. George's Respiratory Questionnaire (SGRQ) total score were observed, with a statistically significant improvement compared to budesonide/formoterol. This Phase III study provided compelling efficacy data compared with an established ICS/LABA and demonstrated the clinical value of single inhaler triple-therapy compared to ICS/LABA therapy in patients with COPD.

The primary purpose of this study is to evaluate lung function and HRQoL after 84 days of treatment with a single inhaler triple therapy combination of FF/UMEC/VI (100/62.5/25 mcg) once daily via the ELLIPTA™ compared with a multiple inhaler combination therapy of Symbicort Metered Dose Inhaler (MDI) (budesonide/formoterol 320/9 mcg) twice daily plus Spiriva HandiHaler (tiotropium 18 mcg) once daily. The study will inform healthcare providers that patients can be effectively and safely switched to FF/UMEC/VI single inhaler therapy from a multiple inhaler triple therapy regimen of Symbicort MDI and Spiriva Handihaler.

Objectives and Endpoints:

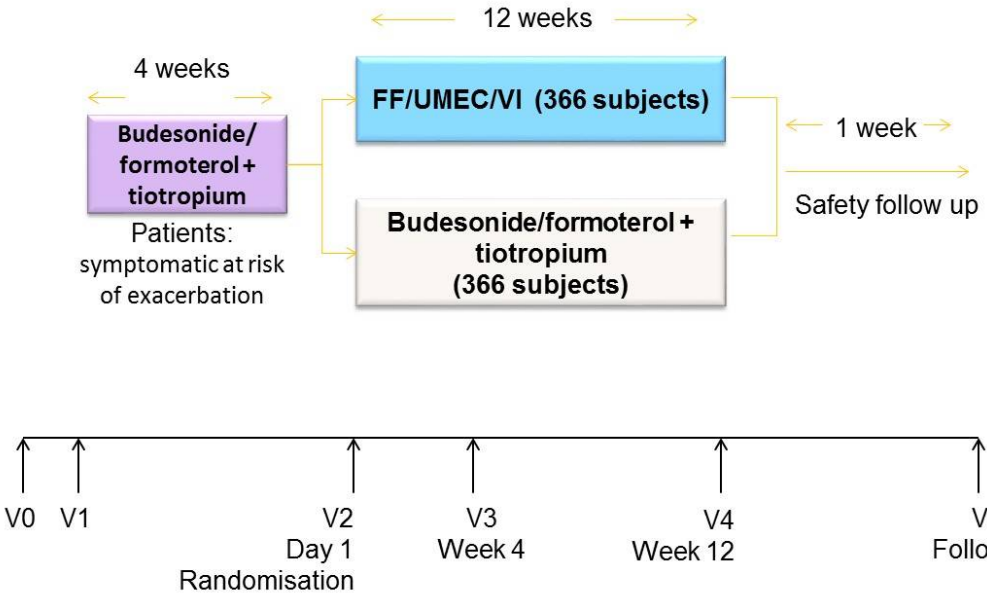
Objectives	Endpoints
Primary	
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on lung function	**Primary** Weighted mean change from baseline in FEV_1 over 0-24 hours at Week 12
	Secondary • Change from baseline in trough FEV_1 on Day 2, Day 28, Day 84 and Day 85 • Weighted mean change from baseline in FEV_1 over 0-24 hours on Day 1

Objectives	Endpoints
Other	
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on Health Status	• Proportion of responders based on the St George's Respiratory Questionnaire (SGRQ) Total Score at Week 4 and Week 12 • Change from baseline in SGRQ Total Score at Week 4 and Week 12
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on Health Status	• Proportion of responders based on the COPD Assessment Test (CAT) Total Score at Week 4 and Week 12 • Change from baseline in CAT Total Score at Week 4 and Week 12
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on COPD exacerbations	Moderate or severe exacerbation event
• Assess how inspiratory airflow limitation affects ability to use the ELLIPTA	Peak Inspiratory Flow Rate (PIFR) at Screening (Week -4)
Safety	
• To evaluate the safety profile of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium over 12 weeks of treatment	• Incidence of adverse events • Vital signs

Overall Design:

This is a Phase IV, 12-week, randomised, double-blind, triple-dummy, parallel group, multicentre study evaluating single inhaler triple therapy (FF/UMEC/VI) once daily via the ELLIPTA, compared to multiple inhaler triple combination therapy budesonide/ formoterol MDI (320/9 mcg) twice daily plus once daily tiotropium (18 mcg), in participants with COPD.

Study design schema



Eligible participants at Screening (V1) will be current or former smokers, with an established clinical history of COPD, receiving daily maintenance COPD therapy for at least 3 months, with a post-bronchodilator FEV1 of <50% predicted (or <80% predicted with a documented history of at least 2 moderate or 1 severe [hospitalised] exacerbation in the last 12 months) and a CAT score of ≥10 at Visit 1 and at Visit 2. Participants will be requested to participate in the study for approximately 17 weeks, consisting of a 4-week run-in period, 12-week treatment period and a 1-week follow-up period.

- **Pre-screening:** Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0), including the informed consent process, must be completed prior to any protocol-required changes to a participant's usual COPD treatment and the initiation of any Visit 1 procedures. Participants will continue treatment with their regular (i.e. pre-study) COPD medication(s) during the pre-screening period, except for medications that are prohibited within a specified time interval prior to Visit 1.
- **Screening/run-in:** Eligible participants will be allowed to continue their usual COPD medications until the day before Screening, Visit 1. On the morning of the Screening Visit participants will refrain from taking their morning dose of their usual COPD medications. Participants who meet all of the eligibility criteria at Visit 1, will enter the 4-week run-in period during which they will discontinue all existing COPD medications and receive their run-in treatment: budesonide/formoterol (320/9 mcg) twice daily plus tiotropium (18 mcg) once daily plus placebo via the ELLIPTA. Participants will not use any other COPD medications (except for those allowed per protocol). Participants will be provided with short-acting albuterol/salbutamol to be used on an as-needed basis (rescue medication) throughout the study. At Screening, each participant will be instructed on the proper use of the ELLIPTA, MDI and HandiHaler and will

self-administer their first doses of their run-in treatment during the Screening Visit. On the morning of the other study visits (Visit 2 onwards), participants will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel.

- **Randomisation/treatment:** On the day before the Randomisation Visit (Visit 2), participants will take their last dose of run-in treatment and will not use any other COPD medications (except for those allowed per protocol) 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.

  At Visit 2 (the Randomisation Visit), participants who meet all of the randomisation criteria will discontinue their run-in treatments and will be randomised in 1:1 ratio to receive one the following double-blind study treatments for 84 days:

  Either:

  FF/UMEC/VI 100/62.5/25 mcg via the ELLIPTA once daily in the morning
  + placebo to match budesonide/formoterol via MDI, two inhalations twice daily
  + placebo to match tiotropium via HandiHaler once daily in the morning

  or,

  Budesonide/formoterol 320/9 mcg via MDI, twice daily*
  + tiotropium 18mcg via HandiHaler once daily in the morning
  + placebo via the ELLIPTA once daily in the morning

  *Participants are required to take two inhalations of budesonide/formoterol 160/4.5 mcg, via the MDI in the morning and two inhalations in the evening. The total dose is therefore 320/9 mcg twice daily.

  At Visit 2 participants will refrain from taking their morning doses of run-in study medication and will self-administer study treatment at the clinic, when instructed to do so. Participants will remain available, preferably at the clinic or approved facility, for at least 24 hours for serial spirometry assessments.

  On the morning of Visits 3 and 4, participants will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel. At Visits 3, and 4 participants will self-administer study treatment whilst at the clinic. Participants will take their last doses of study treatment in the clinic on Day 84 (Visit 4, when instructed to do so by clinic personnel), and preferably continue to remain at the clinic or approved facility until at least 24 hours after their last morning dose, for their clinical assessments, which include serial spirometry assessments. On non-clinic visit days participants are expected to take their study treatment at home each day in the morning and in the evening at approximately the same time, as directed by the clinic.

- **Safety/follow-up:** A safety follow-up telephone contact or clinic visit (Visit 5) will be conducted approximately 7 days after the participant completes all of the

protocol-defined procedures for Visit 4/End of Study (EOS) or, if applicable, the Study Treatment Discontinuation Visit.

Participants that permanently discontinue study treatment are not required to withdraw from the study. If for any reason a participant must permanently discontinue study treatment, every effort should be made by the Investigator/staff to keep the participant in the study and complete all remaining protocol specified clinic visits. However, a participant may voluntarily withdraw from participation in this study at any time. The Investigator may also, at his or her discretion, withdraw a participant from further study participation. Participants who are withdrawn from the study will not be replaced.

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

Number of Participants:

Approximately 800 participants with advanced COPD will enter the run-in period, in order to randomise approximately 732 participants, in order to achieve an estimated 620 evaluable participants in modified per-protocol (mPP) population at Week 12, assuming 10 % premature discontinuation of study treatment and 5% protocol deviation.

Approximately 80 centres globally will be required to recruit participants in the study.

Treatment Groups and Duration:

Participants who meet all the eligibility criteria and who have successfully completed all protocol procedures at Screening will enter the 4-week run-in period and will take budesonide/formoterol (320/9 mcg) twice daily plus tiotropium (18 mcg) once daily plus placebo via the ELLIPTA. Following the run-in period, eligible participants will be randomised (1:1) to one of the following double-blind, triple-dummy treatment groups for 84 days:

Either:

- FF/UMEC/VI 100/62.5/25 mcg via the ELLIPTA once daily in the morning

  + placebo to match budesonide/formoterol via MDI, two inhalations twice daily
  + placebo to match tiotropium via HandiHaler once daily in the morning

or,

- Budesonide/formoterol 160/4.5 mcg via MDI, two inhalations twice daily*

  + tiotropium 18mcg via HandiHaler once daily in the morning

  + placebo via the ELLIPTA once daily in the morning

*Participants are required to take two inhalations of budesonide/formoterol 160/4.5 mcg, via the MDI in the morning and two inhalations in the evening. The total dose is therefore 320/9 mcg twice daily.

Dosing schedule for run-in and treatment periods

	ELLIPTA (1 inhalation)		MDI (2 puffs)		HandiHaler (1 capsule inhaled twice)	
	Active	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**
Run-in						
am		**Y**	**Y**		**Y**	
pm			**Y**			
Treatment						
FF/UMEC/VI group						
am	**Y**			**Y**		**Y**
pm				**Y**		
Budesonide/formoterol + tiotropium group						
am		**Y**	**Y**		**Y**	
pm			**Y**			

The ELLIPTA contains 30 doses (FF/UMEC/VI or placebo) and participants will be instructed to administer one dose from their ELLIPTA once daily in the morning.

Symbicort MDI contains 120 doses: budesonide/formoterol 160/4.5 mcg, two inhalations twice daily.

Tiotropium: Contents of 1 capsule (18 mcg) inhaled once daily using HandiHaler device. *Note*: To ensure drug delivery, two inhalations of the contents of each capsule should be performed.

Key Elements of Analysis Plan:

The null hypothesis is that the difference in 0-24 hour Weighted Mean (WM) FEV_1 between treatment groups is less than or equal to a pre-specified non-inferiority margin Δ:

H_0: $T_1 - T_2 \leq -\Delta$

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

H_1: $T_1 - T_2 > -\Delta$

where T_1 and T_2 are the treatment means for FF/UMEC/VI and budesonide/formoterol + tiotropium (BUD/FOR+TIO), respectively.

The non-inferiority margin has been set at 50 mL.

The primary analysis population will be the modified per-protocol (mPP) population, comprising all participants randomised to treatment except those randomised in error, who do not have a full protocol deviation or other event considered to impact efficacy.

The primary analysis will be performed for mPP population using on-treatment data. The primary analysis will evaluate the endpoint of 0-24 hour WM FEV_1 on Day 84 using a mixed model repeated measure (MMRM) analysis, including covariates baseline FEV_1, visit, geographical region, treatment and visit by baseline interaction. A visit by treatment interaction term will also be included to allow treatment effects to be estimated at each visit separately. The variance-covariance matrix will be assumed unstructured. Baseline FEV_1 is the mean of the two assessments made -30 and -5 minutes pre-dose on Treatment Day 1.

Estimated differences between FF/UMEC/VI and BUD/FOR+TIO will be presented together with 95% confidence intervals (CIs) for the treatment difference and p-value.

Inference to be drawn from the p-values will be as follows:

- Analysis with mPP population: If the treatment comparison on the primary endpoint has a lower confidence limit below the non-inferiority margin, non-inferiority is not demonstrated. No inference will be drawn from p-values for treatment comparisons on any other endpoints.

- Analysis with mPP population: If the treatment comparison on the primary endpoint has a lower confidence limit above the non-inferiority margin but below 0, non-inferiority is established but the p-value will not be used to give an indication of the strength of that non-inferiority. Inference will be drawn from p-values for treatment comparisons (with Intent-To-Treat [ITT] population) on other non-lung function endpoints, ie, SGRQ and CAT which will be called statistically significant if <0.05. No inference will be drawn from p-values on trough FEV1 endpoint.

- Analysis with ITT population: If the treatment comparison on the primary endpoint has a lower confidence limit above 0, superiority is established and the p-value can be used to give an indication of the strength of that superiority. Inference will be drawn from p-values for treatment comparisons on all other endpoints, which will be called statistically significant if <0.05.

A “tipping point” sensitivity analysis of 0-24 hour WM FEV1 on Day 84 will be conducted for the mPP Population. This will explore the impact of missing data by using differing assumptions regarding the mean treatment effect in participants who discontinue study treatment or have data excluded from mPP Population analyses. Assumptions will include scenarios where participants who discontinue FF/UMEC/VI have a lower treatment effect than those who discontinue BUD/FOR+TIO. The analysis results will be used to explore the conditions under which the conclusion of non-inferiority no longer holds.

If superiority on primary endpoint is established with ITT population, similar “tipping point” sensitivity analysis will be conducted for the ITT population in order to explore the conditions under which the conclusion of superiority no longer holds.

The details of the statistical analysis methods for the secondary efficacy endpoints will be provided in the Reporting and Analysis Plan (RAP).

2. SCHEDULE OF ACTIVITIES (SOA)

Protocol Activity	**Pre-Screen**	**Screen**		**Treatment**		**Follow-up**	
	Visit 0	**Visit 1 Screen/ Run-in**	**Visit 2 Randomisation**	**Visit 3**	**Visit 4**	**Study Treatment Discontinuation Visit**	**Visit 5 Safety Follow-up Contact**
Study Day	**-56 to -28**	**Day -28**	**Day 1**	**Day 28**	**Day 84-85**		**Day 91**
Week	**-8 to -4**	**-4**	**0**	**4**	**12**		**13**
Window		**-3/+8d (Day -31 to -21)**		**-4/+2d (Day 24 to 30)**	**-4/+2d (Day 80 to 86)**		**-1/+4d (Day 90 to 95)**
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
Inclusion/Exclusion Criteria		X	X				
Smoking history & status		X			X	X	
Smoking Cessation Counselling		X			X	X	
Register Visit in IWRS	X	X	X	X	X	X	X
CAT [d]		X	X	X	X		
SGRQ-C[d]			X	X	X		
Reversibility Testing and PIFR [e]		X					
Trough FEV1 [o]				X			
24h serial spirometry [f]			X		X		
Inhalation device training		X	X				
Exacerbation Assessment		X	X	X	X	X	X
Physical examination [g]		X			X	X	
Adverse Events Assessment		X	X	X	X	X	X
Vital signs [h]		X			X	X	
ECG		X					
Chest X-ray [i]		X					
Oropharyngeal examination		X	X	X	X	X	
Blood Draw for Genetics research [j]			X				
Hematology/biochemistry [k]		X					
Urine Pregnancy Test [l]		X			X	X	
Hepatitis B and C tests		X					
Dispense run-in treatment		X					
Dispense study treatment			X	X			
Administer run-in treatment in clinic [m]		X					

Protocol Activity	Pre-Screen	Screen		Treatment		Follow-up	
	Visit 0	Visit 1 Screen/ Run-in	Visit 2 Randomisation	Visit 3	Visit 4	Study Treatment Discontinuation Visit	Visit 5 Safety Follow-up Contact
Study Day	-56 to -28	Day -28	Day 1	Day 28	Day 84-85		Day 91
Week	-8 to -4	-4	0	4	12		13
Window		-3/+8d (Day -31 to -21)		-4/+2d (Day 24 to 30)	-4/+2d (Day 80 to 86)		-1/+4d (Day 90 to 95)
Administer study treatment in clinic [n]			X	X	X		
Assess run-in treatment compliance			X				
Assess study treatment compliance				X	X	X	
Collect run-in treatment			X				
Collect study treatment				X	X	X	
Dispense albuterol/salbutamol		X	X	X	X		
Collect albuterol/salbutamol			X	X	X	X	
Dispense paper Medical Problems worksheet	X	X	X	X	X		
Review paper Medical Problems worksheet		X	X	X	X	X	X

a. Informed consent must be conducted at the Pre-screen Visit prior to performing any study procedures including the changing or withholding of medications. The informed consent may be given at Screening Visit 1 if the participant does not take or has not taken any protocol excluded medications. The Pre-screen and Screening Visits can occur on the same day.
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. Participants do not have to participate in the genetic research part of this study, it is optional.
c. Demography may be captured at either the Pre-screen Visit or Screening Visit (for participants who do not have a Pre-screen Visit).
d. SGRQ-C and CAT will be completed electronically and should be conducted in the following order and before other study assessments: CAT, SGRQ-C.
e. At Screening Visit 1 PIFR spirometry and both pre and post-bronchodilator spirometry will be conducted. PIFR will be assessed 10 minutes prior to pre-bronchodilator spirometry. Participants are required to withhold their usual morning doses of their COPD meds including rescue albuterol/salbutamol for the protocol designated period prior to PIFR spirometry and reversibility testing.
f. Serial spirometry at Visit 2 and Visit 4 will be done pre-dose at 30 mins and 5 mins and post dose at 5 mins, 15 mins, 30mins,1hr, 3hrs, 6hrs, 12hrs, 15hrs, 21hrs, 23hrs, 24hrs. Participants that discontinue study treatment but remain in the study will complete serial spirometry at Week 12, if they consent to do so.
g. Physical examination may include height, weight, blood pressure and temperature.
h. Vital signs, including blood pressure and pulse must be performed prior to spirometry and prior to taking morning dose of study treatment.
i. Chest X-ray is required at Screening (or historical x-ray obtained within 3 months prior to Screening) and at any time there is a suspected pneumonia or a mod/severe exacerbation.
j. Genetic consent must be obtained prior to obtaining a blood sample. The sample can be collected at any time after Visit 2, providing consent is obtained.
k. Hematology and chemistry panels will include full and differential blood count and liver chemistry.
l. All female participants of child bearing potential will have a urine pregnancy test at Visits 1, 4 and Study Treatment Discontinuation Visit (if applicable).

m. Participants must withhold their morning dose of existing COPD medication or study treatment and not take their run-in treatment until instructed to do so by study staff.
n. Participants must withhold their morning dose of study treatment at each clinic visit and not take their study treatment until instructed to do so by study staff.
o. Trough FEV_1 will be performed pre-dose at 30 mins and 5 mins prior to taking the morning dose of study treatment, between 6am and 11am and after withholding rescue albuterol/salbutamol for > 4 hours.

When multiple assessments and procedures are performed suggested sequence order is CAT, SGRQ-C, vitals, ECG, spirometry, clinical lab assessments.

3. INTRODUCTION

3.1. Study Rationale

Chronic obstructive pulmonary disease (COPD) guidelines advocate the use of long-acting muscarinic receptor antagonists (LAMA) added to the combination of inhaled corticosteroids (ICS) plus a long-acting β_2-adrenergic receptor agonist (LABA) as second line therapy for the most advanced patients with significant symptoms and a high risk of exacerbations. Regular treatment with Inhaled Corticosteroid (ICS) containing regimens 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 forced expiratory flow in 1 second (FEV_1) <60 % predicted [Aaron, 2007; Cazzola, 2007; Hanania, 2012; Jung, 2012; Siler, 2015; Welte, 2009].

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 United States (US) 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 United Kingdom (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, 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 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; Siler, 2015; Welte, 2009]. These studies have also shown that the number and type of reported adverse events (AE) 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.

GlaxoSmithKline (GSK) is currently developing a once-daily 'closed' triple therapy of a ICS/LAMA/LABA combination [fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) (100/62.5/25 mcg)] in a single inhaler, with the aim of providing a new treatment option for the management of symptomatic COPD patients at risk of

exacerbations which will reduce the exacerbation frequency, allow for a reduced burden of polypharmacy, convenience, and increase the potential for improvement in lung function, HRQoL and symptom control over established dual/monotherapies.

GSK conducted a Phase III study comparing once-daily FF/UMEC/VI to twice-daily Symbiocort MDI (budesonide/formoterol) 400/12 mcg in COPD participants that were symptomatic and at risk of an exacerbation despite receiving maintenance therapy (CTT116853). FF/UMEC/VI demonstrated statistically significant improvements in trough FEV_1, a statistically significant reduction in the annual rate of moderate or severe COPD exacerbations, and a statistically significant reduction of COPD symptoms (using Exacerbations and Chronic Pulmonary Disease – Respiratory Symptoms [E-RS]) when compared to budesonide/formoterol. Additionally, clinically meaningful improvements from baseline in St. George's Respiratory Questionnaire (SGRQ) total score were observed, with a statistically significant improvement compared to budesonide/formoterol [Lipson, 2017]. This Phase III study provided compelling efficacy data compared with an established ICS/LABA and demonstrated the clinical value of single inhaler triple-therapy compared to ICS/LABA therapy in patients with COPD.

The primary purpose of this study is to evaluate lung function and HRQoL after 84 days of treatment with a single inhaler triple therapy combination of FF/UMEC/VI (100/62.5/25 mcg) once daily via the ELLIPTA™ compared with a multiple inhaler combination therapy of Symbicort Metered Dose Inhaler (MDI) (budesonide/formoterol 320/9 mcg) twice daily plus Spiriva HandiHaler (tiotropium 18 mcg) once daily. The study will inform healthcare providers that patients can be switched to FF/UMEC/VI single inhaler therapy from a multiple inhaler triple therapy regimen of Symbicort MDI and Spiriva Handihaler.

3.2. Background

Chronic obstructive pulmonary disease is a progressive disease characterised by increasing obstruction to airflow and the progressive development of respiratory symptoms including chronic cough, increased sputum production, dyspnoea 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, using the ABCD assessment tool, which aimed to more comprehensively assess disease severity and guide therapy choice, ultimately improving COPD management. A 2013 update included an additional criterion to characterise patients that have had a hospitalised exacerbation as high risk, regardless of GOLD status [GOLD, 2013].

GOLD released a revised guideline in 2017 that separates spirometric grades from the ABCD assessment tool (Table 1) [GOLD, 2017].

Table 1 GOLD 2017 Classification

GOLD ABCD Classification	Risk Class Determinant	Symptom Category Determinant*
A: Low risk, less symptoms	≤1 exacerbation, prior year	mMRC <2; CAT <10
B: Low risk, more symptoms	≤1 exacerbation, prior year	mMRC ≥2; CAT ≥10
C: High risk, less symptoms	≥2 exacerbations, prior year *OR* 1 leading to hospitalization, prior year	mMRC <2; CAT <10
D: High risk, more symptoms	≥2 exacerbations, prior year *OR* 1 leading to hospitalisation, prior year	mMRC ≥2; CAT ≥10
* - Symptomatic category determined by either Modified Clinical Research Council (mMRC) or COPD Assessment Test (CAT) score.		
GOLD Airflow Limitation	**Severity**	**FEV_1 (% predicted)**
GOLD 1	Mild	≥80
GOLD 2	Moderate	50 - 79
GOLD 3	Severe	30 - 49
GOLD 4	Very Severe	<30

The GOLD, 2017 guidelines also outlined suggested management strategies for COPD based upon disease severity, including escalation as well as de-escalation strategies. For milder patients (GOLD Group A), the guidelines encourage active risk reduction (e.g., smoking cessation and influenza vaccination) with the addition of bronchodilators. 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 [GOLD, 2017]. Long-acting bronchodilators (LAMAs or LABAs) have been shown to relieve symptoms, increase exercise capacity, improve health-related quality of life and reduce COPD exacerbations to a greater extent than short acting β_2 adrenergic receptor agonists. For advanced cases, or those with repeated exacerbations, the incorporation of ICS or triple therapy, is recommended.

3.3. Benefit/Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2834425 (FF/UMEC/VI) can be found in the Investigator's Brochure (IB). The safety information for budesonide/formoterol and tiotropium can be found in the authorised product label. The current safety profile for FF/UMEC/VI (100/62.5/25 mcg), based on data available to date, is consistent with the pharmacological classes of the components. The following section outlines the risk assessment and mitigation strategy for this protocol.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK2834425 (FF/UMEC/VI), GSK573719 (UMEC), GW642444 (vilanterol), GW685698 (fluticasone furoate)		
Pneumonia in participants with COPD	Pneumonia is a class concern for any ICS-containing product for the treatment of COPD. In a study (CTT116853) [Lipson, 2017] in 1810 randomised COPD participants treated with FF/UMEC/VI or budesonide/formoterol (BUD/FOR) for up to 24 weeks (Intent-To-Treat [ITT] Population), or up to 52 weeks (subset of 430 participants; EXT Population), the incidence of events in the pneumonia adverse event of special interest (AESI) group was 2.2 % and 0.8 % for FF/UMEC/VI and BUD/FOR respectively in the ITT Population, and 1.9 % and 1.8 % for FF/UMEC/VI and BUD/FOR respectively in the EXT Population. There was one fatal case of pneumonia in a participant who received FF/UMEC/VI. The incidence of pneumonia with FF/UMEC/VI in this study was in line with the incidence of pneumonia seen in 24 week studies with FF/VI (<1-2 % with FF/VI 100/25) and less than that observed in 52 week exacerbation studies with FF/VI (6 % with FF/VI 100/25) [Dransfield, 2013]. Similarly, the incidence of pneumonia with	- Participants will be informed of the risk in the informed consent. - Investigators are informed of the risk in the IB. Investigators will be instructed to remain vigilant for the possible development of pneumonia in participants with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. For suspected cases of pneumonia, investigators will be encouraged to arrange a chest X-ray within 48 hours of diagnosis [Section 12.5.2] and to treat appropriately. - Appropriate exclusion criteria as specified in Section 6.2 of the protocol - Instream review of blinded AE/SAE reports. - All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable) as specified in

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	FF/UMEC/VI was less than that observed in a 12-month exacerbation trial with BUD/FOR (6.4 %) [Sharafkhaneh, 2012]. Prior studies with FF/VI have demonstrated risk factors associated with a higher risk of pneumonia in participants with COPD (e.g., advanced age, poor lung function, low body mass index (BMI), current smoking, and a prior history of pneumonia) [Crim, 2009]. These risk factors were present in some participants with pneumonia in study CTT116853 with FF/UMEC/VI; however, the low number of pneumonia events reported in the study precludes drawing any definite conclusions about risk factors. These risk factors should be taken into consideration when using an ICS in participants with COPD. Pneumonia risk will be important in the benefit-risk assessment for FF/UMEC/VI in COPD participants, hence a robust risk mitigation strategy is being proposed. The Pharmacovigilance Risk Assessment Committee (PRAC) recently conducted an Article 31 review to evaluate the risk of pneumonia with use of ICSs in patients with COPD. The PRAC review confirmed that COPD patients treated with inhaled corticosteroids are at increased risk of pneumonia; however the Committee's view was that the benefits of ICSs continue to outweigh their risks. The PRAC also looked	Section 9.2.7. - Chest X-ray read required at baseline and whenever a participant has suspected pneumonia or mod/severe exacerbations during the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	whether there were any differences in the risk of pneumonia between these products, and did not find conclusive evidence of such difference.	
Decreased bone mineral density and associated fractures	Reduction in bone density, and the subsequent risk of fractures, is a known potential risk with corticosteroids. There may be a modest increase in risk of fracture among participants with COPD treated with ICS; but, the results are not consistent across individual studies [Christensson, 2008; Lehouck, 2011; Weldon, 2009]. In study CTT116853, the incidence of events in the decreased bone mineral density and associated fractures AESI group was low, with an incidence of 0.4 % and 0.7 % in the FF/UMEC/VI and BUD/FOR treatment groups respectively in the ITT Population up to 24 weeks, and 0.5 % in both treatment groups in the EXT Population up to 52 weeks. The majority of the fractures in both treatment groups were traumatic in nature.	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB. - Instream review of blinded AE/SAE reports.
Adrenal suppression	Oral corticosteroids are known to have an effect on the hypothalamic-pituitary-adrenal (HPA) axis leading to a reduction in cortisol production. Due to the low dose and low systemic exposure with inhaled corticosteroids, this potential effect is not	- Investigators are informed of the risk in the IB. - Instream review of blinded AE/SAE reports.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	clear, nor is the possible impact of any change in cortisol. The effect of FF/UMEC/VI on cortisol levels has not been studied. In study CTT116853, no events were reported in the adrenal suppression AESI group for FF/UMEC/VI and BUD/FOR. With respect to the FF/VI clinical development program, a formal HPA study, using 24 hour serum cortisol measurements was performed. In addition, multiple studies with COPD (and asthma) participants monitored urinary cortisol. These studies did not show a clinically relevant effect of FF/VI100/25 on the HPA axis. Participants that have received oral corticosteroids, particularly those who have received significant amounts for long periods of time, will be more susceptible to this risk of adrenal suppression. The systemic exposure of FF is very low compared to that of oral corticosteroids, so any concurrent effect will be negligible. The proposed dose (100 mcg) of inhaled FF in this study is unlikely to lead to clinically significant changes in the treatment period since systemic exposure is low.	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Corticosteroid Associated Eye Disorders	Systemic ocular effects (*e.g.* cataract and glaucoma) may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. However, these effects are much less likely to occur with ICS compared with oral corticosteroids. In study CTT116853, the incidence of events in the ocular effects AESI group was low, with an incidence of 0.1 % and 0.4 % in the FF/UMEC/VI and BUD/FOR treatment groups respectively in the ITT Population up to 24 weeks. There were no events reported in the ocular effects AESI in the EXT Population up to 52 weeks. During studies with FF and FF/VI in asthma participants, and with FF/VI and UMEC/VI in COPD participants, 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 participants with asthma.	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB. - Appropriate exclusion criteria as specified in Section 6.2 of the protocol - Instream review of blinded AE/SAE reports. - If a risk is suspected, participants should receive appropriate treatment
Serious cardiovascular events	Cardiovasular (CV) effects are a potential class effect associated with anti-muscarinic and beta agonist therapies. In the COPD population, there is a high prevalence of concurrent CV disease and the	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB. - Appropriate exclusion criteria as specified in

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	prevalence of CV co morbidities increases with worsening severity of COPD. In study CTT116853 [Lipson, 2017], approximately two-thirds of all participants reported CV risk factors at baseline. In this study, cardiovascular effects were the most frequently reported AESI, with a similar incidence between FF/UMEC/VI and BUD/FOR treatment groups in the ITT Population up to 24 weeks (4.3 % and 5.2 % respectively) and the EXT Population up to 52 weeks (8.6 % and 10 % respectively). Within subgroups of cardiovascular effects, hypertension was reported most frequently and with a numerically higher incidence with BUD/FOR (2.3 %) compared with FF/UMEC/VI (1.3 %) in the ITT Population up to 24 weeks, but with a similar incidence in the EXT Population up to 52 weeks (0.9 to 1.0 % across treatment groups). Cardiac arrhythmias were reported the next most frequently and occurred with an incidence of 1.2 % in both treatment groups in the ITT Population up to 24 weeks, and with an incidence of 1.9 % and 3.6 % in the FF/UMEC/VI and BUD/FOR groups in the EXT Population up to 52 weeks. The incidence of serious events in the	Section 6.2 of the protocol, including - Electrocardiogram (ECG) inclusion criteria - Vital sign assessments (heart rate and blood pressure) as per protocol. - Protocol defined stopping criteria as per Section 8.1.1. - Instream review of blinded AE/SAE reports.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	cardiovascular effects AESI was low, with an incidence of 1.0 % and 1.1 % in the FF/UMEC/VI and BUD/FOR groups respectively in the ITT Population up to 24 weeks, and 2.9 % and 1.4 % in the FF/UMEC/VI and BUD/FOR groups respectively in the EXT Population up to 52 weeks. The absolute numbers of fatal events in cardiovascular effects AESI was low in the study, despite the study enrolling participants with a number of CV comorbidities at baseline. A pre-specified Major Adverse Cardiac Event (MACE) analysis was conducted in CTT116853, with broad MACE defined as: ischemic heart disease Standardised MedDRA Queries (SMQ) excluding fatalities, plus central nervous system haemorrhages and cerebrovascular conditions SMQ excluding fatalities, plus adjudicated cardiovascular deaths. The narrow MACE definition included only the preferred terms of myocardial ischaemia and acute myocardial infarction in place of the ischaemic heart disease SMQ. Overall, the absolute number of MACE events using either the broad or narrow definition was low both in the ITT Population up to 24 weeks and EXT Population up to 52 weeks. No clinically relevant differences were observed between FF/UMEC/VI and BUD/FOR based on narrow and broad MACE analysis both in the ITT	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Population up to 24 weeks and EXT Population up to 52 weeks. In study CTT116853 [Lipson, 2017], there were no emerging safety signals from vital signs, ECGs, or Holter data. The effect of FF/UMEC/VI on the QT interval has not been evaluated in a thorough QT (TQT) study. TQT studies for FF/VI and UMEC/VI did not show clinically relevant effects on QT interval at clinical doses of FF, UMEC and VI. The cardiovascular safety profile of FF/UMEC/VI was generally consistent with that of FF/VI and UMEC/VI.	
Hypersensitivity	Hypersensitivity reactions are unlikely to affect the majority of participants. In study CTT116853, in the ITT Population up to 24 weeks, events in the hypersensitivity AESI group occurred at low incidences in the FF/UMEC/VI and BUD/FOR treatment groups (1.1 % in both groups). Similarly, in the EXT Population up to 52 weeks, events in the hypersensitivity AESI group occurred at low incidences (1.4 % and 0.5 % in FF/UMEC/VI and BUD/FOR arms). On treatment hypersensitivity	- Participants will be informed about the risk in the informed consent. Particpants will be advised to seek medical treatment if any signs of hypersensitivity occur. - Investigators are informed of the risk in the IB. - Appropriate exclusion criteria as specified in Section 6.2 of the protocol. - Instream review of blinded AE/SAE reports.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	serious AESI events occurred at low frequency. Risk factors for hypersensitivity are poorly understood but may include exposure to infectious diseases during early childhood, environmental pollution, allergen level and dietary changes [Niggemann, 2014; De Bisschop, 2012]. Although hypersensitivity reactions are unlikely to affect the majority of participants, there may be a few individuals who experience allergic reactions; they will need to be managed on a case by case basis.	
Narrow angle glaucoma	Rare reports of angle closure glaucoma (which may lead into blindness) have been associated with nebulised ipratropium bromide and salbutamol [Packe, 1984]. The incidence of narrow angle glaucoma in the COPD population associated with the use of inhaled bronchodilators (including LAMAs and LABAs) is relatively low. In CTT116853, in the ITT Population up to 24 weeks, events in the glaucoma SMQ were reported at an incidence of 0.1 and 0.4 % in the FF/UMEC/VI and BUD/FOR arms respectively. In the EXT Population up to 52 weeks, no events	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB. - Appropriate exclusion criteria as specified in Section 6.2 of the protocol - Instream review of blinded AE/SAE reports.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	were reported in either treatment arm. In the UMEC/VI development program, there was one report (<1 %) of angle closure glaucoma (UMEC/VI 62.5/25 mcg).	
Bladder outlet obstruction, dysuria and urinary retention	Bladder outlet obstruction and urinary retention are class effects seen with antimuscarinics. In study CTT116853, in the ITT Population up to 24 weeks, the incidence of events in the urinary retention AESI group was low (0.1 % and 0.0 % for FF/UMEC/VI and BUD/FOR respectively) in both treatment groups. There were no events of urinary retention reported in either group in the EXT Population up to 52 weeks. There were no serious events in the urinary retention AESI group in either treatment arm in the ITT Population up to 24 weeks and the EXT Population up to 52 weeks.	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB. - Appropriate exclusion criteria as specified in Section 6.2 of the protocol - Instream review of blinded AE/SAE reports.
Paradoxical bronchospasm	The phenomenon of paradoxical bronchospasm may occur in association with all inhaled medication, and may vary from mild to life threatening. In study CTT116853, the risk of paradoxical bronchospasm was evaluated through the AESI of asthma/bronchospasm. In the ITT Population	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB. - Instream review of blinded AE/SAE reports.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	up to 24 weeks, one participant reported an event in the asthma/bronchospasm AESI (PT of wheezing in a participant on BUD/FOR; non-serious). There were no events reported in the EXT Population up to 52 weeks.	

3.3.2. Risk assessment for Symbicort MDI (Budesonide/ Formoterol) 160/4.5 mcg

Symbicort is a marketed drug that contains both budesonide (ICS; 160 mcg) and formoterol (LABA; 4.5 mcg). Two inhalations from the MDI provide the required 320/9 mcg dose. The dose (320/9 mcg) and formulation, using an MDI, are approved for COPD in the US, the dose and formulation are not approved in Europe. A similar profile of undesirable effects as reported for ICSs and LABAs may occur with budesonide and formoterol respectively. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug-related adverse reactions are pharmacologically predictable side-effects of β_2 adrenoceptor agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment. Please refer to the authorised product label for further information about the risks of using Symbicort. In this study, Symbicort will be used in line with the recommendations provided in the product label.

Since Symbicort contains an ICS and LABA, the risk mitigation strategies for the FF (ICS) and VI (LABA) components of GSK2834425 will be applicable for Symbicort.

3.3.3. Risk Assessment for Spiriva Handihaler (Tiotropium Bromide) 18 mcg

Tiotropium is a marketed drug that contains tiotropium bromide (18 mcg). A similar profile of undesirable effects as reported for anticholinergics (umeclidinium) may occur with tiotropium bromide. The most common drug related adverse reactions are pharmacologically predictable side effects for anti-cholinergic therapy, such as dry mouth, blurred vision, dizziness, headache and cough. Please refer to the authorised product label for further information on the risks of using Spiriva Handihaler. In this study, Spiriva Handihaler will be used in line with the recommendations provided in the product label.

Spiriva Handihaler is an anticholinergic, therefore the risk mitigation strategy for UMEC component of GSK2834425 will be applicable for Spiriva Handilaler.

3.3.4. Benefit Assessment

GlaxoSmithKline is developing FF/UMEC/VI in a single inhaler, with the aim of providing a new treatment option for the management of symptomatic COPD patients at risk for exacerbations which will reduce the exacerbation frequency, allow for a reduced burden of polypharmacy, convenience, and increase the potential for improvement in lung function, HRQoL, and symptom control over established dual/monotherapies.

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

In the US, 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. UMEC is indicated for the long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with COPD.

In the EU, the FF/VI combination is approved for the symptomatic treatment of adults with COPD with an FEV_1 <70 % predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. The UMEC/VI combination is approved as a maintenance bronchodilator to relieve symptoms in adult patients with COPD. UMEC is approved as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

An appropriate safety monitoring strategy is being proposed for all risks associated with the FF/UMEC/VI combination, including the key risks (Section 3.3.1).

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.

Tiotropium (18 mcg) and budesonide/formoterol (400/12 mcg) are marketed drugs for the COPD indication, and have established benefit:risk profiles. Tiotropium and budesonide/formoterol will be used in line with the recommendations provided in the product labels.

3.3.5. Overall Benefit:Risk Conclusion

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

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on lung function	**Primary** Weighted mean change from baseline in FEV_1 over 0-24 hours at Week 12
	Secondary • Change from baseline in trough FEV_1 on Day 2, Day 28, Day 84 and Day 85 • Weighted mean change from baseline in FEV_1 over 0-24 hours on Day 1
Other	
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on Health Status	• Proportion of responders based on the St George's Respiratory Questionnaire (SGRQ) Total Score at Week 4 and Week 12 • Change from baseline in SGRQ Total Score at Week 4 and Week 12
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on Health Status	• Proportion of responders based on the COPD Assessment Test (CAT) Total Score at Week 4 and Week 12 • Change from baseline in CAT Total Score at Week 4 and Week 12
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on COPD exacerbations	• Moderate or severe exacerbation event
• Assess how inspiratory airflow limitation affects ability to use the ELLIPTA	• Peak Inspiratory Flow Rate at Screening (Week -4)

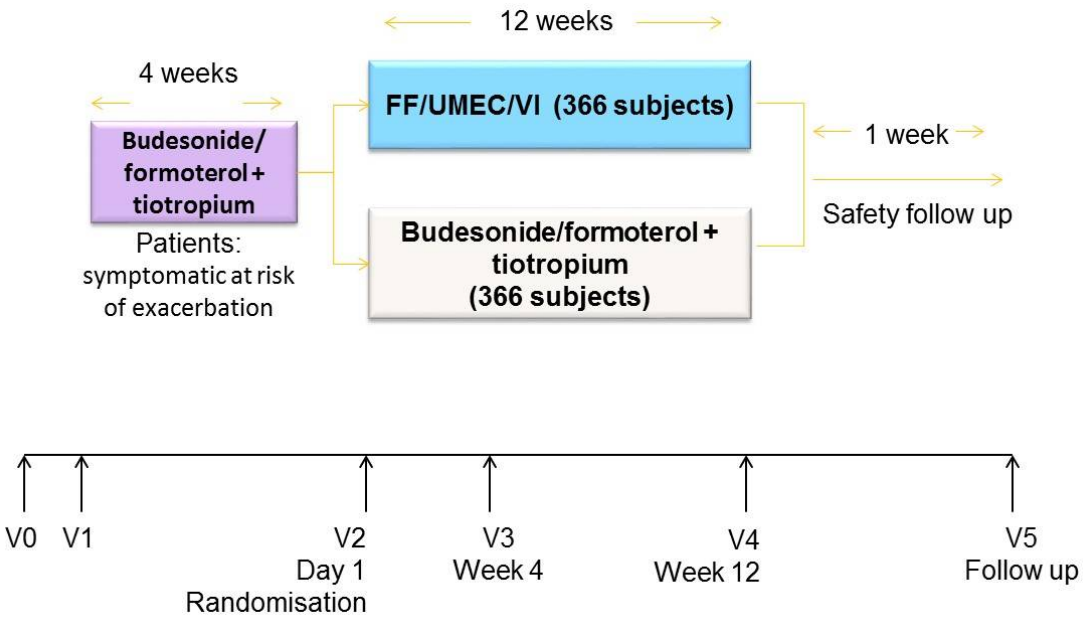
Objectives	Endpoints
Safety	
• To evaluate the safety profile of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium over 84 days of treatment	• Incidence of adverse events • Vital signs

5. STUDY DESIGN

5.1. Overall Design

This is a Phase IV, 12-week, randomised, double-blind, triple dummy, parallel group, multicentre study evaluating single inhaler triple therapy (FF/UMEC/VI) once daily via the ELLIPTA, compared to multiple inhaler triple combination therapy budesonide/formoterol (320/9 mcg) twice daily plus once daily tiotropium (18 mcg), in participants with COPD.

Figure 1 Study design schema



Eligible participants at Screening (V1) will be current or former smokers, with an established clinical history of COPD, receiving daily maintenance COPD therapy for at least 3 months, with a post-bronchodilator FEV1 of <50 % predicted (or <80 % predicted with a documented history of at least 2 moderate or 1 severe [hospitalised] exacerbation in the last 12 months) and a CAT score of ≥10 and Visit 1 and at Visit 2. Participants will be requested to participate in the study for approximately 17 weeks, consisting of a 4-week run-in period, 12-week treatment period and a 1-week follow-up period.

- **Pre-screening:** Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0), including the informed consent process, must be completed prior to any protocol-required changes to a participant's usual COPD treatment and the initiation of any Visit 1 procedures. Participants will continue treatment with their regular (i.e. pre-study) COPD medication(s) during the pre-screening period; however, medications that are prohibited within a specified time interval prior to Visit 1 are defined in Section 6.2 (24).
- **Screening/run-in:** Eligible participants will be allowed to continue their usual COPD medications until the day before Screening, Visit 1. On the morning of the Screening Visit participants will refrain from taking their morning dose of their usual COPD medications. Participants who meet all of the eligibility criteria at Visit 1, will enter the 4-week run-in period during which they will discontinue all existing COPD medications and receive their run-in treatment: budesonide/formoterol (320/9 mcg) twice daily plus tiotropium (18 mcg) once daily plus placebo via the ELLIPTA. Participants will not use any other COPD medications (except for those allowed per protocol). Participants will be provided with short-acting albuterol/salbutamol to be used on an as-needed basis (rescue medication) throughout the study. At Screening, each participant will be instructed on the proper use of the ELLIPTA, MDI and HandiHaler and will self-administer their first doses of their run-in treatment during the Screening Visit. On the morning of the other study visits (Visit 2 onwards), participants will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel.
- **Randomisation/treatment:** On the day before the Randomisation Visit (Visit 2), participants will take their last dose of run-in treatment and will not use any other COPD medications (except for those allowed per protocol) 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.

  At Visit 2 (the Randomisation Visit), participants who meet all of the randomisation criteria (see Section 6.3) will be randomised 1:1 to receive one the following double-blind study treatments for 84 days:

  Either:

  FF/UMEC/VI 100/62.5/25 mcg via the ELLIPTA once daily in the morning
  + placebo to match budesonide/formoterol via MDI, two inhalations twice daily
  + placebo to match tiotropium via HandiHaler once daily in the morning

  or,

  Budesonide/formoterol 160/4.5 mcg via MDI, two inhalations twice daily*
  + tiotropium 18 mcg via HandiHaler once daily in the morning
  + placebo via the ELLIPTA once daily in the morning

*Participants are required to take two inhalations of budesonide/formoterol 160/4.5 mcg, via the MDI in the morning and two inhalations in the evening. The total dose is therefore 320/9 mcg twice daily.

At Visit 2 participants will refrain from taking their morning doses of run-in study medication and will self-administer study treatment at the clinic, when instructed to do so. Participants will remain available, preferably at the clinic or approved facility, for at least 24 hours for serial spirometry assessments.

- On the morning of Visits 3 and 4, participants will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel. Participants will remain at the clinic for at least 24 hours, for serial spirometry assessments. At Visits 3 and 4 participants will self-administer study treatment whilst at the clinic. Participants will take their last doses of study treatment in the clinic on Day 84 (Visit 4, when instructed to do so by clinic personnel), and preferably continue to remain at the clinic or approved facility until at least 24 hours after their last morning dose, for their clinical assessments, which include serial spirometry assessments. Participants are expected on non-clinic visit days to take their study treatment at home in the morning at approximately the same time each day, and at the same time each evening, as directed by the clinic.
- **Safety/follow-up:** A safety follow-up telephone contact or clinic visit (Visit 5) will be conducted approximately 7 days after the participant completes all of the protocol-defined procedures for Visit 4/End of Study (EOS) or, if applicable, the Study Treatment Discontinuation Visit. A participant will be considered to have completed the study when they have completed all phases of the study including screening, run-in, the randomised treatment phase, and safety follow-up.

Participants that permanently discontinue study treatment are not required to withdraw from the study. If for any reason a participant must permanently discontinue study treatment, every effort should be made by the Investigator/staff to keep the participant in the study and complete all remaining protocol specified clinic visits (see Section 8.1). However, a participant may voluntarily withdraw from participation in this study at any time. The Investigator may also, at his or her discretion, withdraw a participant from further study participation. Participants who are withdrawn from the study will not be replaced.

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

5.2. Number of Participants

Approximately 800 participants with advanced COPD will enter the run-in period, in order to randomise approximately 732 participants in order to achieve an estimated 620 evaluable participants in the modified per-protocol (mPP) population at Week 12, assuming 10 % premature discontinuation of study treatment and 5 % protocol deviation. See Section 10 for further details.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including pre-screening, screening, run-in, the randomised treatment phase and the safety follow-up.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities table (SoA) (see Section 2) for the last participant in the trial globally.

5.4. Scientific Rationale for Study Design

This study will use a multicenter, randomised, double-blind, triple-dummy, parallel-group design. A placebo arm is not included because the primary comparison of interest is FF/UMEC/VI vs. Budesonide/formoterol + tiotropium and it is not considered appropriate to include a placebo arm in a study in participants with advanced COPD. Eligible participants must have been on daily maintenance COPD medications for at least 3 months. The 4-week run-in period is necessary in order to assess participant compliance with and ability to use all of the medications together, and allow sufficient time for the results of screening assessments to be returned to the site, in order to establish participant eligibility.

5.5. Dose Justification

The FF/UMEC/VI (100/62.5/25 mcg) dose was selected based on the doses that have been licensed for COPD for the FF/VI (100/25 mcg) and UMEC/VI (62.5/25 mcg) dual combinations through extensive studies in the mono and dual therapy programmes. It is the dose which is currently under regulatory review based on the Phase IIIa FF/UMEC/VI registration programme.

The doses selected for the Symbicort MDI (budesonide/formoterol 320/9 mcg, twice daily) and Spiriva HandiHaler (tiotropium 18 mcg, once daily) is the doses licensed in the US for use in COPD.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. **Informed consent:** capable of giving signed informed consent prior to study start which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. **Type of participant**: Outpatient.

3. **Age**: Participants 40 years of age or older at Screening (Visit 1).

4. **Gender**: Male or female participants.

Female participants:

A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP)

OR

- A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and until the safety follow-up contact after the last dose of study treatment.

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 (Visit 1).

8. **Severity of Disease:**

   Participants must demonstrate at Screening:

   - a post-bronchodilator FEV_1 <50 % predicted normal

   OR

   - a post-bronchodilator FEV_1 <80 % predicted normal and a documented history of ≥2 moderate exacerbations or one severe (hospitalized) exacerbation in the previous 12 months

   Participants must also have a measured post albuterol/salbutamol FEV_1/forced vital capacity (FVC) ratio of <0.70 at screening.

   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 dyspnoea, sputum volume, or sputum purulence (colour). Participant verbal reports are not acceptable.*

9. **Existing COPD maintenance treatment:** participant must have been receiving daily maintenance treatment for their COPD for at least 3 months prior to Screening.

   Note: *Participants taking only as-needed COPD medications are not eligible.*

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

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

2. **Asthma**: Participants with a current diagnosis of asthma. (Participants with a prior history of asthma are eligible if they have a current diagnosis of COPD).

3. **α1-antitrypsin deficiency**: Participants with α1-antitrypsin deficiency as the underlying cause of COPD.

4. **Other respiratory disorders**: Participants with active tuberculosis, lung cancer, and clinically significant: bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung disease or other active pulmonary diseases.

5. **Lung resection**: Participants who have undergone lung volume reduction surgery within the 12 months prior to Screening.

6. **Risk Factors for Pneumonia**: immune suppression (*e.g.* advanced human immunodeficiency virus [HIV] with high viral load and low CD4 count, lupus on immunosuppressants) that in the opinion of the investigator would increase risk of pneumonia or other risk factors for pneumonia (*e.g.* neurological disorders affecting control of the upper airway, such as Parkinson's Disease, Myasthenia Gravis).

   Participants at potentially high risk for pneumonia (*e.g.* very low body mass index [BMI], severely malnourished, or very low FEV_1) 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).

8. **Respiratory tract infection** that has 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 chest X-ray (e.g. significant cardiomegaly, pleural effusion or scarring). All participants will have a chest X-ray at Screening Visit 1 (or historical radiograph or computerized tomography [CT] scan obtained within 3 months prior to screening). **Note**: *Participants who have experienced pneumonia and/or moderate or severe COPD exacerbations within 3 months of screening must provide a post pneumonia/exacerbation chest X-ray 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**: Participants 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 haematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the participant 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:** ALT >2x Upper Limit of Normal (ULN); and bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35 %)

    Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment).

    NOTES:

    - Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.
    - Chronic stable hepatitis B and C (*e.g.*, presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment) are acceptable if participant otherwise meets entry criteria.

12. **Unstable or life threatening cardiac disease:** Participants 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

- New York Heart Association (NYHA) Class IV Heart failure

13. Abnormal and clinically significant 12-lead ECG finding at Visit 1

    - The Investigator will determine the clinical significance of each abnormal ECG finding in relation to the participant's medical history and exclude participants who would be at undue risk by participating in the trial.
    - An abnormal and clinically significant finding that would preclude a participant from entering the trial is defined as a 12-lead ECG tracing that is interpreted at, but not limited to, any of the following:
        i. Atrial Fibrillation (AF) with rapid ventricular rate >120 beats per minute (BPM)
        ii. Sustained and non-sustained Ventricular tachycardia (VT)
        iii. Second degree heart block Mobitz type II and third degree heart block (unless pacemaker or defibrillator had been inserted)
        iv. QT interval corrected for heart rate by ≥500 msec in participants with QRS <120 msec and QTcF ≥530 msec in participants with QRS ≥120 msec
14. **Contraindications**: A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, β_2-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**: Participants with carcinoma that has not been in complete remission for at least 3 years. Participants 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 3 year waiting period if the participant has been considered cured by treatment.

16. **Oxygen therapy**: Use of long-term oxygen therapy (LTOT) described as resting oxygen therapy >3 L/min at screening (Oxygen use ≤3 L/min flow is not exclusionary.)

17. **Medication prior to spirometry**: Participants 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**: Participants who have participated in the acute phase of a Pulmonary Rehabilitation Programme within 4 weeks prior to screening or participants who plan to enter the acute phase of a Pulmonary Rehabilitation Programme during the study. Participants who are in the maintenance phase of a Pulmonary Rehabilitation Programme are not excluded.

19. **Drug/alcohol abuse**: Participants with a known or suspected history of alcohol or drug abuse within the last 2 years.

20. **Non-compliance**: Participants 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**: Participants 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 participant 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 Visit 1:

Medication	No use within the following time intervals prior to Screening
Inhaled short-acting anticholinergics	6 hrs
Inhaled short-acting $beta_2$ agonists[1]	≥4 hrs
Inhaled short-acting anticholinergics + short-acting beta agonist combination	6 hrs
Long term antibiotic therapy	Participants receiving antibiotics for long term therapy (≥30 days) are not eligible for the study. (Antibiotics are allowed for the short term treatment (≤14 days) of an exacerbation or for short term treatment (≤14 days) of other acute infections during the study)
Systemic, oral, parenteral corticosteroids	30 days (During the study oral/systemic corticosteroids may be used for ≤14 days to treat COPD exacerbations/pneumonia) Intra-articular injections are allowed
Any other investigational drug	30 days or 5 half lives whichever is longer.

[1] (rescue albuterol/salbutamol will be provided and is permitted during the study)

6.3. Randomisation Criteria

At the end of the run-in period (Visit 2), study participants must fulfil the following additional criteria in order to be randomised into the study and enter the treatment period:

1. Compliance with run-in study medication

- Compliance with each run-in study medication will be assessed by the Investigator, any participant <80 % or >120 % compliant with any of the three inhalers (ELLIPTA, Handihaler or MDI) will be excluded.

2. COPD exacerbation or pneumonia

- Participants that experience a moderate or a severe COPD exacerbation or pneumonia during the run-in period will be excluded.

3. Changes in COPD medication

- Any participant that requires any change in COPD medication during the run-in period will be excluded. This includes a temporary change in COPD medication.

6.4. Lifestyle Restrictions

- Participants should refrain from smoking for 1 hour prior to each pulmonary function test.
- Participants should abstain from drinking beverages with high levels of caffeine such as tea and coffee for 2 hours prior to each pulmonary function test.

6.5. Pre-screening/Screening/Run-in/Randomisation Failures

A participant will be assigned a participant number at the time the informed consent is signed at Visit 0.

The study site will be responsible for reporting pre-screen failures. The following information will be collected in the electronic case report form (eCRF) for participants who are pre-screen failures: demographic information including race, age and gender; participant number; serious adverse event (SAE) information only for any SAE considered to be related to study participation.

A minimal set of information is required to ensure transparent reporting of screening/run-in/randomisation failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screening/run-in/randomization failure details, eligibility criteria, and any SAEs. Further details are provided in the study-specific eCRF completion guidelines.

For the purposes of this study, pre-screening failures, screening failures and run-in failures will be defined as follows:

Pre-screening failures: those participants that sign the informed consent document but do not have a Visit 1 (Screening) procedure.

Screening failures: those participants that complete at least Visit 1 (Screening) procedure but do not enter the run-in period. A participant who completes Visit 1 assessments and is dispensed the study medication for the run-in period is considered to have entered the run-in period.

Run-in failures: those participants that enter the run-in period but are not randomised (except those randomised in error).

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatment Groups and Duration

Participants who meet all the eligibility criteria and who have successfully completed all protocol procedures at Screening will enter the 4-week run-in period and will take budesonide/formoterol (320/9 mcg) twice daily plus tiotropium (18 mcg) once daily plus placebo via the ELLIPTA. Following the run-in period, participants who meet the randomisation criteria will be randomised (1:1) to one of the following double-blind, double-dummy treatment groups for 84 days:

Either:

FF/UMEC/VI 100/62.5/25 mcg via the ELLIPTA once daily in the morning
+ placebo to match budesonide/formoterol via MDI, two inhalations twice daily
+ placebo to match tiotropium via HandiHaler once daily in the morning

or,

Budesonide/formoterol 160/4.5 mcg via MDI, two inhalations twice daily*
+ tiotropium 18 mcg via HandiHaler once daily in the morning
+ placebo via the ELLIPTA once daily in the morning

*Participants are required to take two inhalations of budesonide/formoterol 160/4.5 mcg, via the MDI in the morning and two inhalations in the evening. The total dose is therefore 320/9 mcg twice daily.

Table 2 Dosing schedule for run-in and treatment periods

	ELLIPTA (1 inhalation)		MDI (2 puffs)		HandiHaler (1 capsule inhaled twice)	
	Active	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**
Run-in						
am		**Y**	**Y**		**Y**	
pm			**Y**			
Treatment						
Active FF/UMEC/VI						
am	**Y**			**Y**		**Y**
pm				**Y**		
Active budesonide/formoterol + tiotropium						
am		**Y**	**Y**		**Y**	
pm			**Y**			

The ELLIPTA contains 30 doses (FF/UMEC/VI or placebo) and participants will be instructed to administer one dose from their ELLIPTA once daily in the morning.

Symbicort MDI contains 120 doses: budesonide/formoterol 160mcg/4.5 mcg, two inhalations twice daily.

Tiotropium or matching placebo: Contents of 1 capsule (18 mcg) inhaled once daily using HandiHaler device. *Note*: To ensure drug delivery, two inhalations of the contents of each capsule should be performed.

Descriptions of the study treatments administered via the ELLIPTA, MDI and the Handihaler are provided in Table 3, Table 4, and Table 5, respectively.

Table 3 Description of FF/UMEC/VI Inhalation Powder in ELLIPTA™

FF/UMEC/VI	**First strip**	**Second strip**
	GW685698 blended with lactose	GW642444 and GSK573719 blended with lactose and magnesium stearate
Dosage Form	ELLIPTA 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	
Placebo to match	**First strip**	**Second strip**
	Lactose	Lactose/Magnesium Stearate
Dosage Form	ELLIPTA with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	NA	NA
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	

Table 4 Description of Symbicort MDI

Symbicort 160mcg/4.5 mcg	**MDI**
Dosage form	MDI with 120 doses
Unit dose strength	Budesonide/ Formoterol 160mcg/4.5mcg
Physical description	Suspension for inhalation
Route of administraton	Inhaled
Placebo to match Symbicort	**Placebo to match MDI**
Dosage form	MDI with 120 doses
Unit dose strength	NA
Physical description	Suspension for inhalation
Route of administration	Inhaled

Table 5 Description of Tiotropium bromide in HandiHaler

Spiriva 18 mcg	**HandiHaler**
Dosage form	Capsule
Unit dose strength	18mcg
Physical description	Hard gelatin capsule containing 18mcg tiotropium bromide blended with lactose
Route of administration	Inhaled
Placebo to match Spiriva	**HandiHaler**
Dosage form	Capsule
Unit dose strength	NA
Physical description	Hard gelatin capsule containing lactose
Route of administration	Inhaled

7.1.1. Medical Devices

- The GSK ELLIPTA medical device will be provided for use in this study.
- Other medical devices (not manufactured by or for GSK provided for use in this study) are the Handihaler and MDI.
- GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study. (see Section 9.2.10).

7.2. Dose Modification

No dose modifications are planned for this study.

7.3. Method of Treatment Assignment

Participants will be assigned to study treatment in accordance with the randomisation schedule. The randomisation code will be generated using a validated computerised system. Participants will be randomised using an Interactive Web Response System (IWRS). The study will use central-based randomisation to allocate treatments. Once a randomisation number is assigned to a participant it cannot be reassigned to any other participant in the study.

7.4. Blinding

This will be a double-blind study and the following will apply.

- The Investigator or treating physician may unblind a participant'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 participant as judged by the Investigator.
- Investigators have direct access to the participant's individual study treatment.
- It is preferred (but not required) that the Investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the participant's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the Investigator must notify GSK within 24 hours after unblinding, but without revealing the treatment assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study.
- The date and event or condition which led to the unblinding (i.e. the primary reason) will be recorded in source documentation and in the eCRF.

Should a participant's treatment assignment be unblinded then the participant may continue the assigned study treatment and be followed-up as per protocol until the completion of the Safety Follow-up assessments.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant 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 participant's treatment assignment, may be sent to Investigators in accordance with local regulations and/or GSK policy. Participants will not be withdrawn from the study.

Masking of tiotropium and placebo to tiotropium capsules

This study will use a triple-dummy design for dosing, whereby participants will be given three inhalers (ELLIPTA, MDI and Handihaler). All participants and site personnel involved in efficacy and safety assessments will be blinded to assigned treatment during the study. Tiotropium capsules have trade markings that are not present on the placebo capsules. This study has a parallel-group design which ensures the capsule type will be consistent for each participant for the duration of the study. In addition, tiotropium and placebo capsules will be closely matched in colour. Both the tiotropium and placebo blister packages will be covered with opaque over-labels with the intent of hiding the information on the tiotropium packaging. The HandiHaler dry powder inhalers will be covered with labels to mask identifying marks on the inhaler. Investigator and site personnel involved in efficacy and safety assessments will be instructed not be present when a participant administers his/her study medication at clinic visits, to guard against the possibility of personnel involved in the collection of efficacy and safety data, identifying the capsules removed from the blisters. Sites are required to have study treatment dosed, dispensed and accounted for by site personnel that are not involved in any efficacy or safety assessments.

7.5. Preparation/Handling/Storage/Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual (SRM).

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupations exposure notify the monitor, Medical Monitor and/or GSK study contact.

A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the Investigator, where is this required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

When participants are dosed at the site, they will receive study treatment under medical supervision. The date and time of each dose administered in the clinic will be recorded in the eCRF. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff.

When participants self-administer study treatment(s) at home, compliance with study treatment will be assessed through querying the participant during the site visits and recording the number of doses remaining in the ELLIPTA and MDI, and the number of capsules of tiotropium bromide (or matching placebo) dispensed and taken by each participant, in the eCRF (see SRM for details).

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

7.7. Concomitant Therapy

All COPD medications used within 3 months prior to screening and during the run-in and study treatment periods (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.

The minimum requirement is that the drug name, reason for use, dose (including unit), frequency, route and the dates of administration are to be recorded.

Note*: Study provided albuterol/salbutamol should not be recorded in the eCRF however non-study supplied albuterol/salbutamol will be recorded in the eCRF.*

Medications initiated after completion of the randomised treatment phase of the study (Visit 4) or started after discontinuation of study treatment must be recorded in the eCRF up to the safety follow-up (Visit 5).

7.7.1. Permitted Medications and Non-Drug Therapies

7.7.1.1. Permitted COPD Medications

The following COPD medications are permitted during the **run-in and the randomised treatment** periods:

- Study supplied albuterol/salbutamol MDI or nebules (must be withheld for at least 4 hours prior to spirometry testing)
- Mucolytics such as acetylcysteine
- Long term oxygen therapy. (To be eligible to enter the study at Visit 1, participants 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 run-in or treatment phases of the study). Oxygen therapy must be captured on the concomitant medication page of the eCRF. Supplemental oxygen is recommended for participants who exhibit oxyhemoglobin desaturation with rest or exertion (*e.g.* SaO2 ≤88 %)
- Maintenance phase of pulmonary rehabilitation treatment (participants are not allowed to initiate treatment during the study)
- Study provided COPD medications in the run-in and the randomised treatment period

The following **COPD medications** are permitted during the **randomised treatment** period:

- 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

- Any COPD medication deemed medically necessary for the short term treatment (≤14days) of a moderate/severe COPD exacerbation or pneumonia

7.7.1.2. Permitted Non-COPD Medications

The following non-COPD medications are permitted during the **run-in and randomised treatment** periods:

- 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 participants 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 QT interval corrected for heart rate [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)

- Cytochrome P450 (CYP)3A4 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)

7.7.2. Prohibited Medications and Non-Drug Therapies

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

Table 6 Concomitant Medications

Medication Prohibited during the randomised treatment period
Inhaled short-acting anticholinergics
Inhaled short-acting beta$_2$ agonists[1]
Inhaled short-acting anticholinergic/short-acting beta2-agonist combination products
Inhaled corticosteroids (ICS)
Inhaled corticosteroids (ICS)/Inhaled long-acting beta$_2$-agonist (LABA) combinations (eg.fluticasone/salmeterol, mometasone furoate/formoterol fumarate, budesonide/formoterol fumarate; fluticasone furoate/vilanterol
Phosphodiesterase 4 (PDE4) inhibitors (roflumilast)
LABA (e.g., indacaterol, olodaterol, salmeterol etc.)
Other LAMAs (aclidinium, glycopyrronium, umeclidinium etc.)
LAMA/LABA combinations
Theophyllines
Sodium cromoglycate and nedocromil sodium
Anti-leukotrienes
Long term antibiotic therapy[2]
Systemic, oral, parenteral corticosteroids[3]
Any other investigational drug

1. (rescue albuterol/salbutamol will be provided and is permitted during the study)
2. (Antibiotics are allowed for the short term treatment (≤14 days) of an exacerbation or for short term treatment (≤14 days) of other acute infections during the study)
3. (During the study oral/systemic corticosteroids may be used for ≤14 days to treat COPD exacerbations/pneumonia)
Intra-articular injections are allowed

Note*: Topical and ophthalmic corticosteroids, and localized corticosteroid injections (intra-articular and epidural) are allowed.*

NOTE: *All COPD medications (except for rescue albuterol/salbutamol, mucolytics and oxygen) are prohibited during the run-in and randomised treatment periods 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, 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 participant currently taking study treatment as these additional medications may*

increase the risk of overdose. If neccessary the Investigator or other health care personnel may stop the participant's study treatment temporarily (≤ 14 days) in order to treat the COPD exacerbation. Participants who require more than two consecutive 14 day courses of treatment (i.e. antibiotics or corticosteroids) should be evaluated for their continuation on study treatment by the Investigator in consultation with the GSK medical monitor.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study because other treatment options are available.

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

At the end of the treatment period (Visit 4), or after study treatment Discontinuation Visit, or withdrawal from study, participants 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 participants that successfully complete Visit 4 on study treatment and for participants that withdraw from the study. For participants that discontinue study treatment, post-treatment concomitant medication should be entered into the eCRF until they complete the visit/telephone contact at the planned Visit 5 date.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants that permanently stop study treatment should return to the clinic as soon as possible, in order to complete the Study Treatment Discontinuation Visit. The evaluations and procedures to be completed are outlined in the SoA (Section 2).

Participants that discontinue study treatment are encouraged to remain in the study and every effort should be made by the Investigator/staff to keep the participant in the study, to collect important efficacy and safety data by telephone contact. Ideally, participants should return to the clinic to complete Visit 4, to collect important spirometry data , however, if this isn't possible, this visit should also be completed by telephone. A safety follow-up phone call (Visit 5) should also be conducted 7 days after Visit 4.

The Investigator/site staff should contact the participant by telephone at the protocol designated visit time intervals to collect the following:

- SAEs
- AEs assessed as related to study participation
- AEs resulting in withdrawal from the study

- COPD exacerbations
- Concomitant medication
- Serial spirometry (Visit 4 only, if participant consents)

Participants have the right to discontinue study treatment before the end of the study. A participant may also be asked to discontinue study treatment at the Investigator's discretion.

A participant may be withdrawn from study treatment at any time. A reason for premature discontinuation of study treatment (e.g., AE, lack of efficacy, protocol deviation, Investigator discretion, consent withdrawn etc.) must be captured in the eCRF.

8.1.1. Protocol defined criteria for discontinuation of study treatment

A participant must be permanently discontinued from study treatment if any of the following stopping criteria are met, participants are however encouraged to remain in the study and complete limited assessments, as detailed in Section 8.1:

- **Liver chemistry stopping and increased monitoring criteria** have been designed to assure participant safety and evaluate liver event etiology (in alignment with the Food and Drug Administration (FDA) premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

  Discontinuation of study treatment for abnormal liver tests should be considered by the Investigator when a participant meets one of the conditions outlined in the algorithm or if the Investigator believes that it is in the best interest of the participant.

  Liver Safety Algorithms and Required Actions and Follow up Assessments can be found in Appendix 4.
- **Pregnancy**: Positive urine pregnancy test.
- **QTc Stopping Criteria**:

  Details on performing ECG assessments can be found in Section 9.4.3.

  - The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled. Safety ECGs and other non-protocol specified ECGs are an exception.
  - For example, if a participant is eligible for the protocol based on QT interval corrected for heart rate by Bazett's formula (QTcB), then QTcB must be used for discontinuation of this individual participant as well.
  - Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*.

- The QTc should be based on averaged QTc values of triplicate electrocardiograms obtained over a brief (*e.g.,* 5-10 minute) recording period.
- For this study, the following QTc stopping criteria will apply and lead to withdrawal from study treatment:
    - an increase in QTc by > 60 msec from baseline
    - or development of a QTc > 530 msec (based on an average of triplicate ECGs)

NOTE: These criteria should be based on the average QTc 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 QTc value of the three ECGs will be used to determine whether the participant should be discontinued from the study.

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.2. Rechallenge

8.1.2.1. Study Treatment Restart or Rechallenge

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

8.2. Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance or administrative reasons.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

In the event of early withdrawal from the study, every effort should be made to have the participant to return to the clinic for a Study Treatment Discontinuation Visit and Safety Follow-up, and to return all study related materials. Assessments to be performed during the Study Treatment Discontinuation Visit and the Safety Follow-up contact are described in the SOA (Section 2).

Participants that have previously discontinued study treatment (and have already completed the Study Treatment Discontinuation Visit) but decide they no longer wish to participate in the study, may withdraw from the study by contacting the site by telephone.

If the participant withdraws from the study at least 7 days after the Study Treatment Discontinuation Visit was completed, the safety follow-up contact (Visit 5) can be conducted at the time the participant notifies the site of their intention to withdraw from the study. Alternatively, the safety follow-up contact should be conducted 7 days after the Study Treatment Discontinuation Visit, if the participants consents to be contacted.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

9. STUDY ASSESSMENTS AND PROCEDURES

Investigator and site personnel involved in efficacy and safety assessments will be instructed not be present when a participant administers his/her study medication at clinic visits. Sites are required to have study treatment dose, dispensed and accounted for by site personnel that are not involved in any efficacy or safety assessments. See Section 7.4 for further details.

- Study procedures and their timing are summarized in the SoA (Section 2).
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- **No study related procedures may be performed until the informed consent form has been signed by the participant.** A Pre-Screening visit (Visit 0) is required in order to administer the informed consent before any changes are made to the participant's current medical regimen. Selection and modification of the participant's medications prior to study participation is based on the physician's judgment according to sound medical practice, principles, and each participant's

needs. A participant's treatment must not be changed merely for the purpose of enabling the participant's participation in the study.

During the Pre-Screening visit (Visit 0) the following information will be captured in the eCRF for each participant:

- Demographic information including race, age and gender
- Participant number
- Register visit in IWRS

The additional following critical baseline assessments will be conducted at Screening (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)
- 12-lead ECG
- Pulse rate, blood pressure measurements
- 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)
- CAT
- Administer and dispense run-in study treatment

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

- Smoking cessation counseling
- Register visit in IWRS
- Dispense albuterol/salbutamol

9.1. Efficacy Assessments

The timings of all efficacy assessments are specified in the SoA (Section 2).

9.1.1. Spirometry

Spirometry measurements will be obtained using spirometry equipment that meets or exceeds the minimal performance recommendations of the American Thoracic Society (ATS) [Miller, 2005]. All sites will use standardised spirometry equipment provided by an external vendor. All participants will have spirometry performed at screening (including PIFR) and each scheduled clinic visit during the treatment period. For FEV_1, FVC and PIFR 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 FEV_1 and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort.

Spirometry must be performed as follows:

- Started approximately between 6:00AM and 11:00AM.
- If applicable, after completing the health outcomes assessments (CAT should be administered first followed by SGRQ-C)
- After withholding albuterol/salbutamol for ≥4 hours.
- At Screening (Visit 1), before the morning dose of run-in medication.
- At Randomisation (Visit 2) and all treatment visits, before the morning dose of study treatment.
- Participants should refrain from smoking for 1 hour prior to each pulmonary function test.
- Participants 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 SRM.

9.1.1.1. 24-hour Serial Spirometry

24-hour serial spirometry will be performed by all participants at Randomization (Visit 2) and Day 84 (Visit 4). In addition, trough FEV_1 data will be collected pre-dose on Day 28 (Visit 3).

Serial spirometry measurements should be taken as close to the following scheduled timepoints as possible:

Pre-dose: 30 mins and 5 mins

Post-dose: 5 mins, 15 mins, 30 mins, 1 hr, 3 hrs, 6 hrs, 12 hrs, 15 hrs, 21 hrs, 23 hrs and 24 hrs

9.1.1.2. Reversibility

At Visit 1, both pre- and post-albuterol/salbutamol spirometry will be obtained. Post-albuterol/salbutamol FEV_1 and FEV_1/FVC findings will be used to determine participant eligibility.

Reversibility testing will be completed as follows: Following pre-albuterol/salbutamol spirometry (three acceptable spirometry efforts), the participant 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.

9.1.1.3. Peak Inspiratory Flow Rate (PIFR)

PIFR will be completed at Screening (Visit 1) only, approximately 10 minutes prior to the start of reversibility testing. Three acceptable spirometry efforts will be obtained.

9.1.2. SGRQ-C

The St George's Respiratory Questionnaire-Chronic Obstructive Pulmonary Disease specific (SGRQ-C) will be completed by participants at Randomisation (Visit 2), Day 28 (Visit 3) and Day 84 (Visit 4). When the SGRQ-C and CAT are collected at the same visit, the CAT should be collected prior to the SGRQ-C.

The SGRQ-C [Meguro, 2007] is a disease-specific questionnaire designed to measure the impact of respiratory disease and its treatment on a COPD participant'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 participants and has been translated and validated for use in most major languages. The SGRQ-C is derived from the original SGRQ, and produces scores equivalent to the SGRQ instrument [Meguro, 2007].

9.1.3. COPD Assessment Test (CAT)

The CAT will be completed by participants at Screening (Visit 1), Randomisation (Visit 2), Day 28 (Visit 3) and Day 84 (Visit 4). CAT should be collected prior to SGRQ-C when collected at the same 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, participants 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.

9.1.4. COPD Exacerbations

COPD exacerbation data will be collected from the start of the randomised double blind treatment period (Visit 2) until the safety follow up contact at Visit 5.

Participants will complete a paper Medical Problems worksheet to record medical problems experienced during the study. This paper worksheet must be reviewed by the Investigator (or designee) at each visit to the study site to assist in the identification of new COPD exacerbations.

All COPD exacerbations will be recorded in the exacerbation eCRF.

Every effort should be made to conduct a chest x-ray within 48 hours of identification of a moderate or severe exacerbation.

Details on COPD Exacerbation Identification, Categorization and Treatment Guidelines are provided in Appendix 5.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 6.

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment or withdraw from the study (see Section 8).

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

- Any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study up to and including the safety follow-up contact at Visit 5.
- All AEs will be collected from the start of Study Screening (Visit 1) until the safety follow-up contact at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 6. The Investigator will submit any updated SAE data to the sponsor or designee within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she

considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the sponsor or designee.

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 6.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Participants will be issued with a paper Medical Problems worksheet to record any medical problems experienced during the study. This paper worksheet will be used to assist participant recall in discussions with the Investigator (or designee), for site staff to then enter as appropriate in the eCRF.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 6.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 6 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

9.2.6. Disease-Related Outcomes – COPD Exacerbations

COPD exacerbations are an expected disease-related outcome.

COPD exacerbations should not be recorded as an adverse event, unless they meet the definition of an SAE (Appendix 6).

9.2.7. 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 (colour) or production
- Auscultatory findings of adventitious sounds (*e.g.* egophony, bronchial breath sounds, rales, etc.)
- Dyspnoea or tachypnea
- Fever (oral temperature >37.5 °C)
- Elevated white blood cells (WBC) (>10,000/mm3 or >15 % immature forms)
- Hypoxemia (HbO_2 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 participants with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in participants with COPD receiving FF/VI included current smokers, participants with a history of prior pneumonia, participants with a body mass index <25 kg/m^2 and participants with an FEV_1<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.

9.2.8. 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 medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

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

9.2.9. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until the safety follow-up contact/visit.
- If a pregnancy is reported, the Investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2.10. Medical Device Incidents (Including Malfunctions)

Medical devices (spacers/holding chambers) are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 7.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2 and Appendix 6 of the protocol.

9.2.10.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the Investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.
- The method of documenting Medical Device Incidents is provided in Appendix 7.

9.2.10.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 9.2). This applies to all participants, including those who discontinue study treatment or the study.
- The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

9.2.10.3. Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device incident.
- The Medical Device Incident Report Form will be sent to the sponsor electronically. If the eCRF is unavailable, then a paper version should be utilized.
- The same individual will be the contact for the receipt of medical device reports and SAE.

9.2.10.4. Regulatory Reporting Requirements for Medical Device Incidents

- The Investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The Investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

9.3. Treatment of 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 eCRF pages. In the event of an overdose of study treatment, 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.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2).

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Vital signs will be performed at the time points specified in the SoA table (Section 2) prior to conducting spirometry and prior to taking study treatment.
- Blood pressure (systolic and diastolic) and pulse measurements will be assessed 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.

9.4.3. Electrocardiograms

- A single 12-lead ECG and rhythm strip will be recorded after measurement of vital signs and prior to spirometry. Recordings will be made at the time-points defined in the SoA table (Section 2). All ECG measurements will be made with the participant in a supine position having rested in this position for approximately 5 minutes before each reading.
- For participants who meet the QTc, protocol defined stopping criteria, triplicate ECGs (over a brief period of time) should be performed (Section 8.1.1).
- 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.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 8 for the list of clinical laboratory tests to be performed and to the SoA (Section 2) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the Investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 8, must be conducted in accordance with the laboratory manual and the SoA (Section 2).

9.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Information regarding genetic/ pharmacogenetic (PGx) research is included in Appendix 9. The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx and genetic assessments before these can be conducted. The approval(s) must be in writing and will clearly specify approval of the PGx and genetic assessments (i.e., approval of Appendix 9).

In some cases, approval of the PGx and genetic 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 PGx and genetic assessments is being deferred and the study, except for PGx and genetic assessments, can be initiated. When PGx and genetic assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx and genetic assessments will not be conducted.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9.10. Smoking Cessation Counselling

During Visits 1 and 4, or Study Discontinuation, participants will be given smoking cessation counselling. This will include advice regarding the following:

- the health effects that smoking may cause
- the health benefits that may result with smoking cessation
- discuss anti-smoking strategies that primary care physicians may be able to provide if participants do not feel capable of discontinuing smoking
- participants may discontinue smoking at any time during the study and will not have to be withdrawn from the study if they do so.

The specific information to be discussed with each participant is provided in the SRM.

10. STATISTICAL CONSIDERATIONS

10.1. Hypotheses

The primary objective of this study is to compare FF/UMEC/VI with budesonide/formoterol + tiotropium (BUD/FOR+TIO) in COPD participants. The primary endpoint is 0- 24 hour weighted mean (WM) FEV_1 at Week 12 (Day 84). The primary analysis is the comparison of this endpoint for FF/UMEC/VI vs. BUD/FOR+TIO with mPP population. The null hypothesis is that the difference in 0-24 hour WM FEV_1 between treatment groups is less than or equal to a pre-specified non-inferiority margin Δ:

H_0: $T_1 - T_2 \leq -\Delta$

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

H_1: $T_1 - T_2 > -\Delta$

where T_1 and T_2 are the treatment means for FF/UMEC/VI and BUD/FOR+TIO, respectively.

The non-inferiority margin has been set at 50 mL.This non-inferiority margin for 0-24 hour WM FEV1 has previously been accepted by the FDA (Combivent vs Ipratropium head to head study).

If the lower bound of the two-sided 9 5% confidence interval around the (FF/UMEC/VI vs. BUD/FOR+TIO,) treatment difference is above -50 mL then FF/UMEC/VI will be considered non-inferior to BUD/FOR+TIO. Further treatment comparisons and inferences to be made based on P-values are detailed in Section 10.4.1.

10.2. Sample Size Determination

The sample size calculations use a one-sided 2.5 % significance level and an estimate of residual standard deviation (SD) for 0-24 hour WM FEV_1 of 230 mL. The estimate of SD is based on mixed models repeated measures [MMRM] analyses of past studies in COPD with 0-24 hour weighted mean as primary endpoint. A study with 620 evaluable participants for the primary analysis will have 90 % power to determine non-inferiority of FF/UMEC/VI to BUD/FOR+TIO based on 0-24 hour WM FEV_1 at Week 12 (Day 84), when the margin of non-inferiority is 50 mL and the true mean treatment difference is assumed to be 10 mL.

It is estimated that approximately 15 % of participants who are randomised will either discontinue IP or be excluded from the modified Per Protocol population at Week 12 and approximately 8 % of participants will drop out from 4-week run-in (including those not meeting randomisation criteria). Therefore, approximately 800 participants will be enrolled to 4-week run-in in order to have 732 participants to be randomised.

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Subject Enrolled (ASE)	• All participants for whom a record exists in the study database, including screen failures and any participant who was not screened but experienced an SAE between the date of informed consent and the planned date of the Screening visit.
Run-in	• All participants who are eligible at Screening and entered Run-in period.
Intent-to Treat (ITT)	• All randomised participants, excluding those who were randomised in error. A participant who is recorded as a screen or run-in failure and also randomszed will be considered to be randomised in error. Any other participant who receives a randomisation number will be considered to have been randomised. • Displays will be based on the treatment to which the participant was randomised.
Modified Per Protocol (mPP)	• All participants in the ITT Population who do not have a full protocol deviation considered to impact efficacy. • Data following a COPD exacerbation or pneumonia will be excluded from analysis due to the potential impact of the exacerbation or the medications used to treat it. • Participants with partial protocol deviations considered to impact efficacy will be included in the mPP Population but will have their data excluded from analyses from the time of deviation onwards. • This population will only be used for the primary analysis for the primary endpoint.

10.4. Statistical Analyses

10.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint, 0-24 hour WM FEV1 on Day 84 will be analyzed with mPP population using mixed model repeated measure (MMRM) analysis, including covariates such as baseline FEV1, visit, geographical region, treatment and visit by baseline interaction. A visit by treatment interaction term will also be included to allow treatment effects to be estimated at each visit separately. The variance-covariance matrix will be assumed unstructured. Baseline FEV1 is the mean of the two assessments made -30 and -5 minutes predose on Treatment Day 1. Estimated differences between FF/UMEC/VI and BUD/FOR+TIO will be presented together with 95 % confidence intervals (CIs) for the treatment difference and P-value. The same analysis will be repeated for the ITT Population. Inference to be drawn from the p-values will be as follows: • Analysis with mPP population: If the treatment comparison on the primary endpoint has a lower confidence limit below the non-inferiority margin, non-inferiority is not demonstrated. No inference will be drawn from p-values for treatment comparisons on any other endpoints. • Analysis with mPP population: If the treatment comparison on the primary endpoint has a lower confidence limit above the non-inferiority margin but below 0, non-inferiority is established but the p-value will not be used to give an indication of the strength of that noninferiority. Inference will be drawn from p-values for treatment comparisons (with ITT population) on other non-lung function endpoints,i.e, SGRQ and CAT, which will be called statistically significant if <0.05. No inference will be drawn from p-values on trough FEV1 endpoint. Analysis with ITT population: If the treatment comparison on the primary endpoint has a lower confidence limit above 0, superiority is established and the p-value can be used to give an indication of the strength of that superiority. Inference will be drawn from p-values for treatment comparisons on all other endpoints, which will be called statistically significant if <0.05. A “tipping point” sensitivity analysis of 0-24hour WM FEV1 on Day 84 will be conducted for the mPP Population. This will explore the impact of missing data by using differing assumptions regarding the mean treatment effect in participants who discontinue study treatment or have data excluded from mPP Population analyses. Assumptions will include scenarios where participants who discontinue FF/UMEC/VI have a lower treatment effect than those who discontinue BUD/FOR+TIO. The analysis results will be used to explore the conditions under which the conclusion of non-inferiority no longer holds.

Endpoint	Statistical Analysis Methods
	If superiority on primary endpoint is established with ITT population, similar "tipping point" sensitivity analysis will be conducted for the ITT population in order to explore the conditions under which the conclusion of superiority no longer holds.
Secondary	• Secondary endpoint change from baseline in trough FEV1 will be analysed for the ITT Population using a mixed model repeated measures (MMRM) analysis, including trough FEV1 recorded at each of visits, Day 2, Day 28, Day 84 and Day 85. The model will include covariates of baseline FEV1, visit, geographical region, treatment and visit by baseline interaction. A visit by treatment interaction term will also be included to allow treatment effects to be estimated at each visit separately. The variance-covariance matrix will be assumed unstructured. Estimated differences between FF/UMEC/VI and TIO will be presented together with 95 % CIs for the difference and p-values.
Other	Will be described in the reporting and analysis plan.

10.4.2. Safety Analyses

All safety analyses will be performed on the ITT Population.

Endpoint	Statistical Analysis Methods
Primary	There is no primary safety analysis.
Secondary	The following safety endpoints will be analysed descriptively by treatment group: • Incidence of adverse events • Incidence of adverse events of special interest (AESI) • Vital signs Details will be described in the reporting and analysis plan

Adverse events (AEs) will be coded using the standard GSK dictionary MedDRA, and grouped by body system. The number and percentage of participants experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be presented for each treatment group. Separate summaries will be provided for all AEs, drug related AEs, fatal AEs, non-fatal SAEs, adverse events of special interest (AESIs) and AEs leading to withdrawal. Deaths and SAEs, if applicable, will be documented in case narrative format.

10.4.3. Other Analyses

Full details of the analyses to be performed on the primary and other efficacy endpoints will be given in the Reporting and Analysis Plan (RAP).

10.4.4. Interim Analyses

No interim analysis is planned for this study.

10.4.5. Exploratory Analyses

These exploratory analyses may be provided in a separate RAP.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Atrial Fibrillation
ALT	Alanine Transaminase
ASE	All Subjects Enrolled
AST	Aspartate Transaminase
ATS	American Thoracic Society
BfS	Federal Office for Radiation Protection
BPM	Beats per minute
BMI	Body Mass Index
BUD	Budesonide
BUN	Blood Urea Nitrogen
CAT	COPD Assessment Test
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Database
CT	Computerized Tomography
CV	Cardiovascular
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of study
EXACT-RS	Exacerbations and Chronic Pulmonary Disease – Respiratory Symptoms tool
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FF	Fluticasone Furoate
FOR	Formoterol
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good clinical practice
GCSP	Global Clinical Safety and Pharmacovigilance
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin

HCP	Health Care Provider
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-Pituitary-Adrenal
HPLC	High-Performance Liquid Chromatography
HRQoL	Health related quality of life
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine Hormone-Releasing System
IWRS	Interactive Web Response System
ITT	Intent-to-Treat
Kg/m^2	Kilograms per meter squared
LABA	Long-Acting Beta-2-Agonists
LAMA	Long-Acting Muscarinic Antagonist
LRTI	Lower Respiratory Tract Infection
LTOT	Long-term oxygen therapy
MACE	Major Adverse Cardiac Event
MAOI	Monoamine Oxidase Inhibitors
MedDRA	Medicinal Dictionary for Regulatory Activities
mcg	Microgram
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDI	Metered Dose Inhaler
min	Minute
mL	Milliliter
mMRC	Modified Clinical Research Council
MMRM	Mixed-Model Repeated Measures
mPP	Modified Per Protocol
MSDS	Material Safety Data Sheet
msec	Millisecond
NA	Not Applicable
NYHA	New York Heart Association
PDE4	Phosphodiestrase 4 inhibitor
PGx	Pharmacogenetic
PRAC	Pharmacovigilance Risk Assessment Committee
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
RBC	Red Blood Cell
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SGRQ-C	St. George's Respiratory Questionnaire for COPD patients
SMQ	Standardised MedDRA Queries
SoA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reaction
TIO	Tiotropium
TQT	Thorough QT
UK	United Kingdom
ULN	Upper Limit of Normal
UMEC	Umeclidinium
US	United States
VI	Vilanterol
VT	Ventricular Tachycardia
WBC	White Blood Cell
WM	Weighted Mean
WOCBP	Woman of child-bearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ELLIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
Spiriva Handihaler
Symbicort

12.2. Appendix 2: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- 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 participants, as appropriate.
- GSK will provide the Investigator with the randomisation codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 25 years from the issue of the final Clinical Study Report/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study treatment development

12.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 7.

Table 7 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1 % per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the Participants.)*

NOTES:
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test

- Additional pregnancy testing should be performed during the treatment period (see SoA) and whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing will be performed using the test kit provided by the central laboratory and in accordance with instructions provided in its package insert

Collection of Pregnancy Information

Female participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participants will be followed to determine the outcome of the pregnancy. The Investigator will collect follow up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to GSK as described in Appendix 6. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- **Any female participant who becomes pregnant while participating in the study will immediately discontinue study medication.**

12.4. Appendix 4: Liver Safety: Required Actions and Follow-up Assessments

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria - Liver Stopping Event</th></tr>
<tr><td>Alanine Transaminase (ALT)-absolute</td><td colspan="2">ALT ≥ 8x ULN</td></tr>
<tr><td>ALT Increase</td><td colspan="2">ALT ≥ 5x ULN but <8x ULN persists for ≥2 weeks
ALT ≥ 3x ULN but <5x ULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td colspan="2">ALT ≥ 3x ULN and bilirubin ≥ 2x ULN (>35 % direct bilirubin)</td></tr>
<tr><td>International Normalized Ratio (INR)[2]</td><td colspan="2">ALT ≥ 3x ULN and INR >1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td colspan="2">ALT ≥ 5x ULN but <8x ULN and cannot be monitored weekly for ≥2 weeks
ALT ≥ 3x ULN but <5x ULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td colspan="2">ALT ≥ 3x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th colspan="2">Actions</th><th>Follow Up Assessments</th></tr>
<tr><td colspan="2">• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve , stabilize, or return to within baseline</td><td>• Viral hepatitis serology[4]
• Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5].
• Blood sample for pharmacokinetic analysis, obtained within 72 hours after last dose[6]</td></tr>
</table>

(see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol • If restart/rechallenge **not allowed per protocol** , permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Serum creatine phosphokinase and lactate dehydrogenase. • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3x ULN **and** bilirubin ≥ 2x ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3x ULN **and** bilirubin ≥ 2x ULN (>35 % direct bilirubin) or ALT ≥ 3x ULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant'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.

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

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5x ULN and <8x ULN **and** bilirubin <2x ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3x ULN and <5x ULN **and** bilirubin <2x ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant 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 participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5x ULN and <8x ULN to ≥3x ULN but <5x ULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3x ULN and bilirubin <2x ULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

References

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

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.

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

12.5.1. Guidelines for Identifying COPD Exacerbations

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

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

- Dyspnoea
- 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

Participants 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 participant 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
- If the participant 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.

Participants with worsening respiratory symptoms will be classified as having:

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

OR

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

- Other respiratory related disease

12.5.2. COPD Exacerbation Severity

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

> **Mild**: Worsening symptoms of COPD that are self-managed by the participant. 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.

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 participant experiences worsening symptoms of COPD which match the definition of an exacerbation as given above.

12.5.3. Treatment of COPD Exacerbations

All medications used for the treatment of exacerbations must be recorded in the source documents and the exacerbation page of the eCRF. All sites should follow the protocol treatment guidelines (as outlined below), but any medications deemed medically necessary may be used to treat a COPD exacerbation. However, caution is advised in using a LABA or LAMA to treat a participant 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 participant's study treatment temporarily in order to treat the COPD exacerbation.

12.5.4. Guidelines for Treatment with Corticosteroids

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

- The duration of treatment with oral/systemic corticosteroids should be ≤14 days (dose and type according to local practice)
- The duration of treatment with oral/systemic corticosteroids should not exceed 14 days unless approval is given by the sponsor or representative

- Any course of oral/systemic corticosteroids started within 7 days of finishing a previous course will be considered as treatment for a single exacerbation

12.5.5. Guidelines for Treatment with Antibiotics

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

- The duration of treatment with antibiotics should 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 for participants to continue on study treatment, 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 participant experiences worsening of symptoms of COPD

12.5.6. Onset and Resolution of COPD Exacerbations

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

The date of onset is the first day (of at least 2 consecutive days) of worsening symptoms.

The date of resolution should be based on when the Investigator and/or participant 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 participant evaluation.

12.5.7. Guideline for assessing multiple mild exacerbations

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

12.5.8. Guideline for assessing exacerbations that increase in severity

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

12.6. Appendix 6: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • 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 study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology and clinical chemistry) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • 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 before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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 it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses 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. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety

assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which 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.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant 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 outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent disability/incapacity

- 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.   • The Investigator will then record all relevant AE/SAE information in the eCRF.

- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to GSK. However, **it is very**

important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK**.**

- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The Investigator or medically-qualified sub-Investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the assigned SAE contact by telephone.

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

SAE Reporting to GSK via Paper CRF

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

12.7. Appendix 7: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition and Documentation of Medical Device Incidents

Definitions of a Medical Device Incident

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

Medical Device Incident Definition
• A medical device incident is 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 participants/user/other person or to a serious deterioration in his/her state of health.
• Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

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

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Foetal distress, foetal death, or any congenital abnormality or birth defects

Examples of incidents
• A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A participant's study treatment is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. • A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the Investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE eCRF page will be completed as described in Appendix 6. • The form will be completed as thoroughly as possible and signed by the Investigator before transmittal to the GSK. • It is very important that the Investigator provides his/her assessment of causality (relationship to the medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

12.8. Appendix 8: Clinical Laboratory Tests

- All protocol required laboratory assessments (haematology and clinical chemistry) must be conducted in accordance with the Laboratory Manual, and Protocol SoA (Section 2). Laboratory requisition forms must be completed and samples must be clearly labelled with the participant number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Laboratory Manual. Reference for all safety parameters will be provided to the site by the laboratory responsible for the assessments.
- All blood samples which will be taken pre-dose, will be sent to a central laboratory for analysis (details provided in the Laboratory Manual). Standard reference ranges will be used.
- If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eCRF.
- Refer to the Laboratory Manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6.1 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 8 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: Mean Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin (MCH)	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [nonfasting]	Calcium	Alkaline phosphatase	
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum / urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) The results of each test must be entered into the CRF.			

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7 All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 x ULN (>35 % direct bilirubin) or ALT ≥3 x ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

12.9. Appendix 9: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a 6 mL blood sample will be collected for DNA analysis.
- DNA samples may be used for research related to study treatment or COPD and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to study treatment or study treatments of this drug class and indication. Genetic research may consist of the analysis of one or more candidate genes (including but not limited to: *PIK3CD*, *PIK3CA*, *IL10*, *CHRNA3*, *CHRNA5*, *DNAH5*, *SUMF1*, and *CELSR1*) or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study treatment or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study treatment (or study treatments of this class) or indication continues but no longer than 15 years after the last participant last visit or other period as per local requirements.
- **Withdraw Process:** If a participant withdraws consent, the Investigator must complete the Genetics Sample Destruction Request Form, which will be provided to the site in the Investigator Site File.
- **Destruction Process:** After the specified storage period of 15 years or on withdrawal of consent, samples will be destroyed by incineration. Samples that are sent for testing to vendors are returned or destroyed as part of the formal agreement and a full record of chain of custody is maintained. A laboratory information management system (LIMS) is used to track and identify samples for destruction.

12.10. Appendix 10: Country-specific requirements

There are currently no country specific requirements.

12.11. Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

TITLE PAGE

Protocol Title: A Phase IV, 12-week, randomised, double-blind, triple dummy study to compare single inhaler triple therapy, fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) with multiple inhaler therapy (budesonide/formoterol plus tiotropium) based on lung function and symptoms in participants with chronic obstructive pulmonary disease

Protocol Number: 207608

Short Title: A randomised study, comparing FF/UMEC/VI single inhaler triple therapy, versus multiple inhaler therapy (budesonide/formoterol plus tiotropium) in participants with chronic obstructive pulmonary disease

Compound Number: GSK573719+GW642444+GW685698 (GSK2834425)

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s): IND number 114873 and EudraCT number 2017-001149-28

Approval Date: 11-OCT-2017

SPONSOR SIGNATORY:

PPD

David A. LiPPPD
Project Physician Leader

11 - oct - 17
Date

PPD

TABLE OF CONTENTS

PAGE

1. SYNOPSIS

Protocol Title: A Phase IV, 12-week, randomised, double-blind, triple dummy study to compare single inhaler triple therapy, fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) with multiple inhaler therapy (budesonide/formoterol plus tiotropium) based on lung function and symptoms in participants with chronic obstructive pulmonary disease

Short Title: A randomised study, comparing FF/UMEC/VI single inhaler triple therapy, versus multiple inhaler therapy (budesonide/formoterol plus tiotropium) in participants with chronic obstructive pulmonary disease

Rationale: Chronic obstructive pulmonary disease (COPD) guidelines advocate the use of long-acting muscarinic receptor antagonists (LAMA) added to the combination of inhaled corticosteroids plus a long-acting β_2-adrenergic receptor agonist (LABA) as second line therapy for the most advanced patients with significant symptoms and a high risk of exacerbations. Regular treatment with ICS containing regimens 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 forced expiratory flow in 1 second (FEV_1) <60% predicted.

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 United States (US) 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. A study in the United Kingdom (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. In the four-year long term safety study conducted with tiotropium, 46% of patients were receiving a concurrent fixed combination of ICS/LABA in addition to tiotropium.

A number of studies have assessed the use of an 'open' triple therapy of fluticasone propionate/salmeterol or budesonide/formoterol (ICS/LABA) with 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. These studies have also shown that the number and type of reported adverse events (AE) 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.

GlaxoSmithKline (GSK) is currently developing a once-daily 'closed' triple therapy of a ICS/LAMA/LABA combination [fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) (100/62.5/25 mcg)] in a single inhaler, with the aim of providing a new treatment option for the management of symptomatic COPD patients at risk of exacerbations which will reduce the exacerbation frequency, allow for a reduced burden

of polypharmacy, convenience, and increase the potential for improvement in lung function, HRQoL and symptom control over established dual/monotherapies.

GSK conducted a Phase III study comparing once-daily FF/UMEC/VI to twice-daily Symbicort MDI (budesonide/formoterol) 400/12 mcg in COPD participants that were symptomatic and at risk of an exacerbation despite receiving maintenance therapy (CTT116853). FF/UMEC/VI demonstrated statistically significant improvements in trough FEV_1, a statistically significant reduction in the annual rate of moderate or severe COPD exacerbations, and a statistically significant reduction of COPD symptoms (using Exacerbations and Chronic Pulmonary Disease – Respiratory Symptoms [E-RS]) when compared to budesonide/formoterol. Additionally, clinically meaningful improvements from baseline in St. George's Respiratory Questionnaire (SGRQ) total score were observed, with a statistically significant improvement compared to budesonide/formoterol. This Phase III study provided compelling efficacy data compared with an established ICS/LABA and demonstrated the clinical value of single inhaler triple-therapy compared to ICS/LABA therapy in patients with COPD.

The primary purpose of this study is to evaluate lung function and HRQoL after 84 days of treatment with a single inhaler triple therapy combination of FF/UMEC/VI (100/62.5/25 mcg) once daily via the ELLIPTA™ compared with a multiple inhaler combination therapy of Symbicort Metered Dose Inhaler (MDI) (budesonide/formoterol 320/9 mcg) twice daily plus Spiriva HandiHaler (tiotropium 18 mcg) once daily. The study will inform healthcare providers that patients can be effectively and safely switched to FF/UMEC/VI single inhaler therapy from a multiple inhaler triple therapy regimen of Symbicort MDI and Spiriva Handihaler.

Objectives and Endpoints:

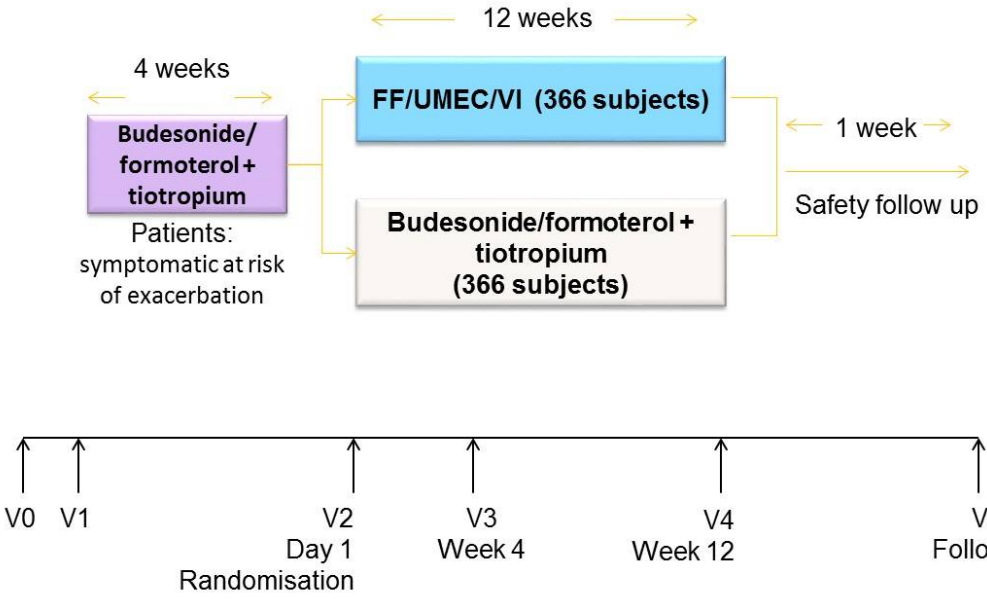
Objectives	Endpoints
Primary	
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on lung function	**Primary** Weighted mean change from baseline in FEV_1 over 0-24 hours at Week 12
	Secondary • Change from baseline in trough FEV_1 on Day 2, Day 28, Day 84 and Day 85 • Weighted mean change from baseline in FEV_1 over 0-24 hours on Day 1

Objectives	Endpoints
Other	
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on Health Status	• Proportion of responders based on the St George's Respiratory Questionnaire (SGRQ) Total Score at Week 4 and Week 12 • Change from baseline in SGRQ Total Score at Week 4 and Week 12
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on Health Status	• Proportion of responders based on the COPD Assessment Test (CAT) Total Score at Week 4 and Week 12 • Change from baseline in CAT Total Score at Week 4 and Week 12
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on COPD exacerbations	Moderate or severe exacerbation event
• Assess how inspiratory airflow limitation affects ability to use the ELLIPTA	Peak Inspiratory Flow Rate (PIFR) at Screening (Week -4)
Safety	
• To evaluate the safety profile of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium over 12 weeks of treatment	• Incidence of adverse events • Vital signs

Overall Design:

This is a Phase IV, 12-week, randomised, double-blind, triple-dummy, parallel group, multicentre study evaluating single inhaler triple therapy (FF/UMEC/VI) once daily via the ELLIPTA, compared to multiple inhaler triple combination therapy budesonide/ formoterol MDI (320/9 mcg) twice daily plus once daily tiotropium (18 mcg), in participants with COPD.

Study design schema



Eligible participants at Screening (V1) will be current or former smokers, with an established clinical history of COPD, receiving daily maintenance COPD therapy for at least 3 months, with a post-bronchodilator FEV1 of <50% predicted (or <80% predicted with a documented history of at least 2 moderate or 1 severe [hospitalised] exacerbation in the last 12 months) and a CAT score of ≥10 at Visit 1 and at Visit 2. Participants will be requested to participate in the study for approximately 17 weeks, consisting of a 4-week run-in period, 12-week treatment period and a 1-week follow-up period.

- **Pre-screening:** Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0), including the informed consent process, must be completed prior to any protocol-required changes to a participant's usual COPD treatment and the initiation of any Visit 1 procedures. Participants will continue treatment with their regular (i.e. pre-study) COPD medication(s) during the pre-screening period, except for medications that are prohibited within a specified time interval prior to Visit 1.
- **Screening/run-in:** Eligible participants will be allowed to continue their usual COPD medications until the day before Screening, Visit 1. On the morning of the Screening Visit participants will refrain from taking their morning dose of their usual COPD medications. Participants who meet all of the eligibility criteria at Visit 1, will enter the 4-week run-in period during which they will discontinue all existing COPD medications and receive their run-in treatment: budesonide/formoterol (320/9 mcg) twice daily plus tiotropium (18 mcg) once daily plus placebo via the ELLIPTA. Participants will not use any other COPD medications (except for those allowed per protocol). Participants will be provided with short-acting albuterol/salbutamol to be used on an as-needed basis (rescue medication) throughout the study. At Screening, each participant will be instructed on the proper use of the ELLIPTA, MDI and HandiHaler and will

self-administer their first doses of their run-in treatment during the Screening Visit. On the morning of the other study visits (Visit 2 onwards), participants will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel.

- **Randomisation/treatment:** On the day before the Randomisation Visit (Visit 2), participants will take their last dose of run-in treatment and will not use any other COPD medications (except for those allowed per protocol) 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.

  At Visit 2 (the Randomisation Visit), participants who meet all of the randomisation criteria will discontinue their run-in treatments and will be randomised in 1:1 ratio to receive one the following double-blind study treatments for 84 days:

  Either:

  FF/UMEC/VI 100/62.5/25 mcg via the ELLIPTA once daily in the morning
  + placebo to match budesonide/formoterol via MDI, two inhalations twice daily
  + placebo to match tiotropium via HandiHaler once daily in the morning

  or,

  Budesonide/formoterol 320/9 mcg via MDI, twice daily*
  + tiotropium 18mcg via HandiHaler once daily in the morning
  + placebo via the ELLIPTA once daily in the morning

  *Participants are required to take two inhalations of budesonide/formoterol 160/4.5 mcg, via the MDI in the morning and two inhalations in the evening. The total dose is therefore 320/9 mcg twice daily.

  At Visit 2 participants will refrain from taking their morning doses of run-in study medication and will self-administer study treatment at the clinic, when instructed to do so. Participants will remain at the clinic for at least 24 hours, for serial spirometry assessments.

  On the morning of Visits 3 and 4, participants will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel. At Visits 3, and 4 participants will self-administer study treatment whilst at the clinic. Participants will take their last doses of study treatment in the clinic on Day 84 (Visit 4, when instructed to do so by clinic personnel), and continue to remain at the clinic until at least 24 hours after their last morning dose, for their clinical assessments, which include serial spirometry assessments.On non-clinic visit days participants are expected to take their study treatment at home each day in the morning and in the evening at approximately the same time, as directed by the clinic.

- **Safety/follow-up:** A safety follow-up telephone contact or clinic visit (Visit 5) will be conducted approximately 7 days after the participant completes all of the

protocol-defined procedures for Visit 4/End of Study (EOS) or, if applicable, the Study Treatment Discontinuation Visit.

Participants that permanently discontinue study treatment are not required to withdraw from the study. If for any reason a participant must permanently discontinue study treatment, every effort should be made by the Investigator/staff to keep the participant in the study and complete all remaining protocol specified clinic visits. However, a participant may voluntarily withdraw from participation in this study at any time. The Investigator may also, at his or her discretion, withdraw a participant from further study participation. Participants who are withdrawn from the study will not be replaced.

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

Number of Participants:

Approximately 800 participants with advanced COPD will enter the run-in period, in order to randomise approximately 732 participants, in order to achieve an estimated 620 evaluable participants in modified per-protocol (mPP) population at Week 12, assuming 10 % premature discontinuation of study treatment and 5% protocol deviation.

Approximately 80 centres globally will be required to recruit participants in the study.

Treatment Groups and Duration:

Participants who meet all the eligibility criteria and who have successfully completed all protocol procedures at Screening will enter the 4-week run-in period and will take budesonide/formoterol (320/9 mcg) twice daily plus tiotropium (18 mcg) once daily plus placebo via the ELLIPTA. Following the run-in period, eligible participants will be randomised (1:1) to one of the following double-blind, triple-dummy treatment groups for 84 days:

Either:

- FF/UMEC/VI 100/62.5/25 mcg via the ELLIPTA once daily in the morning

  + placebo to match budesonide/formoterol via MDI, two inhalations twice daily
  + placebo to match tiotropium via HandiHaler once daily in the morning

or,

- Budesonide/formoterol 160/4.5 mcg via MDI, two inhalations twice daily*

  + tiotropium 18mcg via HandiHaler once daily in the morning

  + placebo via the ELLIPTA once daily in the morning

*Participants are required to take two inhalations of budesonide/formoterol 160/4.5 mcg, via the MDI in the morning and two inhalations in the evening. The total dose is therefore 320/9 mcg twice daily.

Dosing schedule for run-in and treatment periods

	ELLIPTA (1 inhalation)		MDI (2 puffs)		HandiHaler (1 capsule inhaled twice)	
	Active	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**
Run-in						
am		**Y**	**Y**		**Y**	
pm			**Y**			
Treatment						
FF/UMEC/VI group						
am	**Y**			**Y**		**Y**
pm				**Y**		
Budesonide/formoterol + tiotropium group						
am		**Y**	**Y**		**Y**	
pm			**Y**			

The ELLIPTA contains 30 doses (FF/UMEC/VI or placebo) and participants will be instructed to administer one dose from their ELLIPTA once daily in the morning.

Symbicort MDI contains 120 doses: budesonide/formoterol 160/4.5 mcg, two inhalations twice daily.

Tiotropium: Contents of 1 capsule (18 mcg) inhaled once daily using HandiHaler device. *Note*: To ensure drug delivery, two inhalations of the contents of each capsule should be performed.

Key Elements of Analysis Plan:

The null hypothesis is that the difference in 0-24 hour Weighted Mean (WM) FEV_1 between treatment groups is less than or equal to a pre-specified non-inferiority margin Δ:

H_0: $T_1 - T_2 \leq -\Delta$

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

H_1: $T_1 - T_2 > -\Delta$

where T_1 and T_2 are the treatment means for FF/UMEC/VI and budesonide/formoterol + tiotropium (BUD/FOR+TIO), respectively.

The non-inferiority margin has been set at 50 mL.

The primary analysis population will be the modified per-protocol (mPP) population, comprising all participants randomised to treatment except those randomised in error, who do not have a full protocol deviation or other event considered to impact efficacy.

The primary analysis will be performed for mPP population using on-treatment data. The primary analysis will evaluate the endpoint of 0-24 hour WM FEV_1 on Day 84 using a mixed model repeated measure (MMRM) analysis, including covariates baseline FEV_1, visit, geographical region, treatment and visit by baseline interaction. A visit by treatment interaction term will also be included to allow treatment effects to be estimated at each visit separately. The variance-covariance matrix will be assumed unstructured. Baseline FEV_1 is the mean of the two assessments made -30 and -5 minutes pre-dose on Treatment Day 1.

Estimated differences between FF/UMEC/VI and BUD/FOR+TIO will be presented together with 95% confidence intervals (CIs) for the treatment difference and p-value.

Inference to be drawn from the p-values will be as follows:

- Analysis with mPP population: If the treatment comparison on the primary endpoint has a lower confidence limit below the non-inferiority margin, non-inferiority is not demonstrated. No inference will be drawn from p-values for treatment comparisons on any other endpoints.

- Analysis with mPP population: If the treatment comparison on the primary endpoint has a lower confidence limit above the non-inferiority margin but below 0, non-inferiority is established but the p-value will not be used to give an indication of the strength of that non-inferiority. Inference will be drawn from p-values for treatment comparisons (with Intent-To-Treat [ITT] population) on other non-lung function endpoints, ie, SGRQ and CAT which will be called statistically significant if <0.05. No inference will be drawn from p-values on trough FEV1 endpoint.

- Analysis with ITT population: If the treatment comparison on the primary endpoint has a lower confidence limit above 0, superiority is established and the p-value can be used to give an indication of the strength of that superiority. Inference will be drawn from p-values for treatment comparisons on all other endpoints, which will be called statistically significant if <0.05.

A “tipping point” sensitivity analysis of 0-24 hour WM FEV1 on Day 84 will be conducted for the mPP Population. This will explore the impact of missing data by using differing assumptions regarding the mean treatment effect in participants who discontinue study treatment or have data excluded from mPP Population analyses. Assumptions will include scenarios where participants who discontinue FF/UMEC/VI have a lower treatment effect than those who discontinue BUD/FOR+TIO. The analysis results will be used to explore the conditions under which the conclusion of non-inferiority no longer holds.

If superiority on primary endpoint is established with ITT population, similar “tipping point” sensitivity analysis will be conducted for the ITT population in order to explore the conditions under which the conclusion of superiority no longer holds.

The details of the statistical analysis methods for the secondary efficacy endpoints will be provided in the Reporting and Analysis Plan (RAP).

2. SCHEDULE OF ACTIVITIES (SOA)

Protocol Activity	Pre-Screen	Screen		Treatment		Follow-up	
	Visit 0	Visit 1 Screen/ Run-in	Visit 2 Randomisation	Visit 3	Visit 4	Study Treatment Discontinuation Visit	Visit 5 Safety Follow-up Contact
Study Day	-56 to -28	Day -28	Day 1	Day 28	Day 84-85		Day 91
Week	-8 to -4	-4	0	4	12		13
Window		-3/+8d (Day -31 to -21)		-4/+2d (Day 24 to 30)	-4/+2d (Day 80 to 86)		-1/+4d (Day 90 to 95)
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
Inclusion/Exclusion Criteria		X	X				
Smoking history & status		X			X	X	
Smoking Cessation Counselling		X				X	
Register Visit in IWRS	X	X	X	X	X	X	X
CAT [d]		X	X	X	X		
SGRQ-C[d]			X	X	X		
Reversibility Testing and PIFR [e]		X					
Trough FEV1				X			
24h serial spirometry [f]			X		X		
Inhalation device training		X	X				
Exacerbation Assessment		X	X	X	X	X	X
Physical examination [g]		X			X	X	
Adverse Events Assessment		X	X	X	X	X	X
Vital signs [h]		X			X	X	
ECG		X					
Chest X-ray [i]		X					
Oropharyngeal examination		X	X	X	X	X	
Blood Draw for Genetics research [j]			X				
Hematology/biochemistry [k]		X					
Urine Pregnancy Test [l]		X			X	X	
Hepatitis B and C tests		X					
Dispense run-in treatment		X					
Dispense study treatment			X	X			
Administer run-in treatment in clinic [m]		X					

Protocol Activity	Pre-Screen	Screen		Treatment		Follow-up	
	Visit 0	Visit 1 Screen/ Run-in	Visit 2 Randomisation	Visit 3	Visit 4	Study Treatment Discontinuation Visit	Visit 5 Safety Follow-up Contact
Study Day	**-56 to -28**	**Day -28**	**Day 1**	**Day 28**	**Day 84-85**		**Day 91**
Week	**-8 to -4**	**-4**	**0**	**4**	**12**		**13**
Window		**-3/+8d (Day -31 to -21)**		**-4/+2d (Day 24 to 30)**	**-4/+2d (Day 80 to 86)**		**-1/+4d (Day 90 to 95)**
Administer study treatment in clinic [n]			X	X	X		
Assess run-in treatment compliance			X				
Assess study treatment compliance				X	X	X	
Collect study treatment				X	X	X	
Dispense albuterol/salbutamol		X	X	X	X		
Collect albuterol/salbutamol			X	X	X	X	
Dispense paper Medical Problems worksheet	X	X	X	X	X		
Review paper Medical Problems worksheet		X	X	X	X	X	X

a. Informed consent must be conducted at the Pre-screen Visit prior to performing any study procedures including the changing or withholding of medications. The informed consent may be given at Screening Visit 1 if the participant does not take or has not taken any protocol excluded medications. The Pre-screen and Screening Visits can occur on the same day.
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. Participants do not have to participate in the genetic research part of this study, it is optional.
c. Demography may be captured at either the Pre-screen Visit or Screening Visit (for participants who do not have a Pre-screen Visit).
d. SGRQ-C and CAT will be completed electronically and should be conducted in the following order and before other study assessments: CAT, SGRQ-C.
e. At Screening Visit 1 PIFR spirometry and both pre and post-bronchodilator spirometry will be conducted. PIFR will be assessed 10 minutes prior to pre-bronchodilator spirometry. Participants are required to withhold their usual morning doses of their COPD meds including rescue albuterol/salbutamol for the protocol designated period prior to PIFR spirometry and reversibility testing.
f. Serial spirometry at Visit 2 and Visit 4 will be done pre-dose at 30 mins and 5 mins and post dose at 5 mins, 15 mins, 30mins,1hr, 3hrs, 6hrs, 12hrs, 15hrs, 21hrs, 23hrs, 24hrs. Participants that discontinue study treatment but remain in the study will complete serial spirometry at Week 12, if they consent to do so.
g. Physical examination may include height, weight, blood pressure and temperature.
h. Vital signs, including blood pressure and pulse must be performed prior to spirometry and prior to taking morning dose of study treatment.
i. Chest X-ray is required at Screening (or historical x-ray obtained within 3 months prior to Screening) and at any time there is a suspected pneumonia or a mod/severe exacerbation.
j. Genetic consent must be obtained prior to obtaining a blood sample. The sample can be collected at any time after Visit 2, providing consent is obtained.
k. Hematology and chemistry panels will include full and differential blood count and liver chemistry.
l. All female participants of child bearing potential will have a urine pregnancy test at Visits 1, 4 and Study Treatment Discontinuation Visit (if applicable).
m. Participants must withhold their morning dose of existing COPD medication or study treatment and not take their run-in treatment until instructed to do so by study staff.

n. Participants must withhold their morning dose of study treatment at each clinic visit and not take their study treatment until instructed to do so by study staff.

3. INTRODUCTION

3.1. Study Rationale

Chronic obstructive pulmonary disease (COPD) guidelines advocate the use of long-acting muscarinic receptor antagonists (LAMA) added to the combination of inhaled corticosteroids (ICS) plus a long-acting β_2-adrenergic receptor agonist (LABA) as second line therapy for the most advanced patients with significant symptoms and a high risk of exacerbations. Regular treatment with Inhaled Coricosteroid (ICS) containing regimens 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 forced expiratory flow in 1 second (FEV_1) <60 % predicted [Aaron, 2007; Cazzola, 2007; Hanania, 2012; Jung, 2012; Siler, 2015; Welte, 2009].

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 United States (US) 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 United Kingdom (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, 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 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; Siler, 2015; Welte, 2009]. These studies have also shown that the number and type of reported adverse events (AE) 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.

GlaxoSmithKline (GSK) is currently developing a once-daily 'closed' triple therapy of a ICS/LAMA/LABA combination [fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) (100/62.5/25 mcg)] in a single inhaler, with the aim of providing a new treatment option for the management of symptomatic COPD patients at risk of exacerbations which will reduce the exacerbation frequency, allow for a reduced burden of polypharmacy, convenience, and increase the potential for improvement in lung function, HRQoL and symptom control over established dual/monotherapies.

GSK conducted a Phase III study comparing once-daily FF/UMEC/VI to twice-daily Symbiocort MDI (budesonide/formoterol) 400/12 mcg in COPD participants that were

symptomatic and at risk of an exacerbation despite receiving maintenance therapy (CTT116853). FF/UMEC/VI demonstrated statistically significant improvements in trough FEV_1, a statistically significant reduction in the annual rate of moderate or severe COPD exacerbations, and a statistically significant reduction of COPD symptoms (using Exacerbations and Chronic Pulmonary Disease – Respiratory Symptoms [E-RS]) when compared to budesonide/formoterol. Additionally, clinically meaningful improvements from baseline in St. George's Respiratory Questionnaire (SGRQ) total score were observed, with a statistically significant improvement compared to budesonide/formoterol [Lipson, 2017]. This Phase III study provided compelling efficacy data compared with an established ICS/LABA and demonstrated the clinical value of single inhaler triple-therapy compared to ICS/LABA therapy in patients with COPD.

The primary purpose of this study is to evaluate lung function and HRQoL after 84 days of treatment with a single inhaler triple therapy combination of FF/UMEC/VI (100/62.5/25 mcg) once daily via the ELLIPTA™ compared with a multiple inhaler combination therapy of Symbicort Metered Dose Inhaler (MDI) (budesonide/formoterol 320/9 mcg) twice daily plus Spiriva HandiHaler (tiotropium 18 mcg) once daily. The study will inform healthcare providers that patients can be switched to FF/UMEC/VI single inhaler therapy from a multiple inhaler triple therapy regimen of Symbicort MDI and Spiriva Handihaler.

3.2. Background

Chronic obstructive pulmonary disease is a progressive disease characterised by increasing obstruction to airflow and the progressive development of respiratory symptoms including chronic cough, increased sputum production, dyspnoea 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, using the ABCD assessment tool, which aimed to more comprehensively assess disease severity and guide therapy choice, ultimately improving COPD management. A 2013 update included an additional criterion to characterise patients that have had a hospitalised exacerbation as high risk, regardless of GOLD status [GOLD, 2013].

GOLD released a revised guideline in 2017 that separates spirometric grades from the ABCD assessment tool (Table 1) [GOLD, 2017].

Table 1 GOLD 2017 Classification

GOLD ABCD Classification	Risk Class Determinant	Symptom Category Determinant*
A: Low risk, less symptoms	≤1 exacerbation, prior year	mMRC <2; CAT <10
B: Low risk, more symptoms	≤1 exacerbation, prior year	mMRC ≥2; CAT ≥10
C: High risk, less symptoms	≥2 exacerbations, prior year *OR* 1 leading to hospitalization, prior year	mMRC <2; CAT <10
D: High risk, more symptoms	≥2 exacerbations, prior year *OR* 1 leading to hospitalisation, prior year	mMRC ≥2; CAT ≥10
* - Symptomatic category determined by either Modified Clinical Research Council (mMRC) or COPD Assessment Test (CAT) score.		
GOLD Airflow Limitation	**Severity**	**FEV_1 (% predicted)**
GOLD 1	Mild	≥80
GOLD 2	Moderate	50 - 79
GOLD 3	Severe	30 - 49
GOLD 4	Very Severe	<30

The GOLD, 2017 guidelines also outlined suggested management strategies for COPD based upon disease severity, including escalation as well as de-escalation strategies. For milder patients (GOLD Group A), the guidelines encourage active risk reduction (e.g., smoking cessation and influenza vaccination) with the addition of bronchodilators. 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 [GOLD, 2017]. Long-acting bronchodilators (LAMAs or LABAs) have been shown to relieve symptoms, increase exercise capacity, improve health-related quality of life and reduce COPD exacerbations to a greater extent than short acting β_2 adrenergic receptor agonists. For advanced cases, or those with repeated exacerbations, the incorporation of ICS or triple therapy, is recommended.

3.3. Benefit/Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2834425 (FF/UMEC/VI) can be found in the Investigator's Brochure (IB). The safety information for budesonide/formoterol and tiotropium can be found in the authorised product label. The current safety profile for FF/UMEC/VI (100/62.5/25 mcg), based on data available to date, is consistent with the pharmacological classes of the components. The following section outlines the risk assessment and mitigation strategy for this protocol.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK2834425 (FF/UMEC/VI), GSK573719 (UMEC), GW642444 (vilanterol), GW685698 (fluticasone furoate)		
Pneumonia in participants with COPD	Pneumonia is a class concern for any ICS-containing product for the treatment of COPD. In a study (CTT116853) [Lipson, 2017] in 1810 randomised COPD participants treated with FF/UMEC/VI or budesonide/formoterol (BUD/FOR) for up to 24 weeks (Intent-To-Treat [ITT] Population), or up to 52 weeks (subset of 430 participants; EXT Population), the incidence of events in the pneumonia adverse event of special interest (AESI) group was 2.2 % and 0.8 % for FF/UMEC/VI and BUD/FOR respectively in the ITT Population, and 1.9 % and 1.8 % for FF/UMEC/VI and BUD/FOR respectively in the EXT Population. There was one fatal case of pneumonia in a participant who received FF/UMEC/VI. The incidence of pneumonia with FF/UMEC/VI in this study was in line with the incidence of pneumonia seen in 24 week studies with FF/VI (<1-2 % with FF/VI 100/25) and less than that observed in 52 week exacerbation studies with FF/VI (6 % with FF/VI 100/25) [Dransfield, 2013]. Similarly, the incidence of pneumonia with	- Participants will be informed of the risk in the informed consent. - Investigators are informed of the risk in the IB. Investigators will be instructed to remain vigilant for the possible development of pneumonia in participants with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. For suspected cases of pneumonia, investigators will be encouraged to arrange a chest X-ray within 48 hours of diagnosis [Section 12.5.2] and to treat appropriately. - Appropriate exclusion criteria as specified in Section 6.2 of the protocol - Instream review of blinded AE/SAE reports. - All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable) as specified in

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	FF/UMEC/VI was less than that observed in a 12-month exacerbation trial with BUD/FOR (6.4 %) [Sharafkhaneh, 2012]. Prior studies with FF/VI have demonstrated risk factors associated with a higher risk of pneumonia in participants with COPD (e.g., advanced age, poor lung function, low body mass index (BMI), current smoking, and a prior history of pneumonia) [Crim, 2009]. These risk factors were present in some participants with pneumonia in study CTT116853 with FF/UMEC/VI; however, the low number of pneumonia events reported in the study precludes drawing any definite conclusions about risk factors. These risk factors should be taken into consideration when using an ICS in participants with COPD. Pneumonia risk will be important in the benefit-risk assessment for FF/UMEC/VI in COPD participants, hence a robust risk mitigation strategy is being proposed. The Pharmacovigilance Risk Assessment Committee (PRAC) recently conducted an Article 31 review to evaluate the risk of pneumonia with use of ICSs in patients with COPD. The PRAC review confirmed that COPD patients treated with inhaled corticosteroids are at increased risk of pneumonia; however the Committee's view was that the benefits of ICSs continue to outweigh their risks. The PRAC also looked	Section 9.2.7. - Chest X-ray read required at baseline and whenever a participant has suspected pneumonia or mod/severe exacerbations during the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	whether there were any differences in the risk of pneumonia between these products, and did not find conclusive evidence of such difference.	
Decreased bone mineral density and associated fractures	Reduction in bone density, and the subsequent risk of fractures, is a known potential risk with corticosteroids. There may be a modest increase in risk of fracture among participants with COPD treated with ICS; but, the results are not consistent across individual studies [Christensson, 2008; Lehouck, 2011; Weldon, 2009]. In study CTT116853, the incidence of events in the decreased bone mineral density and associated fractures AESI group was low, with an incidence of 0.4 % and 0.7 % in the FF/UMEC/VI and BUD/FOR treatment groups respectively in the ITT Population up to 24 weeks, and 0.5 % in both treatment groups in the EXT Population up to 52 weeks. The majority of the fractures in both treatment groups were traumatic in nature.	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB. - Instream review of blinded AE/SAE reports.
Adrenal suppression	Oral corticosteroids are known to have an effect on the hypothalamic-pituitary-adrenal (HPA) axis leading to a reduction in cortisol production. Due to the low dose and low systemic exposure with inhaled corticosteroids, this potential effect is not	- Investigators are informed of the risk in the IB. - Instream review of blinded AE/SAE reports.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	clear, nor is the possible impact of any change in cortisol. The effect of FF/UMEC/VI on cortisol levels has not been studied. In study CTT116853, no events were reported in the adrenal suppression AESI group for FF/UMEC/VI and BUD/FOR. With respect to the FF/VI clinical development program, a formal HPA study, using 24 hour serum cortisol measurements was performed. In addition, multiple studies with COPD (and asthma) participants monitored urinary cortisol. These studies did not show a clinically relevant effect of FF/VI100/25 on the HPA axis. Participants that have received oral corticosteroids, particularly those who have received significant amounts for long periods of time, will be more susceptible to this risk of adrenal suppression. The systemic exposure of FF is very low compared to that of oral corticosteroids, so any concurrent effect will be negligible. The proposed dose (100 mcg) of inhaled FF in this study is unlikely to lead to clinically significant changes in the treatment period since systemic exposure is low.	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Corticosteroid Associated Eye Disorders	Systemic ocular effects (*e.g.* cataract and glaucoma) may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. However, these effects are much less likely to occur with ICS compared with oral corticosteroids. In study CTT116853, the incidence of events in the ocular effects AESI group was low, with an incidence of 0.1 % and 0.4 % in the FF/UMEC/VI and BUD/FOR treatment groups respectively in the ITT Population up to 24 weeks. There were no events reported in the ocular effects AESI in the EXT Population up to 52 weeks. During studies with FF and FF/VI in asthma participants, and with FF/VI and UMEC/VI in COPD participants, 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 participants with asthma.	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB. - Appropriate exclusion criteria as specified in Section 6.2 of the protocol - Instream review of blinded AE/SAE reports. - If a risk is suspected, participants should receive appropriate treatment
Serious cardiovascular events	Cardiovasular (CV) effects are a potential class effect associated with anti-muscarinic and beta agonist therapies. In the COPD population, there is a high prevalence of concurrent CV disease and the	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB. - Appropriate exclusion criteria as specified in

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	prevalence of CV co morbidities increases with worsening severity of COPD. In study CTT116853 [Lipson, 2017], approximately two-thirds of all participants reported CV risk factors at baseline. In this study, cardiovascular effects were the most frequently reported AESI, with a similar incidence between FF/UMEC/VI and BUD/FOR treatment groups in the ITT Population up to 24 weeks (4.3 % and 5.2 % respectively) and the EXT Population up to 52 weeks (8.6 % and 10 % respectively). Within subgroups of cardiovascular effects, hypertension was reported most frequently and with a numerically higher incidence with BUD/FOR (2.3 %) compared with FF/UMEC/VI (1.3 %) in the ITT Population up to 24 weeks, but with a similar incidence in the EXT Population up to 52 weeks (0.9 to 1.0 % across treatment groups). Cardiac arrhythmias were reported the next most frequently and occurred with an incidence of 1.2 % in both treatment groups in the ITT Population up to 24 weeks, and with an incidence of 1.9 % and 3.6 % in the FF/UMEC/VI and BUD/FOR groups in the EXT Population up to 52 weeks. The incidence of serious events in the	Section 6.2 of the protocol, including - Electrocardiogram (ECG) inclusion criteria - Vital sign assessments (heart rate and blood pressure) as per protocol. - Protocol defined stopping criteria as per Section 8.1.1. - Instream review of blinded AE/SAE reports.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	cardiovascular effects AESI was low, with an incidence of 1.0 % and 1.1 % in the FF/UMEC/VI and BUD/FOR groups respectively in the ITT Population up to 24 weeks, and 2.9 % and 1.4 % in the FF/UMEC/VI and BUD/FOR groups respectively in the EXT Population up to 52 weeks. The absolute numbers of fatal events in cardiovascular effects AESI was low in the study, despite the study enrolling participants with a number of CV comorbidities at baseline. A pre-specified Major Adverse Cardiac Event (MACE) analysis was conducted in CTT116853, with broad MACE defined as: ischemic heart disease Standardised MedDRA Queries (SMQ) excluding fatalities, plus central nervous system haemorrhages and cerebrovascular conditions SMQ excluding fatalities, plus adjudicated cardiovascular deaths. The narrow MACE definition included only the preferred terms of myocardial ischaemia and acute myocardial infarction in place of the ischaemic heart disease SMQ. Overall, the absolute number of MACE events using either the broad or narrow definition was low both in the ITT Population up to 24 weeks and EXT Population up to 52 weeks. No clinically relevant differences were observed between FF/UMEC/VI and BUD/FOR based on narrow and broad MACE analysis both in the ITT	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Population up to 24 weeks and EXT Population up to 52 weeks. In study CTT116853 [Lipson, 2017], there were no emerging safety signals from vital signs, ECGs, or Holter data. The effect of FF/UMEC/VI on the QT interval has not been evaluated in a thorough QT (TQT) study. TQT studies for FF/VI and UMEC/VI did not show clinically relevant effects on QT interval at clinical doses of FF, UMEC and VI. The cardiovascular safety profile of FF/UMEC/VI was generally consistent with that of FF/VI and UMEC/VI.	
Hypersensitivity	Hypersensitivity reactions are unlikely to affect the majority of participants. In study CTT116853, in the ITT Population up to 24 weeks, events in the hypersensitivity AESI group occurred at low incidences in the FF/UMEC/VI and BUD/FOR treatment groups (1.1 % in both groups). Similarly, in the EXT Population up to 52 weeks, events in the hypersensitivity AESI group occurred at low incidences (1.4 % and 0.5 % in FF/UMEC/VI and BUD/FOR arms). On treatment hypersensitivity	- Participants will be informed about the risk in the informed consent. Particpants will be advised to seek medical treatment if any signs of hypersensitivity occur. - Investigators are informed of the risk in the IB. - Appropriate exclusion criteria as specified in Section 6.2 of the protocol. - Instream review of blinded AE/SAE reports.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	serious AESI events occurred at low frequency. Risk factors for hypersensitivity are poorly understood but may include exposure to infectious diseases during early childhood, environmental pollution, allergen level and dietary changes [Niggemann, 2014; De Bisschop, 2012]. Although hypersensitivity reactions are unlikely to affect the majority of participants, there may be a few individuals who experience allergic reactions; they will need to be managed on a case by case basis.	
Narrow angle glaucoma	Rare reports of angle closure glaucoma (which may lead into blindness) have been associated with nebulised ipratropium bromide and salbutamol [Packe, 1984]. The incidence of narrow angle glaucoma in the COPD population associated with the use of inhaled bronchodilators (including LAMAs and LABAs) is relatively low. In CTT116853, in the ITT Population up to 24 weeks, events in the glaucoma SMQ were reported at an incidence of 0.1 and 0.4 % in the FF/UMEC/VI and BUD/FOR arms respectively. In the EXT Population up to 52 weeks, no events	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB. - Appropriate exclusion criteria as specified in Section 6.2 of the protocol - Instream review of blinded AE/SAE reports.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	were reported in either treatment arm. In the UMEC/VI development program, there was one report (<1 %) of angle closure glaucoma (UMEC/VI 62.5/25 mcg).	
Bladder outlet obstruction, dysuria and urinary retention	Bladder outlet obstruction and urinary retention are class effects seen with antimuscarinics. In study CTT116853, in the ITT Population up to 24 weeks, the incidence of events in the urinary retention AESI group was low (0.1 % and 0.0 % for FF/UMEC/VI and BUD/FOR respectively) in both treatment groups. There were no events of urinary retention reported in either group in the EXT Population up to 52 weeks. There were no serious events in the urinary retention AESI group in either treatment arm in the ITT Population up to 24 weeks and the EXT Population up to 52 weeks.	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB. - Appropriate exclusion criteria as specified in Section 6.2 of the protocol - Instream review of blinded AE/SAE reports.
Paradoxical bronchospasm	The phenomenon of paradoxical bronchospasm may occur in association with all inhaled medication, and may vary from mild to life threatening. In study CTT116853, the risk of paradoxical bronchospasm was evaluated through the AESI of asthma/bronchospasm. In the ITT Population	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB. - Instream review of blinded AE/SAE reports.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	up to 24 weeks, one participant reported an event in the asthma/bronchospasm AESI (PT of wheezing in a participant on BUD/FOR; non-serious). There were no events reported in the EXT Population up to 52 weeks.	

3.3.2. Risk assessment for Symbicort MDI (Budesonide/ Formoterol) 160/4.5 mcg

Symbicort is a marketed drug that contains both budesonide (ICS; 160 mcg) and formoterol (LABA; 4.5 mcg). Two inhalations from the MDI provide the required 320/9 mcg dose. The dose (320/9 mcg) and formulation, using an MDI, are approved for COPD in the US, the dose and formulation are not approved in Europe. A similar profile of undesirable effects as reported for ICSs and LABAs may occur with budesonide and formoterol respectively. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug-related adverse reactions are pharmacologically predictable side-effects of β_2 adrenoceptor agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment. Please refer to the authorised product label for further information about the risks of using Symbicort. In this study, Symbicort will be used in line with the recommendations provided in the product label.

Since Symbicort contains an ICS and LABA, the risk mitigation strategies for the FF (ICS) and VI (LABA) components of GSK2834425 will be applicable for Symbicort.

3.3.3. Risk Assessment for Spiriva Handihaler (Tiotropium Bromide) 18 mcg

Tiotropium is a marketed drug that contains tiotropium bromide (18 mcg). A similar profile of undesirable effects as reported for anticholinergics (umeclidinium) may occur with tiotropium bromide. The most common drug related adverse reactions are pharmacologically predictable side effects for anti-cholinergic therapy, such as dry mouth, blurred vision, dizziness, headache and cough. Please refer to the authorised product label for further information on the risks of using Spiriva Handihaler. In this study, Spiriva Handihaler will be used in line with the recommendations provided in the product label.

Spiriva Handihaler is an anticholinergic, therefore the risk mitigation strategy for UMEC component of GSK2834425 will be applicable for Spiriva Handilaler.

3.3.4. Benefit Assessment

GlaxoSmithKline is developing FF/UMEC/VI in a single inhaler, with the aim of providing a new treatment option for the management of symptomatic COPD patients at risk for exacerbations which will reduce the exacerbation frequency, allow for a reduced burden of polypharmacy, convenience, and increase the potential for improvement in lung function, HRQoL, and symptom control over established dual/monotherapies.

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

In the US, 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. UMEC is indicated for the long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with COPD.

In the EU, the FF/VI combination is approved for the symptomatic treatment of adults with COPD with an FEV_1 <70 % predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. The UMEC/VI combination is approved as a maintenance bronchodilator to relieve symptoms in adult patients with COPD. UMEC is approved as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

An appropriate safety monitoring strategy is being proposed for all risks associated with the FF/UMEC/VI combination, including the key risks (Section 3.3.1).

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.

Tiotropium (18 mcg) and budesonide/formoterol (400/12 mcg) are marketed drugs for the COPD indication, and have established benefit:risk profiles. Tiotropium and budesonide/formoterol will be used in line with the recommendations provided in the product labels.

3.3.5. Overall Benefit:Risk Conclusion

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

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on lung function	**Primary** Weighted mean change from baseline in FEV_1 over 0-24 hours at Week 12 **Secondary** • Change from baseline in trough FEV_1 on Day 2, Day 28, Day 84 and Day 85 • Weighted mean change from baseline in FEV_1 over 0-24 hours on Day 1
Other	
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on Health Status	• Proportion of responders based on the St George's Respiratory Questionnaire (SGRQ) Total Score at Week 4 and Week 12 • Change from baseline in SGRQ Total Score at Week 4 and Week 12
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on Health Status	• Proportion of responders based on the COPD Assessment Test (CAT) Total Score at Week 4 and Week 12 • Change from baseline in CAT Total Score at Week 4 and Week 12
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on COPD exacerbations	• Moderate or severe exacerbation event
• Assess how inspiratory airflow limitation affects ability to use the ELLIPTA	• Peak Inspiratory Flow Rate at Screening (Week -4)

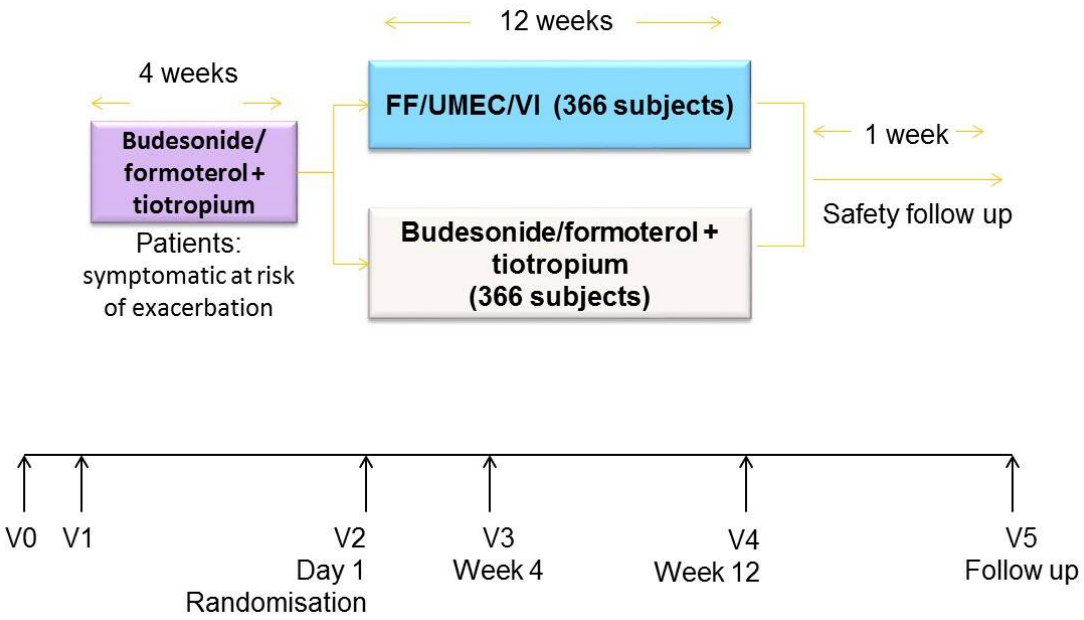
Objectives	Endpoints
Safety	
• To evaluate the safety profile of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium over 84 days of treatment	• Incidence of adverse events • Vital signs

5. STUDY DESIGN

5.1. Overall Design

This is a Phase IV, 12-week, randomised, double-blind, triple dummy, parallel group, multicentre study evaluating single inhaler triple therapy (FF/UMEC/VI) once daily via the ELLIPTA, compared to multiple inhaler triple combination therapy budesonide/formoterol (320/9 mcg) twice daily plus once daily tiotropium (18 mcg), in participants with COPD.

Figure 1 Study design schema



Eligible participants at Screening (V1) will be current or former smokers, with an established clinical history of COPD, receiving daily maintenance COPD therapy for at least 3 months, with a post-bronchodilator FEV1 of <50 % predicted (or <80 % predicted with a documented history of at least 2 moderate or 1 severe [hospitalised] exacerbation in the last 12 months) and a CAT score of ≥10 and Visit 1 and at Visit 2. Participants will be requested to participate in the study for approximately 17 weeks, consisting of a 4-week run-in period, 12-week treatment period and a 1-week follow-up period.

- **Pre-screening:** Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0), including the informed consent process, must be completed prior to any protocol-required changes to a participant's usual COPD treatment and the initiation of any Visit 1 procedures. Participants will continue treatment with their regular (i.e. pre-study) COPD medication(s) during the pre-screening period; however, medications that are prohibited within a specified time interval prior to Visit 1 are defined in Section 7.7.
- **Screening/run-in:** Eligible participants will be allowed to continue their usual COPD medications until the day before Screening, Visit 1. On the morning of the Screening Visit participants will refrain from taking their morning dose of their usual COPD medications. Participants who meet all of the eligibility criteria at Visit 1, will enter the 4-week run-in period during which they will discontinue all existing COPD medications and receive their run-in treatment: budesonide/formoterol (320/9 mcg) twice daily plus tiotropium (18 mcg) once daily plus placebo via the ELLIPTA. Participants will not use any other COPD medications (except for those allowed per protocol). Participants will be provided with short-acting albuterol/salbutamol to be used on an as-needed basis (rescue medication) throughout the study. At Screening, each participant will be instructed on the proper use of the ELLIPTA, MDI and HandiHaler and will self-administer their first doses of their run-in treatment during the Screening Visit. On the morning of the other study visits (Visit 2 onwards), participants will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel.
- **Randomisation/treatment:** On the day before the Randomisation Visit (Visit 2), participants will take their last dose of run-in treatment and will not use any other COPD medications (except for those allowed per protocol) 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.

  At Visit 2 (the Randomisation Visit), participants who meet all of the randomisation criteria (see Section 6.3) will be randomised 1:1 to receive one the following double-blind study treatments for 84 days:

  Either:

  FF/UMEC/VI 100/62.5/25 mcg via the ELLIPTA once daily in the morning
  + placebo to match budesonide/formoterol via MDI, two inhalations twice daily
  + placebo to match tiotropium via HandiHaler once daily in the morning

  or,

  Budesonide/formoterol 160/4.5 mcg via MDI, two inhalations twice daily*
  + tiotropium 18 mcg via HandiHaler once daily in the morning
  + placebo via the ELLIPTA once daily in the morning

*Participants are required to take two inhalations of budesonide/formoterol 160/4.5 mcg, via the MDI in the morning and two inhalations in the evening. The total dose is therefore 320/9 mcg twice daily.

At Visit 2 participants will refrain from taking their morning doses of run-in study medication and will self-administer study treatment at the clinic, when instructed to do so. Participants will remain at the clinic for at least 24 hours, for serial spirometry assessments.

- On the morning of Visits 3 and 4, participants will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel. Participants will remain at the clinic for at least 24 hours, for serial spirometry assessments. At Visits 3 and 4 participants will self-administer study treatment whilst at the clinic. Participants will take their last doses of study treatment in the clinic on Day 84 (Visit 4, when instructed to do so by clinic personnel), and continue to remain at the clinic until at least 24 hours after their last morning dose, for their clinical assessments, which include serial spirometry assessments. Participants are expected on non-clinic visit days to take their study treatment at home in the morning at approximately the same time each day, and at the same time each evening, as directed by the clinic.
- **Safety/follow-up:** A safety follow-up telephone contact or clinic visit (Visit 5) will be conducted approximately 7 days after the participant completes all of the protocol-defined procedures for Visit 4/End of Study (EOS) or, if applicable, the Study Treatment Discontinuation Visit. A participant will be considered to have completed the study when they have completed all phases of the study including screening, run-in, the randomised treatment phase, and safety follow-up.

Participants that permanently discontinue study treatment are not required to withdraw from the study. If for any reason a participant must permanently discontinue study treatment, every effort should be made by the Investigator/staff to keep the participant in the study and complete all remaining protocol specified clinic visits (see Section 8.1). However, a participant may voluntarily withdraw from participation in this study at any time. The Investigator may also, at his or her discretion, withdraw a participant from further study participation. Participants who are withdrawn from the study will not be replaced.

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

5.2. Number of Participants

Approximately 800 participants with advanced COPD will enter the run-in period, in order to randomise approximately 732 participants in order to achieve an estimated 620 evaluable participants in the modified per-protocol (mPP) population at Week 12, assuming 10 % premature discontinuation of study treatment and 5 % protocol deviation. See Section 10 for further details.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including pre-screening, screening, run-in, the randomised treatment phase and the safety follow-up.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities table (SoA) (see Section 2) for the last participant in the trial globally.

5.4. Scientific Rationale for Study Design

This study will use a multicenter, randomised, double-blind, triple-dummy, parallel-group design. A placebo arm is not included because the primary comparison of interest is FF/UMEC/VI vs. Budesonide/formoterol + tiotropium and it is not considered appropriate to include a placebo arm in a study in participants with advanced COPD. Eligible participants must have been on daily maintenance COPD medications for at least 3 months. The 4-week run-in period is necessary in order to assess participant compliance with and ability to use all of the medications together, and allow sufficient time for the results of screening assessments to be returned to the site, in order to establish participant eligibility.

5.5. Dose Justification

The FF/UMEC/VI (100/62.5/25 mcg) dose was selected based on the doses that have been licensed for COPD for the FF/VI (100/25 mcg) and UMEC/VI (62.5/25 mcg) dual combinations through extensive studies in the mono and dual therapy programmes. It is the dose which is currently under regulatory review based on the Phase IIIa FF/UMEC/VI registration programme.

The doses selected for the Symbicort MDI (budesonide/formoterol 320/9 mcg, twice daily) and Spiriva HandiHaler (tiotropium 18 mcg, once daily) is the doses licensed in the US for use in COPD.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. **Informed consent:** capable of giving signed informed consent prior to study start which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. **Type of participant**: Outpatient.

3. **Age**: Participants 40 years of age or older at Screening (Visit 1).

4. **Gender**: Male or female participants.

Female participants:

A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP)

OR

- A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and until the safety follow-up contact after the last dose of study treatment.

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 (Visit 1).

8. **Severity of Disease:**

   Participants must demonstrate at Screening:

   - a post-bronchodilator FEV_1 <50 % predicted normal

   OR

   - a post-bronchodilator FEV_1 <80 % predicted normal and a documented history of ≥2 moderate exacerbations or one severe (hospitalized) exacerbation in the previous 12 months

   Participants must also have a measured post albuterol/salbutamol FEV_1/forced vital capacity (FVC) ratio of <0.70 at screening.

   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 dyspnoea, sputum volume, or sputum purulence (colour). Participant verbal reports are not acceptable.*

9. **Existing COPD maintenance treatment:** participant must have been receiving daily maintenance treatment for their COPD for at least 3 months prior to Screening.

   Note: *Participants taking only as-needed COPD medications are not eligible.*

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

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

2. **Asthma**: Participants with a current diagnosis of asthma. (Participants with a prior history of asthma are eligible if they have a current diagnosis of COPD).

3. **α1-antitrypsin deficiency**: Participants with α1-antitrypsin deficiency as the underlying cause of COPD.

4. **Other respiratory disorders**: Participants with active tuberculosis, lung cancer, and clinically significant: bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung disease or other active pulmonary diseases.

5. **Lung resection**: Participants who have undergone lung volume reduction surgery within the 12 months prior to Screening.

6. **Risk Factors for Pneumonia**: immune suppression (*e.g.* advanced human immunodeficiency virus [HIV] with high viral load and low CD4 count, lupus on immunosuppressants) that in the opinion of the investigator would increase risk of pneumonia or other risk factors for pneumonia (*e.g.* neurological disorders affecting control of the upper airway, such as Parkinson's Disease, Myasthenia Gravis).

   Participants at potentially high risk for pneumonia (*e.g.* very low body mass index [BMI], severely malnourished, or very low FEV_1) 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).

8. **Respiratory tract infection** that has 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 chest X-ray (e.g. significant cardiomegaly, pleural effusion or scarring). All participants will have a chest X-ray at Screening Visit 1 (or historical radiograph or computerized tomography [CT] scan obtained within 3 months prior to screening). **Note**: *Participants who have experienced pneumonia and/or moderate or severe COPD exacerbations within 3 months of screening must provide a post pneumonia/exacerbation chest X-ray 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**: Participants 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 haematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the participant 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:** ALT >2x Upper Limit of Normal (ULN); and bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35 %)

    Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment).

    NOTES:

    - Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.
    - Chronic stable hepatitis B and C (*e.g.*, presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment) are acceptable if participant otherwise meets entry criteria.

12. **Unstable or life threatening cardiac disease:** Participants 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

- New York Heart Association (NYHA) Class IV Heart failure

13. Abnormal and clinically significant 12-lead ECG finding at Visit 1

    - The Investigator will determine the clinical significance of each abnormal ECG finding in relation to the participant's medical history and exclude participants who would be at undue risk by participating in the trial.
    - An abnormal and clinically significant finding that would preclude a participant from entering the trial is defined as a 12-lead ECG tracing that is interpreted at, but not limited to, any of the following:
        i. Atrial Fibrillation (AF) with rapid ventricular rate >120 beats per minute (BPM)
        ii. Sustained and non-sustained Ventricular tachycardia (VT)
        iii. Second degree heart block Mobitz type II and third degree heart block (unless pacemaker or defibrillator had been inserted)
        iv. QT interval corrected for heart rate by Fridericia's formula (QTcF) ≥500 msec in participants with QRS <120 msec and QTcF ≥530 msec in participants with QRS ≥120 msec
14. **Contraindications**: A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, β_2-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**: Participants with carcinoma that has not been in complete remission for at least 3 years. Participants 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 3 year waiting period if the participant has been considered cured by treatment.

16. **Oxygen therapy**: Use of long-term oxygen therapy (LTOT) described as resting oxygen therapy >3 L/min at screening (Oxygen use ≤3 L/min flow is not exclusionary.)

17. **Medication prior to spirometry**: Participants 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**: Participants who have participated in the acute phase of a Pulmonary Rehabilitation Programme within 4 weeks prior to screening or participants who plan to enter the acute phase of a Pulmonary Rehabilitation Programme during the study. Participants who are in the maintenance phase of a Pulmonary Rehabilitation Programme are not excluded.

19. **Drug/alcohol abuse**: Participants with a known or suspected history of alcohol or drug abuse within the last 2 years.

20. **Non-compliance**: Participants 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**: Participants 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 participant 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 Visit 1:

Medication	No use within the following time intervals prior to Screening
Inhaled short-acting anticholinergics	6 hrs
Inhaled short-acting $beta_2$ agonists[1]	≥4 hrs
Inhaled short-acting anticholinergics + short-acting beta agonist combination	6 hrs
Long term antibiotic therapy	Participants receiving antibiotics for long term therapy (≥30 days) are not eligible for the study. (Antibiotics are allowed for the short term treatment (≤14 days) of an exacerbation or for short term treatment (≤14 days) of other acute infections during the study)
Systemic, oral, parenteral corticosteroids	30 days (During the study oral/systemic corticosteroids may be used for ≤14 days to treat COPD exacerbations/pneumonia) Intra-articular injections are allowed
Any other investigational drug	30 days or 5 half lives whichever is longer.

[1] (rescue albuterol/salbutamol will be provided and is permitted during the study)

6.3. Randomisation Criteria

At the end of the run-in period (Visit 2), study participants must fulfil the following additional criteria in order to be randomised into the study and enter the treatment period:

1. Compliance with run-in study medication

- Compliance with each run-in study medication will be assessed by the Investigator, any participant <80 % or >120 % compliant with any of the three inhalers (ELLIPTA, Handihaler or MDI) will be excluded.

2. COPD exacerbation or pneumonia

- Participants that experience a moderate or a severe COPD exacerbation or pneumonia during the run-in period will be excluded.

3. Changes in COPD medication

- Any participant that requires any change in COPD medication during the run-in period will be excluded. This includes a temporary change in COPD medication.

6.4. Lifestyle Restrictions

- Participants should refrain from smoking for 1 hour prior to each pulmonary function test.
- Participants should abstain from drinking beverages with high levels of caffeine such as tea and coffee for 2 hours prior to each pulmonary function test.

6.5. Pre-screening/Screening/Run-in/Randomisation Failures

A participant will be assigned a participant number at the time the informed consent is signed at Visit 0.

The study site will be responsible for reporting pre-screen failures. The following information will be collected in the electronic case report form (eCRF) for participants who are pre-screen failures: demographic information including race, age and gender; participant number; serious adverse event (SAE) information only for any SAE considered to be related to study participation.

A minimal set of information is required to ensure transparent reporting of screening/run-in/randomisation failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screening/run-in/randomization failure details, eligibility criteria, and any SAEs. Further details are provided in the study-specific eCRF completion guidelines.

For the purposes of this study, pre-screening failures, screening failures and run-in failures will be defined as follows:

Pre-screening failures: those participants that sign the informed consent document but do not have a Visit 1 (Screening) procedure.

Screening failures: those participants that complete at least Visit 1 (Screening) procedure but do not enter the run-in period. A participant who completes Visit 1 assessments and is dispensed the study medication for the run-in period is considered to have entered the run-in period.

Run-in failures: those participants that enter the run-in period but are not randomised (except those randomised in error).

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatment Groups and Duration

Participants who meet all the eligibility criteria and who have successfully completed all protocol procedures at Screening will enter the 4-week run-in period and will take budesonide/formoterol (320/9 mcg) twice daily plus tiotropium (18 mcg) once daily plus placebo via the ELLIPTA. Following the run-in period, participants who meet the randomisation criteria will be randomised (1:1) to one of the following double-blind, double-dummy treatment groups for 84 days:

Either:

FF/UMEC/VI 100/62.5/25 mcg via the ELLIPTA once daily in the morning
+ placebo to match budesonide/formoterol via MDI, two inhalations twice daily
+ placebo to match tiotropium via HandiHaler once daily in the morning

or,

Budesonide/formoterol 160/4.5 mcg via MDI, two inhalations twice daily*
+ tiotropium 18 mcg via HandiHaler once daily in the morning
+ placebo via the ELLIPTA once daily in the morning

*Participants are required to take two inhalations of budesonide/formoterol 160/4.5 mcg, via the MDI in the morning and two inhalations in the evening. The total dose is therefore 320/9 mcg twice daily.

Table 2 Dosing schedule for run-in and treatment periods

	ELLIPTA (1 inhalation)		MDI (2 puffs)		HandiHaler (1 capsule inhaled twice)	
	Active	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**
Run-in						
am		**Y**	**Y**		**Y**	
pm			**Y**			
Treatment						
Active FF/UMEC/VI						
am	**Y**			**Y**		**Y**
pm				**Y**		
Active budesonide/formoterol + tiotropium						
am		**Y**	**Y**		**Y**	
pm			**Y**			

The ELLIPTA contains 30 doses (FF/UMEC/VI or placebo) and participants will be instructed to administer one dose from their ELLIPTA once daily in the morning.

Symbicort MDI contains 120 doses: budesonide/formoterol 160mcg/4.5 mcg, two inhalations twice daily.

Tiotropium or matching placebo: Contents of 1 capsule (18 mcg) inhaled once daily using HandiHaler device. *Note*: To ensure drug delivery, two inhalations of the contents of each capsule should be performed.

Descriptions of the study treatments administered via the ELLIPTA, MDI and the Handihaler are provided in Table 3, Table 4, and Table 5, respectively.

Table 3 Description of FF/UMEC/VI Inhalation Powder in ELLIPTA™

FF/UMEC/VI	**First strip**	**Second strip**
	GW685698 blended with lactose	GW642444 and GSK573719 blended with lactose and magnesium stearate
Dosage Form	ELLIPTA 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	

Placebo to match	First strip	Second strip
	Lactose	Lactose/Magnesium Stearate
Dosage Form	ELLIPTA with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	NA	NA
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	

Table 4 Description of Symbicort MDI

Symbicort 160mcg/4.5 mcg	**MDI**
Dosage form	MDI with 120 doses
Unit dose strength	Budesonide/ Formoterol 160mcg/4.5mcg
Physical description	Solution for inhalation
Route of administraton	Inhaled
Placebo to match Symbicort	**Placebo to match MDI**
Dosage form	MDI with 120 doses
Unit dose strength	NA
Physical description	Solution for inhalation
Route of administration	Inhaled

Table 5 Description of Tiotropium bromide in HandiHaler

Spiriva 18 mcg	**HandiHaler**
Dosage form	Capsule
Unit dose strength	18mcg
Physical description	Hard gelatin capsule containing 18mcg tiotropium bromide blended with lactose
Route of administration	Inhaled

Placebo to match Spiriva	HandiHaler
Dosage form	Capsule
Unit dose strength	NA
Physical description	Hard gelatin capsule containing lactose
Route of administration	Inhaled

7.1.1. Medical Devices

- The GSK ELLIPTA medical device will be provided for use in this study.
- Other medical devices (not manufactured by or for GSK provided for use in this study) are the Handihaler and MDI.
- GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study. (see Section 9.2.10).

7.2. Dose Modification

No dose modifications are planned for this study.

7.3. Method of Treatment Assignment

Participants will be assigned to study treatment in accordance with the randomisation schedule. The randomisation code will be generated using a validated computerised system. Participants will be randomised using an Interactive Web Response System (IWRS). The study will use central-based randomisation to allocate treatments. Once a randomisation number is assigned to a participant it cannot be reassigned to any other participant in the study.

7.4. Blinding

This will be a double-blind study and the following will apply.

- The Investigator or treating physician may unblind a participant'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 participant as judged by the Investigator.
- Investigators have direct access to the participant's individual study treatment.

- It is preferred (but not required) that the Investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the participant's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the Investigator must notify GSK within 24 hours after unblinding, but without revealing the treatment assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study.
- The date and event or condition which led to the unblinding (i.e. the primary reason) will be recorded in source documentation and in the eCRF.

Should a participant's treatment assignment be unblinded then the participant may continue the assigned study treatment and be followed-up as per protocol until the completion of the Safety Follow-up assessments.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant 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 participant's treatment assignment, may be sent to Investigators in accordance with local regulations and/or GSK policy. Participants will not be withdrawn from the study.

Masking of tiotropium and placebo to tiotropium capsules

This study will use a triple-dummy design for dosing, whereby participants will be given three inhalers (ELLIPTA, MDI and Handihaler). All participants and site personnel involved in efficacy and safety assessments will be blinded to assigned treatment during the study. Tiotropium capsules have trade markings that are not present on the placebo capsules. This study has a parallel-group design which ensures the capsule type will be consistent for each participant for the duration of the study. In addition, tiotropium and placebo capsules will be closely matched in colour. Both the tiotropium and placebo blister packages will be covered with opaque over-labels with the intent of hiding the information on the tiotropium packaging. The HandiHaler dry powder inhalers will be covered with labels to mask identifying marks on the inhaler. Investigator and site personnel involved in efficacy and safety assessments will be instructed not be present when a participant administers his/her study medication at clinic visits, to guard against the possibility of personnel involved in the collection of efficacy and safety data, identifying the capsules removed from the blisters. Sites are required to have study treatment dosed, dispensed and accounted for by site personnel that are not involved in any efficacy or safety assessments.

7.5. Preparation/Handling/Storage/Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored

in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual (SRM).

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupations exposure notify the monitor, Medical Monitor and/or GSK study contact.

A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the Investigator, where is this required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

When participants are dosed at the site, they will receive study treatment under medical supervision. The date and time of each dose administered in the clinic will be recorded in the eCRF. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff.

When participants self-administer study treatment(s) at home, compliance with study treatment will be assessed through querying the participant during the site visits and recording the number of doses remaining in the ELLIPTA and MDI, and the number of capsules of tiotropium bromide (or matching placebo) dispensed and taken by each participant, in the eCRF (see SRM for details).

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

7.7. Concomitant Therapy

All COPD medications used within 3 months prior to screening and during the run-in and study treatment periods (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.

The minimum requirement is that the drug name, reason for use, dose (including unit), frequency, route and the dates of administration are to be recorded.

Note: *Study provided albuterol/salbutamol should not be recorded in the eCRF however non-study supplied albuterol/salbutamol will be recorded in the eCRF.*

Medications initiated after completion of the randomised treatment phase of the study (Visit 4) or started after discontinuation of study treatment must be recorded in the eCRF up to the safety follow-up (Visit 5).

7.7.1. Permitted Medications and Non-Drug Therapies

7.7.1.1. Permitted COPD Medications

The following COPD medications are permitted during the **run-in and the randomised treatment** periods:

- Study supplied albuterol/salbutamol MDI or nebules (must be withheld for at least 4 hours prior to spirometry testing)
- Mucolytics such as acetylcysteine
- Long term oxygen therapy. (To be eligible to enter the study at Visit 1, participants 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 run-in or treatment phases of the study). Oxygen therapy must be captured on the concomitant medication page of the eCRF. Supplemental oxygen is recommended for participants who exhibit oxyhemoglobin desaturation with rest or exertion (*e.g.* SaO2 ≤88 %)
- Maintenance phase of pulmonary rehabilitation treatment (participants are not allowed to initiate treatment during the study)
- Study provided COPD medications in the run-in and the randomised treatment period

The following **COPD medications** are permitted during the **randomised treatment** period:

- 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
- Any COPD medication deemed medically necessary for the short term treatment (≤14days) of a moderate/severe COPD exacerbation or pneumonia

7.7.1.2. Permitted Non-COPD Medications

The following non-COPD medications are permitted during the **run-in and randomised treatment** periods:

- 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 participants 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 QT interval corrected for heart rate [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)

- Cytochrome P450 (CYP)3A4 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)

7.7.2. Prohibited Medications and Non-Drug Therapies

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

Table 6 Concomitant Medications

Medication Prohibited during the randomised treatment period
Inhaled short-acting anticholinergics
Inhaled short-acting beta$_2$ agonists[1]
Inhaled short-acting anticholinergic/short-acting beta2-agonist combination products
Inhaled corticosteroids (ICS)
Inhaled corticosteroids (ICS)/Inhaled long-acting beta$_2$-agonist (LABA) combinations (eg.fluticasone/salmeterol, mometasone furoate/formoterol fumarate, budesonide/formoterol fumarate; fluticasone furoate/vilanterol
Phosphodiesterase 4 (PDE4) inhibitors (roflumilast)
LABA (e.g., indacaterol, olodaterol, salmeterol etc.)
Other LAMAs (aclidinium, glycopyrronium, umeclidinium etc.)
LAMA/LABA combinations
Theophyllines
Sodium cromoglycate and nedocromil sodium
Anti-leukotrienes
Long term antibiotic therapy[2]
Systemic, oral, parenteral corticosteroids[3]
Any other investigational drug

1. (rescue albuterol/salbutamol will be provided and is permitted during the study)
2. (Antibiotics are allowed for the short term treatment (≤14 days) of an exacerbation or for short term treatment (≤14 days) of other acute infections during the study)
3. (During the study oral/systemic corticosteroids may be used for ≤14 days to treat COPD exacerbations/pneumonia)
Intra-articular injections are allowed

Note: *Topical and ophthalmic corticosteroids, and localized corticosteroid injections (intra-articular and epidural) are allowed.*

NOTE: *All COPD medications (except for rescue albuterol/salbutamol, mucolytics and oxygen) are prohibited during the run-in and randomised treatment periods 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, 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 participant currently taking study treatment as these additional medications may increase the risk of overdose. If neccessary the Investigator or other health care personnel may stop the participant's study treatment temporarily (≤ 14 days) in order to treat the COPD exacerbation. Participants who require more than two consecutive 14 day courses of treatment (i.e. antibiotics or corticosteroids) should be evaluated for their continuation on study treatment by the Investigator in consultation with the GSK medical monitor.*

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study because other treatment options are available.

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

At the end of the treatment period (Visit 4), or after study treatment Discontinuation Visit, or withdrawal from study, participants 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 participants that successfully complete Visit 4 on study treatment and for participants that withdraw from the study. For participants that discontinue study treatment, post-treatment concomitant medication should be entered into the eCRF until they complete the visit/telephone contact at the planned Visit 5 date.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants that permanently stop study treatment should return to the clinic as soon as possible, in order to complete the Study Treatment Discontinuation Visit. The evaluations and procedures to be completed are outlined in the SoA (Section 2).

Participants that discontinue study treatment are encouraged to remain in the study and every effort should be made by the Investigator/staff to keep the participant in the study, to collect important efficacy and safety data by telephone contact. Ideally, participants should return to the clinic to complete Visit 4, to collect important spirometry data , however, if this isn't possible, this visit should also be completed by telephone. A safety follow-up phone call (Visit 5) should also be conducted 7 days after Visit 4.

The Investigator/site staff should contact the participant by telephone at the protocol designated visit time intervals to collect the following:

- SAEs
- AEs assessed as related to study participation
- AEs resulting in withdrawal from the study
- COPD exacerbations
- Concomitant medication
- Serial spirometry (Visit 4 only, if participant consents)

Participants have the right to discontinue study treatment before the end of the study. A participant may also be asked to discontinue study treatment at the Investigator's discretion.

A participant may be withdrawn from study treatment at any time. A reason for premature discontinuation of study treatment (e.g., AE, lack of efficacy, protocol deviation, Investigator discretion, consent withdrawn etc.) must be captured in the eCRF.

8.1.1. Protocol defined criteria for discontinuation of study treatment

A participant must be permanently discontinued from study treatment if any of the following stopping criteria are met, participants are however encouraged to remain in the study and complete limited assessments, as detailed in Section 8.1:

- **Liver chemistry stopping and increased monitoring criteria** have been designed to assure participant safety and evaluate liver event etiology (in alignment with the Food and Drug Administration (FDA) premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

  Discontinuation of study treatment for abnormal liver tests should be considered by the Investigator when a participant meets one of the conditions outlined in the algorithm or if the Investigator believes that it is in the best interest of the participant.

  Liver Safety Algorithms and Required Actions and Follow up Assessments can be found in Appendix 4.
- **Pregnancy**: Positive urine pregnancy test.
- **QTc Stopping Criteria**:

  Details on performing ECG assessments can be found in Section 9.4.3.

  - The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula

may not be changed or substituted once the participant has been enrolled. Safety ECGs and other non-protocol specified ECGs are an exception.

- For example, if a participant is eligible for the protocol based on QT interval corrected for heart rate by Bazett's formula (QTcB), then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*.
- The QTc should be based on averaged QTc values of triplicate electrocardiograms obtained over a brief (*e.g.,* 5-10 minute) recording period.
- For this study, the following QTc stopping criteria will apply and lead to withdrawal from study treatment:
    - QTc>500 msec or uncorrected QT>600 msec
    - Change from baseline: QTc>60 msec
- For participants with underlying bundle branch block, follow the discontinuation criteria listed below:
    - Baseline QTc with Bundle Branch Block <450 msec, Discontinuation QTc with Bundle Branch Block >500 msec
    - Baseline QTc with Bundle Branch Block <450-480 msec, Discontinuation QTc with Bundle Branch Block ≥530 msec

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.2. Rechallenge

8.1.2.1. Study Treatment Restart or Rechallenge

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

8.2. Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance or administrative reasons.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

In the event of early withdrawal from the study, every effort should be made to have the participant to return to the clinic for a Study Treatment Discontinuation Visit and Safety Follow-up, and to return all study related materials. Assessments to be performed during

the Study Treatment Discontinuation Visit and the Safety Follow-up contact are described in the SOA (Section 2).

Participants that have previously discontinued study treatment (and have already completed the Study Treatment Discontinuation Visit) but decide they no longer wish to participate in the study, may withdraw from the study by contacting the site by telephone.

If the participant withdraws from the study at least 7 days after the Study Treatment Discontinuation Visit was completed, the safety follow-up contact (Visit 5) can be conducted at the time the participant notifies the site of their intention to withdraw from the study. Alternatively, the safety follow-up contact should be conducted 7 days after the Study Treatment Discontinuation Visit, if the participants consents to be contacted.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

9. STUDY ASSESSMENTS AND PROCEDURES

Investigator and site personnel involved in efficacy and safety assessments will be instructed not be present when a participant administers his/her study medication at clinic visits. Sites are required to have study treatment dose, dispensed and accounted for by site personnel that are not involved in any efficacy or safety assessments. See Section 7.4 for further details.

- Study procedures and their timing are summarized in the SoA (Section 2).
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- **No study related procedures may be performed until the informed consent form has been signed by the participant.** A Pre-Screening visit (Visit 0) is required in order to administer the informed consent before any changes are made to the participant's current medical regimen. Selection and modification of the participant's medications prior to study participation is based on the physician's judgment according to sound medical practice, principles, and each participant's needs. A participant's treatment must not be changed merely for the purpose of enabling the participant's participation in the study.

During the Pre-Screening visit (Visit 0) the following information will be captured in the eCRF for each participant:

- Demographic information including race, age and gender
- Participant number
- Register visit in IWRS

The additional following critical baseline assessments will be conducted at Screening (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)
- 12-lead ECG
- Pulse rate, blood pressure measurements
- 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)
- CAT
- Administer and dispense run-in study treatment

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

- Smoking cessation counseling
- Register visit in IWRS
- Dispense albuterol/salbutamol

9.1. Efficacy Assessments

The timings of all efficacy assessments are specified in the SoA (Section 2).

9.1.1. Spirometry

Spirometry measurements will be obtained using spirometry equipment that meets or exceeds the minimal performance recommendations of the American Thoracic Society (ATS) [Miller, 2005]. All sites will use standardised spirometry equipment provided by an external vendor. All participants will have spirometry performed at screening (including PIFR) and each scheduled clinic visit during the treatment period. For FEV_1, FVC and PIFR 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 FEV_1 and FVC from the 3 acceptable efforts should be recorded, even if they do not come from the same effort.

Spirometry must be performed as follows:

- Started approximately between 6:00AM and 11:00AM.
- If applicable, after completing the health outcomes assessments (SGRQ-C should be administered first followed by CAT)
- After withholding albuterol/salbutamol for ≥4 hours.
- At Screening (Visit 1), before the morning dose of run-in medication.
- At Randomisation (Visit 2) and all treatment visits, before the morning dose of study treatment.
- Participants should refrain from smoking for 1 hour prior to each pulmonary function test.
- Participants 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 SRM.

9.1.1.1. 24-hour Serial Spirometry

24-hour serial spirometry will be performed by all participants at Randomization (Visit 2) and Day 84 (Visit 4). In addition, trough FEV_1 data will be collected pre-dose on Day 28 (Visit 3).

Serial spirometry measurements should be taken as close to the following scheduled timepoints as possible:

Pre-dose: 30 mins and 5 mins

Post-dose: 5 mins, 15 mins, 30 mins, 1 hr, 3 hrs, 6 hrs, 12 hrs, 15 hrs, 21 hrs, 23 hrs and 24 hrs

9.1.1.2. Reversibility

At Visit 1, both pre- and post-albuterol/salbutamol spirometry will be obtained. Post-albuterol/salbutamol FEV_1 and FEV_1/FVC findings will be used to determine participant eligibility.

Reversibility testing will be completed as follows: Following pre-albuterol/salbutamol spirometry (three acceptable spirometry efforts), the participant 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.

9.1.1.3. Peak Inspiratory Flow Rate (PIFR)

PIFR will be completed at Screening (Visit 1) only, approximately 10 minutes prior to the start of reversibility testing. Three acceptable spirometry efforts will be obtained.

9.1.2. SGRQ-C

The St George's Respiratory Questionnaire-Chronic Obstructive Pulmonary Disease specific (SGRQ-C) will be completed by participants at Randomisation (Visit 2), Day 28 (Visit 3) and Day 84 (Visit 4).

The SGRQ-C [Meguro, 2007] is a disease-specific questionnaire designed to measure the impact of respiratory disease and its treatment on a COPD participant'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 participants and has been translated and validated for use in most major languages. The SGRQ-C is derived from the original SGRQ, and produces scores equivalent to the SGRQ instrument [Meguro, 2007].

9.1.3. COPD Assessment Test (CAT)

The CAT will be completed by participants at Screening (Visit 1), Randomisation (Visit 2), Day 28 (Visit 3) and Day 84 (Visit 4).

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, participants 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.

9.1.4. COPD Exacerbations

COPD exacerbation data will be collected from the start of the randomised double blind treatment period (Visit 2) until the safety follow up contact at Visit 5.

Participants will complete a paper Medical Problems worksheet to record medical problems experienced during the study. This paper worksheet must be reviewed by the Investigator (or designee) at each visit to the study site to assist in the identification of new COPD exacerbations.

All COPD exacerbations will be recorded in the exacerbation eCRF.

Every effort should be made to conduct a chest x-ray within 48 hours of identification of a moderate or severe exacerbation.

Details on COPD Exacerbation Identification, Categorization and Treatment Guidelines are provided in Appendix 5.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 6.

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment or withdraw from the study (see Section 8).

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

- Any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study up to and including the safety follow-up contact at Visit 5.

- All AEs will be collected from the start of Study Screening (Visit 1) until the safety follow-up contact at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 6. The Investigator will submit any updated SAE data to the sponsor or designee within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the sponsor or designee.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 6.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Participants will be issued with a paper Medical Problems worksheet to record any medical problems experienced during the study. This paper worksheet will be used to assist participant recall in discussions with the Investigator (or designee), for site staff to then enter as appropriate in the eCRF.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 6.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific

regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 6 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

9.2.6. Disease-Related Outcomes – COPD Exacerbations

COPD exacerbations are an expected disease-related outcome.

COPD exacerbations should not be recorded as an adverse event, unless they meet the definition of an SAE (Appendix 6).

9.2.7. 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 (colour) or production
- Auscultatory findings of adventitious sounds (*e.g.* egophony, bronchial breath sounds, rales, etc.)
- Dyspnoea or tachypnea
- Fever (oral temperature >37.5 °C)
- Elevated white blood cells (WBC) (>10,000/mm3 or >15 % immature forms)

- Hypoxemia (HbO_2 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 participants with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in participants with COPD receiving FF/VI included current smokers, participants with a history of prior pneumonia, participants with a body mass index <25 kg/m^2 and participants with an FEV_1<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.

9.2.8. 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 medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

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

9.2.9. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until the safety follow-up contact/visit.
- If a pregnancy is reported, the Investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 3.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2.10. Medical Device Incidents (Including Malfunctions)

Medical devices (spacers/holding chambers) are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 7.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2 and Appendix 6 of the protocol.

9.2.10.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the Investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.
- The method of documenting Medical Device Incidents is provided in Appendix 7.

9.2.10.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 9.2). This applies to all participants, including those who discontinue study treatment or the study.
- The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

9.2.10.3. Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device incident.
- The Medical Device Incident Report Form will be sent to the sponsor electronically. If the eCRF is unavailable, then a paper version should be utilized.
- The same individual will be the contact for the receipt of medical device reports and SAE.

9.2.10.4. Regulatory Reporting Requirements for Medical Device Incidents

- The Investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The Investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

9.3. Treatment of 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 eCRF pages. In the event of an overdose of study treatment, 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.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 2).

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- Vital signs will be performed at the time points specified in the SoA table (Section 2) prior to conducting spirometry and prior to taking study treatment.
- Blood pressure (systolic and diastolic) and pulse measurements will be assessed 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.

9.4.3. Electrocardiograms

- A single 12-lead ECG and rhythm strip will be recorded after measurement of vital signs and spirometry. Recordings will be made at the time-points defined in the SoA table (Section 2). All ECG measurements will be made with the participant in a supine position having rested in this position for approximately 5 minutes before each reading.
- For participants who meet the QTc, protocol defined stopping criteria, triplicate ECGs (over a brief period of time) should be performed (Section 8.1.1).
- 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.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 8 for the list of clinical laboratory tests to be performed and to the SoA (Section 2) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the Investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 8, must be conducted in accordance with the laboratory manual and the SoA (Section 2).

9.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Information regarding genetic/ pharmacogenetic (PGx) research is included in Appendix 9. The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx and genetic assessments before these can be conducted. The approval(s) must be in writing and will clearly specify approval of the PGx and genetic assessments (i.e., approval of Appendix 9).

In some cases, approval of the PGx and genetic 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 PGx and genetic assessments is being deferred and the study, except for PGx and genetic assessments, can be initiated. When PGx and genetic assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx and genetic assessments will not be conducted.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Hypotheses

The primary objective of this study is to compare FF/UMEC/VI with budesonide/formoterol + tiotropium (BUD/FOR+TIO) in COPD participants. The primary endpoint is 0- 24 hour weighted mean (WM) FEV_1 at Week 12 (Day 84). The primary analysis is the comparison of this endpoint for FF/UMEC/VI vs. BUD/FOR+TIO with mPP population. The null hypothesis is that the difference in 0-24 hour WM FEV_1 between treatment groups is less than or equal to a pre-specified non-inferiority margin Δ:

H_0: $T_1 - T_2 \leq -\Delta$

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

H_1: $T_1 - T_2 > -\Delta$

where T_1 and T_2 are the treatment means for FF/UMEC/VI and BUD/FOR+TIO, respectively.

The non-inferiority margin has been set at 50 mL.This non-inferiority margin for 0-24 hour WM FEV1 has previously been accepted by the FDA (Combivent vs Ipratropium head to head study).

If the lower bound of the two-sided 9 5% confidence interval around the (FF/UMEC/VI vs. BUD/FOR+TIO,) treatment difference is above -50 mL then FF/UMEC/VI will be considered non-inferior to BUD/FOR+TIO. Further treatment comparisons and inferences to be made based on P-values are detailed in Section 10.4.1.

10.2. Sample Size Determination

The sample size calculations use a one-sided 2.5 % significance level and an estimate of residual standard deviation (SD) for 0-24 hour WM FEV_1 of 230 mL. The estimate of SD is based on mixed models repeated measures [MMRM] analyses of past studies in COPD with 0-24 hour weighted mean as primary endpoint. A study with 620 evaluable participants for the primary analysis will have 90 % power to determine non-inferiority of FF/UMEC/VI to BUD/FOR+TIO based on 0-24 hour WM FEV_1 at Week 12 (Day 84), when the margin of non-inferiority is 50 mL and the true mean treatment difference is assumed to be 10 mL.

It is estimated that approximately 15 % of participants who are randomised will either discontinue IP or be excluded from the modified Per Protocol population at Week 12 and approximately 8 % of participants will drop out from 4-week run-in (including those not meeting randomisation criteria). Therefore, approximately 800 participants will be enrolled to 4-week run-in in order to have 732 participants to be randomised.

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Subject Enrolled (ASE)	• All participants for whom a record exists in the study database, including screen failures and any participant who was not screened but experienced an SAE between the date of informed consent and the planned date of the Screening visit.
Run-in	• All participants who are eligible at Screening and entered Run-in period.
Intent-to Treat (ITT)	• All randomised participants, excluding those who were randomised in error. A participant who is recorded as a screen or run-in failure and also randomszed will be considered to be randomised in error. Any other participant who receives a randomisation number will be considered to have been randomised. • Displays will be based on the treatment to which the participant was randomised.
Modified Per Protocol (mPP)	• All participants in the ITT Population who do not have a full protocol deviation considered to impact efficacy. • Data following a COPD exacerbation or pneumonia will be excluded from analysis due to the potential impact of the exacerbation or the medications used to treat it. • Participants with partial protocol deviations considered to impact

Population	Description
	efficacy will be included in the mPP Population but will have their data excluded from analyses from the time of deviation onwards. • This population will only be used for the primary analysis for the primary endpoint.

10.4. Statistical Analyses

10.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint, 0-24 hour WM FEV1 on Day 84 will be analyzed with mPP population using mixed model repeated measure (MMRM) analysis, including covariates such as baseline FEV1, visit, geographical region, treatment and visit by baseline interaction. A visit by treatment interaction term will also be included to allow treatment effects to be estimated at each visit separately. The variance-covariance matrix will be assumed unstructured. Baseline FEV1 is the mean of the two assessments made -30 and -5 minutes predose on Treatment Day 1. Estimated differences between FF/UMEC/VI and BUD/FOR+TIO will be presented together with 95 % confidence intervals (CIs) for the treatment difference and P-value. The same analysis will be repeated for the ITT Population. Inference to be drawn from the p-values will be as follows: • Analysis with mPP population: If the treatment comparison on the primary endpoint has a lower confidence limit below the non-inferiority margin, non-inferiority is not demonstrated. No inference will be drawn from p-values for treatment comparisons on any other endpoints. • Analysis with mPP population: If the treatment comparison on the primary endpoint has a lower confidence limit above the non-inferiority margin but below 0, non-inferiority is established but the p-value will not be used to give an indication of the strength of that noninferiority. Inference will be drawn from p-values for treatment comparisons (with ITT population) on other non-lung function endpoints,i.e, SGRQ and CAT, which will be called statistically significant if <0.05. No inference will be drawn from p-values on trough FEV1 endpoint. Analysis with ITT population: If the treatment comparison on the primary endpoint has a lower confidence limit above 0, superiority is established and the p-value can be used to give an indication of the strength of that superiority. Inference will be drawn from p-values for treatment comparisons on all other endpoints, which will be called statistically significant if <0.05. A “tipping point” sensitivity analysis of 0-24hour WM FEV1 on Day 84 will be conducted for the mPP Population. This will explore the impact of missing data by using differing assumptions regarding the mean treatment effect in participants who discontinue study treatment or have data excluded from mPP Population analyses. Assumptions will include scenarios where participants who discontinue FF/UMEC/VI have a lower treatment effect than those who discontinue BUD/FOR+TIO. The analysis results will be used to explore the conditions under which the conclusion of non-inferiority no longer holds.

Endpoint	Statistical Analysis Methods
	If superiority on primary endpoint is established with ITT population, similar "tipping point" sensitivity analysis will be conducted for the ITT population in order to explore the conditions under which the conclusion of superiority no longer holds.
Secondary	• Secondary endpoint change from baseline in trough FEV_1 will be analysed for the ITT Population using a mixed model repeated measures (MMRM) analysis, including trough FEV_1 recorded at each of visits, Day 2, Day 28, Day 84 and Day 85. The model will include covariates of baseline FEV_1, visit, geographical region, treatment and visit by baseline interaction. A visit by treatment interaction term will also be included to allow treatment effects to be estimated at each visit separately. The variance-covariance matrix will be assumed unstructured. Estimated differences between FF/UMEC/VI and TIO will be presented together with 95 % CIs for the difference and p-values.
Other	Will be described in the reporting and analysis plan.

10.4.2. Safety Analyses

All safety analyses will be performed on the ITT Population.

Endpoint	Statistical Analysis Methods
Primary	There is no primary safety analysis.
Secondary	The following safety endpoints will be analysed descriptively by treatment group: • Incidence of adverse events • Incidence of adverse events of special interest (AESI) • Vital signs Details will be described in the reporting and analysis plan

Adverse events (AEs) will be coded using the standard GSK dictionary MedDRA, and grouped by body system. The number and percentage of participants experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be presented for each treatment group. Separate summaries will be provided for all AEs, drug related AEs, fatal AEs, non-fatal SAEs, adverse events of special interest (AESIs) and AEs leading to withdrawal. Deaths and SAEs, if applicable, will be documented in case narrative format.

10.4.3. Other Analyses

Full details of the analyses to be performed on the primary and other efficacy endpoints will be given in the Reporting and Analysis Plan (RAP).

10.4.4. Interim Analyses

No interim analysis is planned for this study.

10.4.5. Exploratory Analyses

These exploratory analyses may be provided in a separate RAP.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Atrial Fibrillation
ALT	Alanine Transaminase
ASE	All Subjects Enrolled
AST	Aspartate Transaminase
ATS	American Thoracic Society
BfS	Federal Office for Radiation Protection
BPM	Beats per minute
BMI	Body Mass Index
BUD	Budesonide
BUN	Blood Urea Nitrogen
CAT	COPD Assessment Test
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Database
CT	Computerized Tomography
CV	Cardiovascular
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of study
EXACT-RS	Exacerbations and Chronic Pulmonary Disease – Respiratory Symptoms tool
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FF	Fluticasone Furoate
FOR	Formoterol
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good clinical practice
GCSP	Global Clinical Safety and Pharmacovigilance
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin

HCP	Health Care Provider
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-Pituitary-Adrenal
HPLC	High-Performance Liquid Chromatography
HRQoL	Health related quality of life
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine Hormone-Releasing System
IWRS	Interactive Web Response System
ITT	Intent-to-Treat
Kg/m^2	Kilograms per meter squared
LABA	Long-Acting Beta-2-Agonists
LAMA	Long-Acting Muscarinic Antagonist
LRTI	Lower Respiratory Tract Infection
LTOT	Long-term oxygen therapy
MACE	Major Adverse Cardiac Event
MAOI	Monoamine Oxidase Inhibitors
MedDRA	Medicinal Dictionary for Regulatory Activities
mcg	Microgram
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDI	Metered Dose Inhaler
min	Minute
mL	Milliliter
mMRC	Modified Clinical Research Council
MMRM	Mixed-Model Repeated Measures
mPP	Modified Per Protocol
MSDS	Material Safety Data Sheet
msec	Millisecond
NA	Not Applicable
NYHA	New York Heart Association
PDE4	Phosphodiestrase 4 inhibitor
PGx	Pharmacogenetic
PRAC	Pharmacovigilance Risk Assessment Committee
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
RBC	Red Blood Cell
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SGRQ-C	St. George's Respiratory Questionnaire for COPD patients
SMQ	Standardised MedDRA Queries
SoA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reaction
TIO	Tiotropium
TQT	Thorough QT
UK	United Kingdom
ULN	Upper Limit of Normal
UMEC	Umeclidinium
US	United States
VI	Vilanterol
VT	Ventricular Tachycardia
WBC	White Blood Cell
WM	Weighted Mean
WOCBP	Woman of child-bearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ELLIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
Spiriva Handihaler
Symbicort

12.2. Appendix 2: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- 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 participants, as appropriate.
- GSK will provide the Investigator with the randomisation codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 25 years from the issue of the final Clinical Study Report/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study treatment development

12.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 7.

Table 7 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1 % per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the Participants.)*

NOTES:
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test

- Additional pregnancy testing should be performed during the treatment period (see SoA) and whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing will be performed using the test kit provided by the central laboratory and in accordance with instructions provided in its package insert

Collection of Pregnancy Information

Female participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participants will be followed to determine the outcome of the pregnancy. The Investigator will collect follow up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to GSK as described in Appendix 6. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- **Any female participant who becomes pregnant while participating in the study will immediately discontinue study medication.**

12.4. Appendix 4: Liver Safety: Required Actions and Follow-up Assessments

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria - Liver Stopping Event</th></tr>
<tr><td>Alanine Transaminase (ALT)-absolute</td><td colspan="2">ALT ≥ 8x ULN</td></tr>
<tr><td>ALT Increase</td><td colspan="2">ALT ≥ 5x ULN but <8x ULN persists for ≥2 weeks
ALT ≥ 3x ULN but <5x ULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td colspan="2">ALT ≥ 3x ULN and bilirubin ≥ 2x ULN (>35 % direct bilirubin)</td></tr>
<tr><td>International Normalized Ratio (INR)[2]</td><td colspan="2">ALT ≥ 3x ULN and INR >1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td colspan="2">ALT ≥ 5x ULN but <8x ULN and cannot be monitored weekly for ≥2 weeks
ALT ≥ 3x ULN but <5x ULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td colspan="2">ALT ≥ 3x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve , stabilize, or return to within baseline</td><td colspan="2">• Viral hepatitis serology[4]
• Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5].
• Blood sample for pharmacokinetic analysis, obtained within 72 hours after last dose[6]</td></tr>
</table>

(see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol • If restart/rechallenge **not allowed per protocol** , permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Serum creatine phosphokinase and lactate dehydrogenase. • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3x ULN **and** bilirubin ≥ 2x ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3x ULN **and** bilirubin ≥ 2x ULN (>35 % direct bilirubin) or ALT ≥ 3x ULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant'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.

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

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5x ULN and <8x ULN **and** bilirubin <2x ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3x ULN and <5x ULN **and** bilirubin <2x ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant 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 participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5x ULN and <8x ULN to ≥3x ULN but <5x ULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3x ULN and bilirubin <2x ULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

References

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

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.

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

12.5.1. Guidelines for Identifying COPD Exacerbations

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

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

- Dyspnoea
- 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

Participants 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 participant 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
- If the participant 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.

Participants with worsening respiratory symptoms will be classified as having:

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

OR

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

- Other respiratory related disease

12.5.2. COPD Exacerbation Severity

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

> **Mild**: Worsening symptoms of COPD that are self-managed by the participant. 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.

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 participant experiences worsening symptoms of COPD which match the definition of an exacerbation as given above.

12.5.3. Treatment of COPD Exacerbations

All medications used for the treatment of exacerbations must be recorded in the source documents and the exacerbation page of the eCRF. All sites should follow the protocol treatment guidelines (as outlined below), but any medications deemed medically necessary may be used to treat a COPD exacerbation. However, caution is advised in using a LABA or LAMA to treat a participant 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 participant's study treatment temporarily in order to treat the COPD exacerbation.

12.5.4. Guidelines for Treatment with Corticosteroids

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

- The duration of treatment with oral/systemic corticosteroids should be ≤14 days (dose and type according to local practice)
- The duration of treatment with oral/systemic corticosteroids should not exceed 14 days unless approval is given by the sponsor or representative

- Any course of oral/systemic corticosteroids started within 7 days of finishing a previous course will be considered as treatment for a single exacerbation

12.5.5. Guidelines for Treatment with Antibiotics

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

- The duration of treatment with antibiotics should 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 for participants to continue on study treatment, 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 participant experiences worsening of symptoms of COPD

12.5.6. Onset and Resolution of COPD Exacerbations

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

The date of onset is the first day (of at least 2 consecutive days) of worsening symptoms.

The date of resolution should be based on when the Investigator and/or participant 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 participant evaluation.

12.5.7. Guideline for assessing multiple mild exacerbations

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

12.5.8. Guideline for assessing exacerbations that increase in severity

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

12.6. Appendix 6: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • 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 study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • 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 before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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 it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses 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. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety

assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which 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.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant 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 outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent disability/incapacity

- 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.   • The Investigator will then record all relevant AE/SAE information in the eCRF.

- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to GSK. However, **it is very**

important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK**.**

- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The Investigator or medically-qualified sub-Investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the assigned SAE contact by telephone.

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

SAE Reporting to GSK via Paper CRF

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

12.7. Appendix 7: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition and Documentation of Medical Device Incidents

Definitions of a Medical Device Incident

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

Medical Device Incident Definition
• A medical device incident is 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 participants/user/other person or to a serious deterioration in his/her state of health.
• Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

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

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Foetal distress, foetal death, or any congenital abnormality or birth defects

Examples of incidents
• A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A participant's study treatment is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. • A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the Investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE eCRF page will be completed as described in Appendix 6. • The form will be completed as thoroughly as possible and signed by the Investigator before transmittal to the GSK. • It is very important that the Investigator provides his/her assessment of causality (relationship to the medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

12.8. Appendix 8: Clinical Laboratory Tests

- All protocol required laboratory assessments (haematology, clinical chemistry and urinalysis) must be conducted in accordance with the Laboratory Manual, and Protocol SoA (Section 2). Laboratory requisition forms must be completed and samples must be clearly labelled with the participant number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Laboratory Manual. Reference for all safety parameters will be provided to the site by the laboratory responsible for the assessments.
- All blood samples which will be taken pre-dose, will be sent to a central laboratory for analysis (details provided in the Laboratory Manual). Standard reference ranges will be used.
- If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eCRF.
- Refer to the Laboratory Manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6.1 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 8 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: Mean Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin (MCH)	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [nonfasting]	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum / urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] The results of each test must be entered into the CRF.			

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7 All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 x ULN (>35 % direct bilirubin) or ALT ≥3 x ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

12.9. Appendix 9: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a 6 mL blood sample will be collected for DNA analysis.
- DNA samples may be used for research related to study treatment or COPD and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to study treatment or study treatments of this drug class and indication. Genetic research may consist of the analysis of one or more candidate genes (including but not limited to: *PIK3CD*, *PIK3CA*, *IL10*, *CHRNA3*, *CHRNA5*, *DNAH5*, *SUMF1*, and *CELSR1*) or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study treatment or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study treatment (or study treatments of this class) or indication continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

12.10. Appendix 10: Country-specific requirements

There are currently no country specific requirements.