TITLE PAGE

Protocol Title: Phase IV, 12-week, single arm, open label study evaluating the safety and efficacy of fixed dose triple combination FF/UMEC/VI administered once daily in the morning via a dry powder inhaler in participants with chronic obstructive pulmonary disease in India.

Study Identifier: 212655/ Amendment 04

Compound Number or Name: GSK2834425

Brief Title: A single-arm, open-label study to evaluate the safety and efficacy of FF/UMEC/VI in participants with COPD.

Study Phase: Phase 4

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s): N/A

Medical Monitor Name and Contact Information [will be provided separately OR can be found in the Study Reference Manual]

SPONSOR SIGNATORY:

David J. Slade M.D.
Clinical Development Lead
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Approval Date: 03 May 2023

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 4	03 May 2023	TMF-16036460
Amendment 3	29 Nov 2022	TMF-15155358
Amendment 2	30-MAR-2021	TMF-11895735
Amendment 1	17-Nov-2020	2020N442016_01
Original Protocol	29-Jul-2020	2020N442016_00

Amendment 4 (date): 03 May 2023

Overall Rationale for the amendment

Protocol Amendment 03 was approved by DCGI. However, some of the intended updates for PA3 were inadvertently missed and are retained, in the protocol. This amendment is to correct these typographical errors.

Section # and Name	**Description of Change**	**Brief Rationale**
1.2 Schema	In the study design schema, Visit 3 on day 28 has been mentioned as week 12. This is a typographical error, and it has been corrected to week 4 which is in line with day 28.	Correction of a typographical error
4.1 Overall Design	In the study design schema, Visit 3 on day 28 has been mentioned as week 12. This is a typographical error, and it has been corrected to week 4 which is in line with day 28.	Correction of a typographical error
8.1.1 Spirometry	All participants will have spirometry performed at screening and each scheduled clinic visit during the treatment period. Corrected to, All participants will have spirometry performed at each	Spirometry at screening is not required as per PA.3. This was inadvertently missed out from being deleted in this sentence.

Section # and Name	Description of Change	Brief Rationale
	scheduled clinic visit during the treatment period.	
8.1.1 Spirometry	Spirometry equipment will be provided through a centralized vendor and will calculate the percent reversibility for each participant. Corrected to, Spirometry equipment will be provided through a centralized vendor.	Calculation of percent reversibility is not required as per PA.3. This was inadvertently missed out from being deleted in this sentence
8. 3	Method of Detecting AEs and SAEs Corrected to 8.3.2 Method of Detecting AEs and SAEs	Addition of number to the section
8.3	8.3.2 Follow-up of AEs and SAEs Corrected to 8.3.3 Follow-up of AEs and SAEs	Correction of numbering sequence
8.3	8.3.3 Adverse Events of Special interest Corrected to 8.3.4 Adverse Events of Special interest	Correction of numbering sequence
8.3	8.3.4 Regulatory reporting requirements for SAEs/AESI Corrected to 8.3.5 Regulatory reporting requirements for SAEs/AESI	Correction of numbering sequence

Section # and Name	Description of Change	Brief Rationale
8.3	8.3.5 Pregnancy corrected to 8.3.6 Pregnancy	Correction of numbering sequence
8.3	8.3.6 Cardiovascular and Death events corrected to 8.3.7 Cardiovascular and Death events	Correction of numbering sequence
8.3	8.3.7 The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed as per SAE reporting timelines Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs Corrected to 8.3.8 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs	Correction of numbering sequence and typographical error in the title
8.3	8.3.8 Drug/Inhaler Combination Product Deficiencies corrected to 8.3.9 Drug/Inhaler Combination Product Deficiencies	Correction of numbering sequence
8.3.7	For all death and any cardiovascular events detailed in Appendix 6, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding	Correction of formatting error

Section # and Name	Description of Change	Brief Rationale
	cardiovascular (including sudden cardiac death) and non-cardiovascular death. The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion. **Corrected to** For all death and any cardiovascular events detailed in Appendix 6, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death. The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion. The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be	

Section # and Name	Description of Change	Brief Rationale
	completed as per SAE reporting timelines	

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title

Phase IV, 12-week, single arm, open label study evaluating the safety and efficacy of fixed dose triple combination FF/UMEC/VI administered once daily in the morning via a dry powder inhaler in participants with chronic obstructive pulmonary disease in India.

Brief Title: A single-arm, open-label study to evaluate the safety and efficacy of FF/UMEC/VI in participants with COPD.

Rationale:

Fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) is approved in many countries including the USA, EU, and India for the treatment of chronic obstructive pulmonary disease (COPD). Many multi-centre, multi-national studies have been conducted with FF/UMEC/VI, however, these studies did not include India as a participating country. As part of post approval commitment, Phase IV study for FF/UMEC/VI in India will be conducted, to provide safety and efficacy data from the Indian population.

The primary purpose of this study is to evaluate the safety and efficacy of a single inhaler triple therapy combination of FF/UMEC/VI (100mcg/62.5mcg/25mcg) administered once daily via the ELLIPTA™ inhaler, following 12 weeks of treatment.

Objectives and Endpoints/Estimands:

Objectives	Estimands/Endpoints
Primary	
• To evaluate the safety profile of FF/UMEC/VI over 12 weeks in patients from India	The primary Estimand is defined by the following: • Endpoint: incidence of adverse events (AE), serious adverse events (SAE) and adverse events of special interest (AESIs). • Summary measure: number and percentage of participants experiencing an AEs, SAEs and number and percentage of participants experiencing AESIs by system organ class and by preferred term.

Objectives	Estimands/Endpoints
	• Population of interest: COPD patients in India. • Key intercurrent events: discontinuation of treatment (for any reason) • Strategy for intercurrent events: a While on Treatment strategy will be used for treatment discontinuation. This estimates the percentage of participants experiencing an AE or SAE while taking treatment. • Participants that test positive for COVID-19 will immediately discontinue study treatment. Therefore COVID-19 will be included as the intercurrent event of study treatment discontinuation and will be handled with While on Treatment strategy for the primary estimand A supplementary estimand will be defined using identical properties as for the primary estimand (summary measure, population of interest and key intercurrent events), however this supplementary estimand will report all AEs regardless of the discontinuation of study treatment. <u>Endpoints:</u> • Incidence of AEs, SAEs and AESIs <u>Strategy for intercurrent events:</u> • Treatment policy strategy will be used for treatment discontinuation. This summary will therefore be inclusive of all on-treatment and post-treatment AEs.
Secondary	
• To evaluate the effect of FF/UMEC/VI on lung function	The secondary Estimands are defined by the following: • Endpoints:

Objectives	Estimands/Endpoints
	○ change from baseline in trough FEV1 on Day 85 (trough FEV1 on Day 85 is defined as the mean of the FEV1 values obtained 24 hours after morning dosing on Day 84) ○ change from baseline in trough FEV1 on Day 28 (trough FEV1 on Day 28 is defined as the mean of the FEV1 values obtained prior to dosing on Day 28) • Summary measure: ○ mean change from baseline in trough FEV1 on Day 85 ○ mean change from baseline in trough FEV1 on Day 28 • Population of interest: COPD patients in India. • Key intercurrent events: discontinuation of treatment • Strategy for intercurrent events: a hypothetical strategy will be used for treatment discontinuation. This estimates the effect under the hypothetical scenario that participants had not discontinued treatment. • Participants that test positive for COVID-19 will immediately discontinue study treatment. Therefore COVID-19 will be included as the intercurrent event of study treatment discontinuation and will be handled with hypothetical strategy for the secondary estimands.

Overall Design:

This is a phase IV, 12-week, single arm, multi-centre study evaluating single inhaler triple therapy (FF/UMEC/VI) once daily via the ELLIPTA (see Section 1.2 for study schematic). Approximately 306 participants will be screened in order to enroll 229 to the study treatment phase, to achieve 220 evaluable participants at the end of the study. At the start of the treatment period, participants will discontinue all existing COPD medications but may continue their study-supplied rescue salbutamol on an as-needed basis (rescue medication) throughout the study.

Clinic Visits will occur at Pre-Screening (Visit 0), Screening (Visit 1), Start of Treatment (Day 1, Visit 2), Day 28 (Visit 3), and Day 85 (Visit 5). Day 84 (Telephonic Visit 4) and Safety follow-up (Visit 6) conducted 1 week after completing the 12-week treatment period will be a telephone contact. Participants will sign an informed consent form (ICF) at a Pre-Screen or Screening Visit and will be assigned a participant identifier. Note: Visit 0 and Screening (Visit 1) may occur on the same day based on discretion of the study participant and discretion of Investigator

Number of Participants:

Approximately 306 participants will be screened in order to achieve 220 evaluable participants at the end of the study (assuming 4% withdrawal from study treatment).

Intervention Groups and Duration:

Participants who have consented meet all the eligibility criteria and who have successfully completed all protocol procedures at screening will receive the following study intervention for 12 weeks:

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

On the morning of study clinic Visit 2 (start of treatment), Day 28 (Visit 3) and telephonic contact Day 84 (telephonic Visit 4), participants will refrain from taking their morning dose of study intervention/COPD medication until instructed to do so by clinic personnel. Participants will take their last dose of study treatment on Day 84 and will return for their final clinical assessments on Day 85 (Visit 5). A safety follow-up (Visit 6) will be conducted by phone call approximately one week later. Participants may continue their study-supplied rescue salbutamol from the start of the study treatment phase until the end of the treatment period.

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

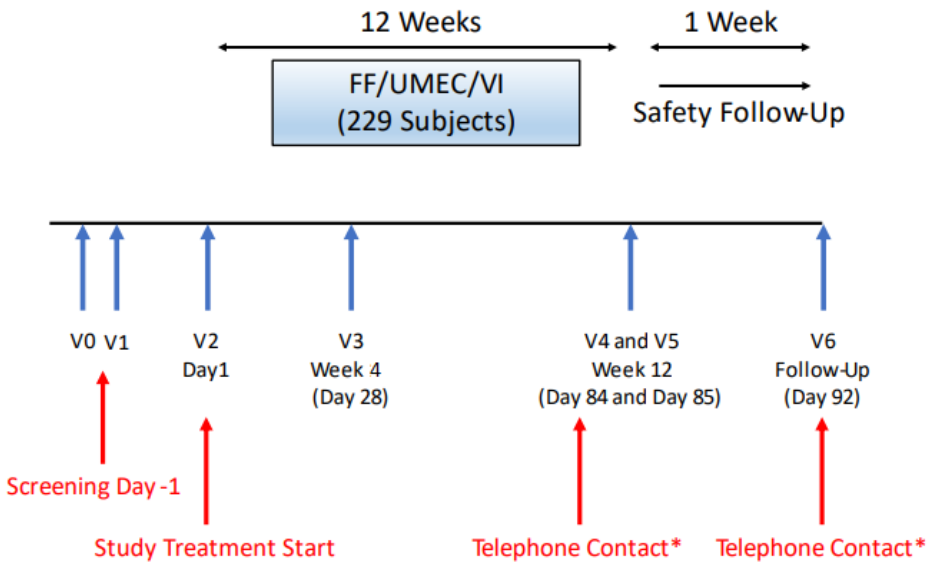
The total duration of participant participation will be approximately 13 weeks, 12-week treatment period and a 1-week follow-up period.

Participants that permanently discontinue study intervention 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. 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.

Data Monitoring/ Other Committee: No

1.2. Schema



1.3. Schedule of Activities (SoA)

Protocol Activity	**Pre-Screen**	**Screen**	**Treatment**					**Follow-up**
	Visit 0	**Visit 1 Screen**	**Visit 2**	**Visit 3**	**Visit 4[e]** (Telephonic)	**Visit 5**	**Study treatment discontinuation**	**Safety Follow-up Visit 6[f]**
Study Day			**Week 0/Day 1**	**Week 4/Day 28**	**Week 12/Day 84**	**Week 12/Day 85**		**1-week Follow-up/Day 92**
Window		**(Day -1)**		**-4/+2d (Day 24 to 30)**	**-4/+2d (Day 80 to 86)**	**-4/+2d (Day 81 to 87)**		**-1/+4d (Day 91 to 96)**
Written Informed Consent [a]	X	X						
Demography [b]	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					
COVID-19 test [c]		X						
Smoking History		X						
Smoking status		X				X	X	
Smoking Cessation Counselling		X				X	X	
CAT		X						
Baseline/Trough Spirometry [d]			X	X		X		
Exacerbation Assessment			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	
Urine Pregnancy Test [j]		X				X	X	
Dispense study treatment			X	X				
Administer study treatment [k]			X	X	X			
Assess current COPD treatment compliance			X					

Protocol Activity	Pre-Screen	Screen	Treatment					Follow-up
	Visit 0	Visit 1 Screen	Visit 2	Visit 3	Visit 4[e] (Telephonic)	Visit 5	Study treatment discontinuation	Safety Follow-up Visit 6[f]
Study Day			Week 0/Day 1	Week 4/Day 28	Week 12/Day 84	Week 12/Day 85		1-week Follow-up/Day 92
Window		(Day -1)		-4/+2d (Day 24 to 30)	-4/+2d (Day 80 to 86)	-4/+2d (Day 81 to 87)		-1/+4d (Day 91 to 96)
Assess study treatment compliance				X		X	X	
Collect study treatment						X	X	
Dispense salbutamol as required		X	X	X		X		
Collect salbutamol						X	X	
Dispense paper Medical Problems worksheet		X	X	X		X		
Review paper Medical Problems worksheet			X	X		X	X	

a. Informed consent must be conducted 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. Demography may be captured at either the Pre-screen Visit or Screening Visit (for participants who do not have a Pre-screen Visit).
c. The test should be done at Visit 1, using a molecular (PCR [polymerase chain reaction] or antigen test) approved by the country regulatory authorities.
d. At Visits 2 and 3, trough FEV_1 will be performed pre-dose prior to taking the morning dose of study treatment/COPD medication, between 8am and 11am and after withholding rescue salbutamol for > 4 hours. Trough FEV_1 on Day 85 (Visit 5) will be performed 24 hours after morning dosing on Day 84 (Visit 4), after withholding rescue salbutamol for > 4 hours.
e. At Day 84 (Visit 4), participant will be instructed by the investigator telephonically to take the morning dose of study treatment/COPD medication, between 8am and 11am and reminded to: 1) withhold rescue salbutamol for > 4 hours prior to visit 5 and 2) withhold the Day 85 (Visit 5) dose of Investigative Product until after spirometry (Trough FEV) has been completed.
f. A safety follow-up at Day 92 (Visit 6) will be conducted telephonically.
g. Physical examination may include height and weight.
h. Vital signs, including temperature, blood pressure and pulse must be performed prior to spirometry..
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. All female participants of child-bearing potential will have a urine pregnancy test at Visits 1, 5 and Treatment Discontinuation Visit (if applicable).
k. Participants will receive their first dose study treatment in the clinic at Visit 2. At Visits 3 and 4 participants must refrain from taking their morning dose of study treatment until instructed to do so by study staff. Visit 3 study treatment administration will be in the clinic and Visit 4 study treatment administration will be at home.

When multiple assessments and procedures are performed suggested sequence order is CAT, vitals, ECG, spirometry. Study procedures to be completed during a COVID-19 pandemic are detailed in Appendix 4.

2. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) guidelines advocate the use of long-acting muscarinic receptor antagonists (LAMA) added to the combination of an inhaled corticosteroid (ICS) plus a long-acting β2-adrenergic receptor agonists (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 exacerbations in patients with a forced expiratory flow in 1 second (FEV1) <60 % predicted [Aaron, 2007; Cazzola, 2007; Hanania, 2012; Jung, 2012; Siler, 2015; Welte, 2009].

GlaxoSmithKline (GSK) has developed 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, to provide a new treatment option for the management of symptomatic COPD patients at risk for exacerbations. FF/UMEC/VI is approved in many countries including the USA, EU and India for the treatment of COPD. FF/UMEC/VI has been shown to reduce all-cause mortality, exacerbation frequency, improve lung function, HRQoL and symptom control over established dual/monotherapies [Lipson, 2020; Lipson, 2017; Lipson, 2018; Ferguson, 2020].

2.1. Study Rationale

Fluticasone furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) is approved in many countries including the USA, EU, and India for the treatment of chronic obstructive pulmonary disease (COPD). Many multi-centre, multi-national studies have been conducted with FF/UMEC/VI, however, these studies did not include India as a participating country. As part of the post approval commitment for fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) in India, a Phase IV study will be conducted, to provide safety and efficacy data from the Indian population.

The purpose of this study is to evaluate the safety and efficacy of a single inhaler triple therapy combination of FF/UMEC/VI (100mcg/62.5mcg/25mcg) administered once daily via the ELLIPTA™, following 12 weeks of treatment, in COPD participants in India.

2.2. Background

The Phase III program for FF/UMEC/VI included two large studies of 6 to 12 months in duration. Studies CTT116853 (FULFIL) and CTT116855 (IMPACT).

Study CTT116853 (FULFIL) was a Phase III, 23-week, randomised, double-blind, double-dummy, parallel-group study (with an extension to 52 weeks on blinded therapy in a subset of subjects) comparing the efficacy, safety, and tolerability of FF/UMEC/VI once-daily via Ellipta with budesonide/formoterol (400/12 mcg) twice daily via Turbuhaler in participants with COPD. 1810 patients were randomized and included in the ITT population. Co-primary endpoints were change from baseline in trough FEV_1 and

change from baseline in St George's Respiratory Questionnaire (SGRQ) total score at Week 24.

The study demonstrated clinically meaningful and statistically significant improvements in lung function and health related quality of life and reductions in moderate/severe COPD exacerbations for FF/UMEC/VI compared to budesonide/formoterol.

The overall safety profile of FF/UMEC/VI in study CTT116853 was in line with the pharmacologic class of each component and with the previously approved dual combinations FF/VI and UMEC/VI, and no new safety signals emerged in the ITT Population to 24 weeks and an Extension Population to 52 weeks.

Study CTT116855 (IMPACT) was a Phase III, 52-week, randomized, double-blind, 3-arm parallel group study, comparing the efficacy, safety and tolerability of FF/UMEC/VI with FF/VI and UMEC/VI, all administered once daily in the morning via the Ellipta, in participants with COPD. The primary endpoint was the annual rate of moderate/severe exacerbations.

A total of 10,355 participants were randomized and included in the ITT population. The primary objective of the study was met by demonstrating the superiority of FF/UMEC/VI over FF/VI and UMEC/VI for the co-primary treatment comparisons of the annual rate of on-treatment moderate/severe exacerbations in subjects with moderate to very severe COPD at risk of exacerbation. Treatment with FF/UMEC/VI resulted in a statistically significant reduction of on-treatment moderate/severe exacerbations of 15% compared with FF/VI ($p<0.001$) and 25% compared with UMEC/VI ($p<0.001$).

FF/UMEC/VI also resulted in statistically significantly improvements in non-exacerbation-related measures of trough FEV1, SGRQ Total Score, CAT score, TDI focal score, rescue-medication use and night-time awakenings compared with both FF/VI and UMEC/VI demonstrating a wide range of benefit across objective evaluations of lung function, subjective evaluations of HRQoL, and patient-reported measures associated with disease symptoms. FF/UMEC/VI also reduced all-mortality compared to UMEC/VI.

The overall safety profile of FF/UMEC/VI was in line with the pharmacologic class of each component and with the previously approved dual combinations FF/VI and UMEC/VI; no new safety signals were identified.

A detailed description of the chemistry, pharmacology, efficacy and safety of FF/UMEC/VI is provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of FF/UMEC/VI may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) GSK2834425 (FF/UMEC/VI)		
Pneumonia in participants with COPD	Pneumonia is a class concern for any inhaled corticosteroid (ICS)-containing product for the treatment of COPD. In a 52-week study (CTT116855), in a total of 10,355 randomised COPD patients with a history of moderate/severe exacerbations, there was a higher incidence of any event in the pneumonia AESI group in the ICS-containing FF/UMEC/VI (317 participants [8%], rate of 95.8 per 1,000 participant-years) and FF/VI (292 participants [7%], rate of 96.6 per 1,000 participant-years) groups compared with the UMEC/VI group (97 participants [5%], rate of 61.2 per 1,000 participant-years). Known risk factors for pneumonia in patients with COPD include older age, male gender, prior pneumonia, low BMI, current smoking and more severe airflow limitation. These risk factors should be taken into consideration when using an ICS in participants with COPD.	- 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 and to treat appropriately (see Section 8.2.3). - Appropriate exclusion criteria as specified in Section 5.2 of the protocol - All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable) as specified in Section 8.2.3.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		- Chest X-ray read required at baseline and encouraged whenever a participant has suspected pneumonia or mod/severe exacerbations during the study.
Serious cardiovascular events	Cardiovascular (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 prevalence of CV co morbidities increases with worsening severity of COPD. In study CTT116855 (also designated a category 3 safety study, as requested by the EU CHMP), for the Cardiovascular (CV) effects AESI, there were similar incidences and exposure adjusted rates across the FF/UMEC/VI, FF/VI and UMEC/VI treatment groups (10% to 11% and 157.0 to 167.2, respectively). In the Major adverse cardiac events (MACE) analysis 2% in the FF/UMEC/VI group, 1% in the FF/VI group, and 2% in the UMEC/VI group reported any MACE).	- 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 5.2 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 7.1.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	There were no emerging safety signals based on review of the vital signs, ECGs and Holter data (where performed) across FF/UMEC/VI clinical development studies to date. 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.	
Adrenal suppression	Oral corticosteroids are known to influence the hypothalamic-pituitary-adrenal (HPA) axis leading to a reduction in cortisol production. Due to the low dose and low systemic exposure with ICSs, this potential effect is not clear, nor is the possible impact of any change in cortisol. In study CTT116855, no events were reported in the adrenal suppression AESI group for FF/UMEC/VI. With respect to the FF/VI clinical development program, a formal HPA study and multiple studies with COPD (and asthma) participants monitored urinary	-Investigators are informed of the risk in the IB

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	cortisol. These studies did not show a clinically relevant effect of FF/VI 100/25 on the HPA axis.	
Corticosteroid Associated Eye Disorders (glaucoma, cataract, raised intra-ocular pressure)	Systemic ocular effects (*e.g.* cataract and glaucoma) may occur with any ICS, particularly at high doses prescribed for long periods. However, these effects are much less likely to occur with ICSs compared with oral corticosteroids. In study CTT116855, the incidences of Ocular Effects AESI were low and similar across treatment groups (1% in each group). During studies 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 5.2 of the protocol - If a risk is suspected, participants should receive appropriate assessment & treatment
Anticholinergic effects (including constipation nausea, dry mouth, glaucoma, raised intraocular pressure and blurred vision, urinary retention)	Pharmacologic class effects of LAMAs include anticholinergic effects, such as glaucoma and urinary retention.	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 study CTT116855, for the anticholinergic syndrome (SMQ) AESI, there were similar incidence and exposure-adjusted rates across the FF/UMEC/VI, FF/VI and UMEC/VI treatment groups (incidence: 4%, 3% and 3%. Glaucoma SMQ incidence was 1%, <1% and 1% in FF/UMEC/VI, FF/VI and UMEC/VI treatment). Urinary retention AESI incidence was <1% in all treatment groups.	- Appropriate exclusion criteria as specified in Section 5.2 of the protocol - If a risk is suspected, participants should receive appropriate assessment & treatment
Decreased bone mineral density (BMD) and associated fractures	Decreased bone mineral density (BMD) 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 CTT116855, the incidences of Decreased BMD and associated fractures	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	AESI were similar between the FF/UMEC/VI, FF/VI and UMEC/VI treatment groups (2% in each group). A post-authorisation BMD safety study with FF/VI demonstrated non-inferiority of FF/VI 100/25 mcg to VI 25 mcg on the primary endpoint of the percent change from baseline in overall adjusted BMD per year at the total hip by the pre-defined noninferiority margin of -1% (HZC102972).	
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 CTT116855, the exposure adjusted rates for the Asthma/bronchospasm (SMQ) AESI across the FF/UMEC/VI, FF/VI and UMEC/VI treatment groups (<1% for all three groups respectively).	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB.
Hypersensitivity	Hypersensitivity may occur in response to various allergens, and hypersensitivity reactions have been previously described for ICS, LAMA and LABA drug classes.	- Participants will be informed about the risk in the informed consent. - Investigators are informed of the risk in the IB.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In study CTT116855, the incidences of Hypersensitivity AESI were similar between the FF/UMEC/VI, FF/VI and UMEC/VI treatment groups (5% in all groups). The vast majority of relevant events were considered not related following a detailed evaluation. Rare post-marketing cases of anaphylaxis, angioedema, urticaria and rash have been reported for FF/UMEC/VI.	- Appropriate exclusion criteria as specified in Section 5.2 of the protocol.
Study Procedure Risks		
Exposure to ionizing radiation from chest x-ray.	The dose from a single chest X-ray should not exceed 20 microsieverts (µSv) and this corresponds to a lifetime risk of a fatal malignancy of about 1 in 1 million (ICRP 103), which falls into the 'trivial' risk category as defined by ICRP 62. The study will minimize exposure by using x-rays acquired as part of clinical care whenever possible. It is expected that all subjects will require a single chest x-ray, but occasionally they may have a maximum of 3 chest X-rays (up to maximum 60 µSv within this study, lifetime risk of fatal	-Only participants at /or above 40 years of age will be eligible for inclusion. - Women of childbearing potential (WOCBP) will only be allowed to participate if they are using highly effective contraception. - Women of childbearing potential (WOCBP) will have pregnancy tests as specified in the SOA. -All procedures will be performed by a qualified technician.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	malignancy of approximately 1 in 300,000).	
Other		
COVID-19	The WHO has declared the outbreak of respiratory illness caused by the Severe Acute Respiratory Syndrome Coronavirus-2 as a global pandemic. Initial observational data [Zhao, 2020] indicate that patients with COPD may be at significantly higher risk of developing severe disease manifestations. No definitive data is currently available on the impact of any medication classes taken by inhalation.	-Exclusion criteria pertaining to current COVID-19 infection including close contact with other infected patients (Section 5.2). -Testing for COVID-19 at screening. -Withdrawal criteria in case of COVID-19 infection (Section 7.1.4)

2.3.2. Benefit Assessment

COPD guidelines advocate the use of one or more long-acting bronchodilators (LAMA or LABA) in addition to ICS as therapy treatment option for the most advanced patients with significant symptoms and a high risk of exacerbations [GOLD, 2020].

Participants enrolled in this study will receive FF/UMEC/VI once daily. Participants are anticipated to derive clinical benefit from this combination of study treatments. In a disease where polypharmacy is common, the FF/UMEC/VI, once-daily combination has the potential to optimise bronchodilator therapy, improve patient adherence to therapy and, as a result, improve overall disease management.

2.3.3. Overall Benefit: Risk Conclusion

The clinical development programme for FF/UMEC/VI demonstrated a favourable benefit/risk for patients with COPD. This has led to approval and marketing of FF/UMEC/VI for a COPD indication in many countries worldwide. Current risks that have been identified for these therapeutic classes are based on the known pharmacology of the individual components: ICS, LAMA and LABA.

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 are justified by the anticipated benefits from active treatment that may be afforded to patients with COPD.

3. OBJECTIVES AND ENDPOINTS/ESTIMANDS

Objectives	Estimands/Endpoints
Primary	
• To evaluate the safety profile of FF/UMEC/VI over 12 weeks in patients from India	The primary Estimand is defined by the following: • Endpoint: incidence of adverse events (AE), serious adverse events (SAE) and adverse events of special interest (AESIs). • Summary number and percentage of participants experiencing an AEs, SAEs and number and percentage of participants experiencing AESIs by system organ class and by preferred term. • Population of interest: COPD patients in India. • Key intercurrent events: discontinuation of treatment • Strategy for intercurrent events: a While on Treatment strategy will be used for treatment discontinuation. This estimates the percentage of participants experiencing an AE or SAE while taking treatment. • Participants that test positive for COVID-19 will immediately discontinue study treatment. Therefore COVID-19 will be included as the intercurrent event of study treatment discontinuation and will be handled with While on Treatment strategy for the primary estimand A supplementary estimand will be defined using identical properties as for the primary estimand (summary measure, population of interest and key intercurrent events), however this supplementary

Objectives	Estimands/Endpoints
	estimand will report all AEs regardless of the discontinuation of study treatment. Endpoints: • Incidence of AEs, SAEs and AESIs Strategy for intercurrent events: • Treatment policy strategy will be used for treatment discontinuation. This summary will therefore be inclusive of all on-treatment and post-treatment AEs.
Secondary	
• To evaluate the effect of FF/UMEC/VI on lung function	The secondary Estimands are defined by the following: • Endpoints: o change from baseline in trough FEV1 on Day 85 (trough FEV1 on Day 85 is defined as the mean of the FEV1 values obtained 24 hours after morning dosing on Day 84) o change from baseline in trough FEV1 on Day 28 (trough FEV1 on Day 28 is defined as the mean of the FEV1 values obtained prior to dosing on Day 28) • Summary measure: o mean change from baseline in trough FEV1 on Day 85 o mean change from baseline in trough FEV1 on Day 28 • Population of interest: COPD patients in India. • Key intercurrent events: discontinuation of treatment • Strategy for intercurrent events: a hypothetical strategy will be used for treatment discontinuation. This estimates the effect under the hypothetical scenario that participants had not discontinued treatment.

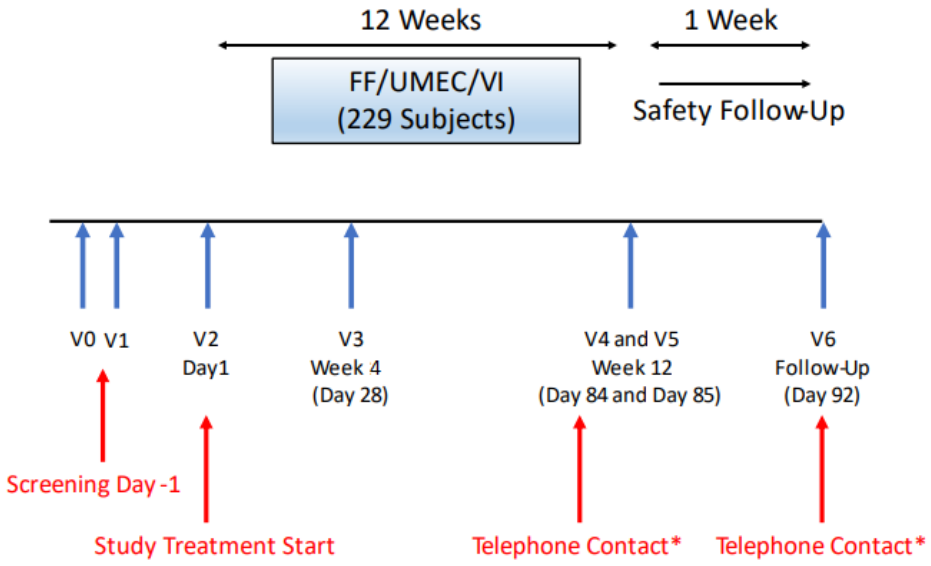
Objectives	Estimands/Endpoints
	• Participants that test positive for COVID-19 will immediately discontinue study treatment. Therefore COVID-19 will be included as the intercurrent event of study treatment discontinuation and will be handled with hypothetical strategy for the secondary estimands.

4. STUDY DESIGN

4.1. Overall Design

This is a phase IV, 12-week, single arm, multicentre study evaluating single inhaler triple therapy (FF/UMEC/VI) once daily via the ELLIPTA inhaler.

Figure 1 Study Design Schema



* At day 84 (telephonic visit), participant will be instructed by the investigator telephonically to take the morning dose of study treatment/COPD medication, between 8am and 11am

Approximately 306 participants will be screened in order to enroll 229 (assuming 25% screen failure) to the study treatment phase and achieve 220 evaluable participants at the end of the study (assuming 4% withdrawal from study treatment).

At the start of the treatment period, participants will discontinue all existing COPD medications but may continue their study-supplied rescue salbutamol on an as-needed basis (rescue medication) throughout the study.

Clinic Visits will occur at Pre-Screening (Visit 0), Screening (Visit 1), Start of Treatment (Day 1, Visit 2), Day 28 (Visit 3), and Day 85 (Visit 5). Day 84 (telephonic Visit 4) and Safety follow-up (Visit 6) conducted 1 week after completing the 12-week treatment period will be a telephone contact. Participants will sign an informed consent form (ICF) at a Pre-Screen or Screening Visit and will be assigned a participant identifier.

4.2. Scientific Rationale for Study Design.

Though safety and efficacy of FF/UMEC/VI in patients with COPD has been established in various clinical studies across USA, Europe, and a number of other countries including Japan and China, this will be the first clinical study to assess safety and efficacy in patients in India.

This study will use a multicenter, single arm design. A single arm study is considered sufficient, based on the wealth of data already generated for FF/UMEC/VI, in extensive studies conducted globally, containing multiple treatment arms and comparators. Eligible participants must have been on daily maintenance COPD medications for at least 3 months.

4.3. Jsustification for Dose

FF/UMEC/VI (100/62.5/25mcg) is approved for the treatment of COPD in over 15 countries/regions, including the United States (US), Canada, the EU, Japan, and other countries worldwide.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including screening, treatment phase and 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 1.3) for the last participant in the study.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

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

2. **Type of 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 2 during the treatment period and until the safety follow-up contact after the last dose of study intervention.

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. Patient with history of ≥2 moderate exacerbations or one severe (hospitalized) exacerbation in the previous 12 months, and with a score of ≥10 on the CAT eligible for the study treatment in the opinion of the investigator and documented post salbutamol FEV1/FVC ratio of <0.70

8. **Existing COPD maintenance treatment:** Participant must be receiving daily long-acting maintenance treatment for their COPD for at least 3 months prior to Screening. To be eligible for the study treatment phase, participants must be compliant with their

existing COPD maintenance therapy (in the opinion of the investigator) for the preceding two weeks prior to screening.
Note: *Participants receiving only short-acting COPD medications are not eligible.*

9. A negative test for **active COVID-19** at Visit 1. The test should be done using a molecular (PCR or antigen test) approved by the country regulatory authorities.

5.2. Exclusion Criteria

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

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

2. **Asthma**: 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. **Reversibility:** Documented (medical records) evidence of reversibility. Reversibility is defined as an increase in FEV1 of ≥ 12% and ≥200mL following administration of salbutamol. Participants defined as non-reversible will have a post-salbutamol increase in FEV1 of <200mL or a ≥200mL increase that is <12% from pre-salbutamol baseline.
4. **α1-antitrypsin deficiency**: Participants with α1-antitrypsin deficiency as the underlying cause of COPD.

5. **Other respiratory disorders**: Participants with active tuberculosis, lung cancer, and clinically significant (in the opinion of the investigator): bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases.

6. **Lung resection**: Participants with lung volume reduction surgery within the 12 months prior to Screening.

7. **Risk Factors for Pneumonia**: immune suppression (*e.g.* advanced HIV with high viral load and low CD4 count, Lupus on immunosuppressants that 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).

   Patients at potentially high risk for pneumonia (*e.g.* very low BMI, severely malnourished, or very low FEV1) will only be included at the discretion of the investigator.

8. **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 and/or antibiotics (if applicable). In addition, any participant that experiences pneumonia and/or moderate or severe COPD

exacerbation within the preceding two weeks prior to screening during the will be excluded.

9. **Respiratory tract infection** that has not resolved at least 7 days prior to Screening.

10. Participants with known **COVID-19 positive contacts** within the past 14 days should be excluded for at least 14 days since the exposure and the subject remains symptom free.

    - Participants with symptoms suggestive of active COVID-19 infection e.g. fever, cough (new or worsened), etc. are also excluded

11. **Abnormal Chest x-ray**: Chest x-ray (posteroanterior and lateral) reveals evidence of pneumonia or a clinically significant abnormality not believed to be due to the presence of COPD, or another condition that would hinder the ability to detect an infiltrate on CXR (e.g. significant cardiomegaly, pleural effusion or scarring). All participants will have a chest x-ray at Screening Visit 1 (or historical radiograph or CT scan obtained within 3 months prior to screening).

12. **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.

13. **Unstable liver disease** as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices or persistent jaundice, cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

    Note: *Chronic stable hepatitis B and C are acceptable if the participant otherwise meets entry criteria*.

14. **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

    - NYHA Class IV Heart failure

15. **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 of ≥500 msec in participants with QRS <120 msec and QTcF ≥530 msec in participants with QRS ≥120 msec

16. **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.

17. **Cancer**: Participants with carcinoma that has not been in complete remission for at least 5 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 5 year waiting period if the subject has been considered cured by treatment.

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

19. **Pulmonary rehabilitation**: participants must not start the acute phase of a pulmonary rehabilitation program within the 4 weeks prior to Visit 1.

20. **Medication prior to spirometry**: Participants who are medically unable to withhold their salbutamol for the 4-hour period required prior to spirometry testing at each study visit.

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

22. **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.

23. **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.

24. **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.

25. **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.

25**. Medication prior to screening:** Use of the following medications within the following time intervals prior to Visit 1 or during the study:

Table 1 Prohibited Medications Prior to Screening

Medication	No use within the following time intervals prior to Screening
Antibiotic therapy	30 days
Systemic, Oral, parenteral corticosteroids	30 days Intra-articular injections are allowed
Any other investigational drug	30 days or 5 half-lives whichever is longer.

5.3. Treatment phase Criteria

At Start of Treatment (Visit 2), study participants must fulfil the following additional criteria, to enter the treatment phase:

1. **Compliance with current COPD maintenance therapy**
   - Participants who are non-compliant to their current COPD maintenance therapy for two weeks prior to screening (in the opinion of the investigator) will be excluded.
2. **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 and/or antibiotics (if applicable). In addition, any participant that experiences pneumonia and/or moderate or severe COPD exacerbation within the preceding two weeks prior to screening will be excluded.

5.4. Lifestyle Considerations

Participants should avoid the following activities prior to each pulmonary function test:

- smoking and/or vaping and/or water pipe use for 1 hour
- consumption of intoxicants for 8 hours
- drinking beverages with high levels of caffeine such as tea and coffee for 2 hours
- vigorous exercise for 1 hour

5.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen 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, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

5.6. Criteria for Temporarily Delaying Enrollment/Administration of Study Intervention

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

Participants will receive FF/UMEC/VI (see Table 2) and should inhale once from the ELLIPTA inhaler in the morning each day for the duration of the 12-week treatment period.

Table 2 Description of ELLIPTA™

FF/UMEC/VI	First strip	Second strip
	CCI [redacted]	
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	
Sourcing	Provided centrally by the sponsor	
Packaging and labelling	Each Ellipta inhaler will be labeled and placed in a labelled foil pouch with a desiccant. The foil pouch will then be placed in a window carton.	

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive FF/UMEC/VI and only authorized site staff may supply or administer FF/UMEC/VI. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled 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 intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual.
- Under normal conditions of handling and administration, study intervention 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 occupational 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.

6.3. Measures to Minimize Bias: Randomization and Blinding

Blinding will not be used as this is an open label, single-arm study.

6.4. Study Intervention Compliance

At scheduled study visits participants will receive FF/UMEC/VI under medical supervision. The date and time of each dose administered in the clinic will be recorded in the eCRF. When participants self-administer study treatment at home, compliance will be assessed through querying each participant during site visits and recording the number of doses remaining in the ELLIPTA inhaler, in the source documents and eCRF.

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 participants that are non-compliant. Participants that continue to be non-compliant after multiple visits may be permanently discontinued from study treatment, following consultation with the GSK team.

6.5. Dose Modification

No dose modifications are planned for this study.

6.6. Continued Access to FF/UMEC/VI after the End of the Study

Following participation completion of the study, the treating physician should determine what the most appropriate COPD maintenance medication is for each participant. FF/UMEC/VI is commercially available in India, and will be a possible treatment option for patients, following completion of the study.

6.7. 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 as the IB.

6.8. Concomitant Therapy

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

All non-COPD medications taken during the study (in the treatment phase and up to the safety follow-up contact) 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 (start and end dates) are to be recorded.

Note*: Study provided 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 treatment phase of the study (Visit 5) or started after discontinuation of study treatment must be recorded in the eCRF up to the safety follow-up contact.

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

6.8.1. Permitted Medications and Non-Drug Therapies

6.8.1.1. Permitted COPD Medications

The following COPD medications are permitted during the treatment period:

- Study supplied salbutamol MDI or nebules (must be withheld for at least 4 hours prior to pulmonary function testing)
- Mucolytics such as acetylcysteine
- Long term oxygen therapy (flow rate of ≤3 litres/minute at rest). Oxygen therapy may be adjusted as deemed medically necessary at any time during the treatment phase 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 %)
- Study provided COPD medications in the treatment period
- Any COPD medication deemed medically necessary for the short-term treatment (≤14 days) of a moderate/severe COPD exacerbation or pneumonia (such as oral or injectable corticosteroids and/or antibiotics). Any participant that experiences a moderate/severe COPD exacerbation or pneumonia within two weeks prior to screening (in the opinion of the investigator) should be excluded.

6.8.1.2. Permitted Non-COPD Medications

The following non-COPD medications are permitted during the treatment period:

- 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. Cardio-selective 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)

6.8.2. Prohibited Medications and Non-Drug Therapies

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

Table 3 Concomitant Prohibited Medications

Medications Prohibited during the 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 beta2-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 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 salbutamol, mucolytics and oxygen) are prohibited during the study treatment period, 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 necessary, 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.

6.8.3. Rescue Medicine

The study site will supply salbutamol rescue medication that will be provided locally.

Although the use of rescue medications is allowable at any time during the study, rescue medication should be withheld for at least 4h hour prior to all pulmonary function tests. Sites should not perform spirometry on subjects who have taken a SABA/salbutamol within 4 hours prior to pulmonary function tests. The subjects will need to wait at the site, or be rescheduled for the next day, whichever is feasible

7. DISCONTINUATION OF FF/UMEC/VI AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of FF/UMEC/VI

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

Participants that permanently stop FF/UMEC/VI should return to the clinic as soon as possible, in order to complete the Treatment Discontinuation visit. The evaluations and procedures to be completed are outlined in the SoA (Section 1.3)

Participants that discontinue FF/UMEC/VI 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.

If possible, participants should return to the clinic to complete all scheduled visits. If this isn't possible, visits should be completed by telephone. Ideally, participants should return to the clinic to complete Visit 5, to collect important spirometry data, however, if this isn't possible, this visit could be completed by telephone. A safety follow-up phone call (Visit 6) should also be conducted 7 days after Visit 5.

Following discontinuation of study intervention, if participants are unwilling to return to the clinic for their scheduled visits, 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 discontinuation of study intervention or withdrawal from the study
- COPD exacerbations
- Concomitant medication
- A safety follow-up phone call (Visit 6) should also be conducted 7 days after Visit 5.

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

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study intervention 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 3.

7.1.2. QTc Stopping Criteria

Details on performing ECG assessments can be found in Section 8.2.6.

- 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.

7.1.3. Pregnancy stopping criteria

- Any female participant that becomes pregnant while participating in the study will discontinue study intervention. Participants are encouraged to remain in the study and every effort should be made by the Investigator/staff to keep the participant in the study. Please see Section 8.3.6 for further details on reporting pregnancies and associated follow-up.

7.1.4. COVID-19 stopping criteria

All participants suspected to have contracted COVID-19 must be tested using a molecular (PCR or antigen test) approved by the regulatory authorities in India.

Participants that test positive for COVID-19 must immediately discontinue study intervention and complete the Study Treatment Discontinuation Visit. Participants are encouraged to remain in the study and every effort should be made by the Investigator/staff to keep the participant in the study.

7.2. Participant 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, behavioural, or compliance reasons. This is expected to be uncommon.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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.

7.3. 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 participant 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.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- 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 intervention.
- 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.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- **No study related procedures may be performed until the informed consent form has been signed by the participant.** 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.

The timings of all efficacy assessments are specified in the SoA (Section 1.3).

Revised study assessments and detailed guidance on study conduct during future COVID-19 epidemic waves are detailed in Appendix 4.

8.1. Efficacy Assessments

8.1.1. 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 - each scheduled clinic visit during the treatment period. For FEV_1 and FVC determinations, at least 3 acceptable spirometry efforts (with no more than 8) should be obtained. Acceptable spirometry efforts should have a satisfactory start of test and end of test (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.
- After completing the CAT health outcomes assessment (Visit 1 only)
- After withholding albuterol/salbutamol for ≥4 hours.
- Before the morning dose of maintenance COPD medication or study treatment.
- Participants should refrain from smoking and/or vaping and use of a water pipe 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.
- Participants should not consume intoxicant for 8 hours prior to each pulmonary function test
- Vigorous exercise should be avoided for at least 1 hour prior to each pulmonary function test.

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

Spirometry equipment will be provided through a centralized vendor.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.
Adverse events (AEs) and Serious Adverse Events (SAEs) will be coded using the standard GSK dictionary, Medical Dictionary for Regulatory Activities (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. Initial SAEs to be reported to GSK, Health Authority and Ethics Committee, within 24 hours of occurrence. Follow up SAEs to be reported to GSK, Health Authority and Ethics Committee, within 24 hours of site awareness.
Incidence of COVID-19 will be reported as an AE and SAE., as applicable. Additional safety analysis to evaluate the impact of COVID-19 on safety assessment may be performed. Details will be provided in the RAP.

8.2.1. Safety Endpoints

- Adverse Events, Serious Adverse Events, Adverse Event of Special Interests (AESIs)
- Assessments include Physical examination, vital signs, Oropharyngeal examination, Electrocardiogram

8.2.2. COPD exacerbations

For this study, a COPD exacerbation is defined as a worsening of COPD symptoms requiring the use of any treatment other than study medication or rescue salbutamol. This includes the use of antibiotics, systemic corticosteroids and/or emergency treatment of hospitalisation.

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

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 on the COPD exacerbations page of the eCRF.

A moderate COPD exacerbation is defined as requiring systemic corticosteroids and/or antibiotics. A severe COPD exacerbation is defined as requiring hospitalization.

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

Subjects who experience a moderate or severe COPD exacerbation within two weeks prior to screening (in the opinion of the investigator) will be discontinued from the study and are not allowed to be re-screened.

COPD exacerbations are associated with the disease under study and will not be recorded as AEs unless the exacerbation meets the definition of a “serious” AE as defined in Section 10.6 of this protocol. Exacerbations that meet the definition of “serious” will be recorded on the appropriate eCRF section and should be reported to GSK, Health Authority and the Ethics Committee within 24 hours of occurrence.

Medications used to treat a COPD exacerbation will be recorded in the COPD concomitant medication section of the eCRF.

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

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

8.2.3. 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.

Participants who experience a pneumonia during within two weeks prior to screening (in the opinion of the investigator) will be discontinued from the study and are not allowed to be re-screened.

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. 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 pneumonia is reported or suspected and recorded in the source documents and on the pneumonia page of the eCRF if applicable.

8.2.4. 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.

8.2.5. Vital Signs

- Vital signs will be measured in a sitting position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.

- Vital signs will be performed at the time points specified in the SoA table (Section 1.3) prior to conducting spirometry and prior to taking study treatment.
- A single set of values will be collected and recorded in the source documentation and eCRF.

8.2.6. 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 1.3). 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 7.1.2).
- 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.

8.2.7. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria and the SoA table.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.2.8. COVID-19 testing

- Refer to Section 5.1 Inclusion Criteria for COVID-19 testing entry criteria and the SoA table.
- Additional COVID-19 tests may be performed, as determined by the investigator or local guidelines.
- All positive COVID-19 tests should be reported on the COVID-19 eCRFs and the AE/SAE eCRFs, as well as the exacerbation/pneumonia eCRFs, as appropriate.
- Participants that test positive for COVID-19 should discontinue study intervention, as specified in Section 7.1.4.
- Positive tests should be reported to the appropriate government authorities, per local regulations.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AE) or serious adverse events (SAEs) can be found in Section 10.6.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified 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 intervention or the study, or that caused the participant to discontinue the study intervention or study (see Section 7).

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.

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

- All AEs and SAEs will be collected from the start of intervention (Visit 2) until the follow-up contact (Visit 6) at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions not as AEs.
- All SAEs will be recorded and reported to the sponsor or designee, Health Authorities and EC, immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data (Follow up report) to the sponsor within 24 hours of it being available and awareness of the same.

  Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. 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 intervention or study participation, the investigator must promptly notify the sponsor within the timelines mentioned above.

8.3.2. 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.

8.3.3. 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, and non-serious events, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 6.

8.3.4. Adverse events of special interest

Within the FF, UMEC, and VI clinical development programs for asthma/COPD, the following ICS, LAMA, and LABA class effects were considered adverse events of special interest (AESIs) (Table 4).

Table 4 Adverse Events of Special Interest (AESI) Definitions

Special interest group	Special interest subgroup	PTs/SMQs for inclusion
CV effects	Cardiac arrhythmia	Cardiac arrhythmia (SMQ), excluding congenital and neonatal arrhythmias
	Cardiac failure	Cardiac failure (SMQ)
	Cardiac ischemia	Ischemic Heart Disease (SMQ)
	Stroke	CNS haemorrhages and cerebrovascular conditions (SMQ)
	Hypertension	Hypertension (SMQ)
Pneumonia [1]	Pneumonia	Infective pneumonia (SMQ)
LRTI (excluding infective pneumonia SMQ)		Selected PTs
Decreased BMD and associated fractures		Osteoporosis/osteopenia (SMQ) Selected PTs
Hypersensitivity		Hypersensitivity (SMQ) Angioedema (SMQ) Anaphylactic reaction (SMQ)
Anticholinergic syndrome		Anticholinergic Syndrome SMQ
Gastrointestinal obstruction		Gastrointestinal obstruction SMQ
Adrenal suppression		Selected PTs
Antimuscarinic ocular effects/ corticosteroid-associated eye disorders	Glaucoma (antimuscarinic/ corticosteroid)	Glaucoma (SMQ)
	Cataracts (corticosteroids)	Lens disorder (SMQ)

Special interest group	Special interest subgroup	PTs/SMQs for inclusion
Effects on glucose		Hyperglycaemia/ new onset diabetes mellitus (SMQ)
Local steroid effects		Selected PTs
Urinary retention		Selected PTs
Effects on potassium		Selected PTs
Tremor		Selected PTs
Asthma/bronchospasm for asthma-related intubations and deaths		Asthma/bronchospasm SMQ
Dry mouth/drying of airway secretions		Selected PTs (narrow and broad focus) [2]

Abbreviations: BMD, bone mineral density; CNS, central nervous system; CV, cardiovascular; LRTI, lower respiratory tract infection; PT, preferred term; RAP, Reporting and Analysis Plan; SMQ, standardized MedDRA queries.

1. All diagnosed pneumonias (with or without radiographic confirmation) were to be recorded on the adverse event page of the eCRF and on the pneumonia page of the eCRF. All suspected pneumonias were required to be confirmed by the presence of new infiltrates on a posteroanterior and lateral chest x-ray (≤48 h of suspected event) (details provided in Protocol Section 7.5.1.6).
2. Includes nasopharyngitis.

8.3.5. Regulatory Reporting Requirements for SAEs/AESI

- Prompt notification by the investigator to the sponsor of an SAE/AESI is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 intervention 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.
- For SAEs/AESIs, the investigator must always provide an assessment of causality at the time of the initial report.
- An investigator who receives an investigator safety report describing an SAE/ AESI or other specific safety information (e.g., summary or listing of SAEs) 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.
- 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.

8.3.6. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the safety follow-up visit.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate pregnancy notification form and submit it to GSK within 24 hours of awareness of the pregnancy. While pregnancy itself is not considered to be an AE or

SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed up to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.5. 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 discontinue study intervention but may remain in the study (if consent is not withdrawn).

8.3.7. Cardiovascular and Death Events

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

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

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed as per SAE reporting timelines

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

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 (see Section 8.2.2 and Appendix 5 for further details).

8.3.9. Drug/Inhaler Combination Product Deficiencies

- FF/UMEC/VI administered via the ELLIPTA inhaler is a GSK drug/inhaler combination product. GSK must be notified if this Drug/Inhaler combination product fails to function properly as a result of an inhaler deficiency. Inhaler deficiencies should be reported as outlined in the SRM, and not as a safety event. Inhaler deficiencies will be reported to the sponsor within 24 hours.

- It is possible for a reportable safety event to occur at the same time as a device malfunction. Safety events are reported as described in Section 8.3.

8.4. Pharmacokinetics

PK parameters are not evaluated in this study.

8.5. Genetics

Genetics are not evaluated in this study.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.8. Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

There will be no formal hypothesis testing.

9.2. Sample Size Determination

The primary objective of the study is to evaluate the safety profile of FF/UMEC/VI over 12 weeks of treatment. The primary endpoint is incidence of AEs, SAEs and AESIs. Sample size is determined based on the calculation of the probability of observing an AE. Table 5 provides the probabilities of observing various numbers of AEs based on a series of theoretical risks of an event occurring in a given patient in a study of 12 weeks duration, given a sample size of 220. For example, for a theoretical risk of an AE of 1/100 in this 12 week study, we would have a greater than 89% chance of observing at least one subject having the AE.

Table 5 Probabilities of observing a given number of subjects experiencing an adverse events or more (k) for given theoretical risks in a study of 12 weeks duration for a sample size of 220 patients

	Theoretical Risk of an Event*					
k	0.0500	0.0300	0.0100	0.0050	0.0010	0.0001
1	>0.9999	0.9988	0.8904	0.6680	0.1976	0.0218
2	0.9998	0.9904	0.6469	0.3011	0.0209	0.0002
3	0.9990	0.9621	0.3776	0.0991	0.0015	<0.0001
4	0.9958	0.8984	0.1799	0.0254	<0.0001	
5	0.9866	0.7915	0.0715	0.0053		
6	0.9658	0.6488	0.0242	0.0009		
7	0.9266	0.4906	0.0071	0.0001		
8	0.8634	0.3410	0.0018	<0.0001		
9	0.7748	0.2178	0.0004			
10	0.6651	0.1281	<0.0001			

*Theoretical risk of an event occurring in a given subject in a study of 12 weeks duration.

A study with 220 evaluable participants will also provide a precision of 32ml in estimating the treatment effect of change from baseline in trough FEV1 on Day 85. The precision is defined as the half width of 95% confidence interval (CI). The calculations assume an estimate of residual standard deviation (SD) of 240mL (based on mixed model repeated measures [MMRM] analyses of Trelegy Phase IIb FULFIL study).

Total 229 participants will be enrolled in study treatment phase to achieve 220 evaluable participants at the end of the study assuming 4% withdrawal from the study treatment.

Assuming 25% screen failure rate, approximately 306 participants will be screened. If a future COVID-19 pandemic increases the number of participants that discontinue study

intervention or increases the amount of missing spirometry data the sample size may be increased. Please see Appendix 4 for further details. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Screened	• 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.
Enrolled	• All participants who signed the ICF and screen passed
Intent-to Treat (ITT)	• All participants who received at least one dose of study treatment.

9.3. Statistical Analyses

The statistical analysis plan will be finalized prior to data lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary, and secondary endpoints.

9.3.1. Efficacy Analysis

All efficacy analyses will be performed on the ITT Population.

The efficacy endpoints are change from baseline in trough FEV1 on Day 85, and Day 28.

The estimands for these endpoints are defined below:

- Endpoint:
    - change from baseline in trough FEV1 on Day 85 (trough FEV1 on Day 85 is defined as the mean of the FEV1 values obtained 24 hours after morning dosing on Day 84)
    - change from baseline in trough FEV1 on Day 28 (trough FEV1 on Day 28 is defined as the mean of the FEV1 values obtained prior to dosing on Day 28)
- Summary measure:
    - mean change from baseline in trough FEV1 on Day 85
    - mean change from baseline in trough FEV1 on Day 28
- Population of interest: COPD patients in India.
- Key intercurrent events: discontinuation of treatment
- Strategy for intercurrent events: a hypothetical strategy will be used for intercurrent event of treatment discontinuation. Trough FEV1 data collected up to the time of

treatment discontinuation will be used in the analysis. This estimates effect under the hypothetical scenario that participants do not discontinue treatment.
- Participants that test positive for COVID-19 will immediately discontinue study treatment. Therefore COVID-19 will be included as the intercurrent event of study treatment discontinuation and will be handled with hypothetical strategy for the estimand.

The endpoint of change from baseline in trough FEV1 will be analysed using a mixed model repeated measures (MMRM) analysis. The analysis will include change from baseline in trough FEV1 at Day 28, and Day 85. Mean change from baseline in trough FEV1 will be summarised and presented with 95% confidence interval by visit. Trough FEV1 collected after treatment discontinuation will be set to missing. Missing data will be assumed to be missing at random (MAR).

Taking prohibited medication during the treatment period is an important protocol deviation (PD) and will be included in the PD summary. However, this is not considered as an intercurrent event for the estimands.

A supplementary estimand will be estimated using treatment policy strategy for the intercurrent event of treatment discontinuation unrelated to the COVID-19 pandemic and using hypothetical strategy for the intercurrent event of treatment discontinuation related to the COVID-19 pandemic. This supplementary treatment effect will only be estimated if >5% of the ITT subjects discontinued study treatment.

9.3.2. Safety Analysis

All safety analyses will be performed on the ITT Population.

The primary Estimand is defined by the following:

- Endpoint: AE, SAE and AESI.
- Summary measure:
  - number and percentage of participants experiencing an AE
  - number and percentage of participants experiencing a SAE
  - number and percentage of patients experiencing an AESI
- Population of interest: COPD patients in India.
- Key intercurrent events: discontinuation of treatment
- Strategy for intercurrent events: a While on Treatment strategy will be used for treatment discontinuation. This estimates the percentage of participants experiencing an AE, SAE or AESI while taking treatment.
- Participants that test positive for COVID-19 will immediately discontinue study treatment. Therefore COVID-19 will be included as the intercurrent event of study treatment discontinuation and will be handled with While on Treatment strategy for the primary estimand.

A supplementary estimand will be defined using identical properties as for the primary estimand (summary measure, population of interest and key intercurrent events), however

this supplementary estimand will report all AEs regardless of the discontinuation of study treatment.

- Endpoints: Incidence of AEs, SAEs and AESIs
- Strategy for intercurrent events: Treatment policy strategy will be used for treatment discontinuation. This summary will therefore be inclusive of all on-treatment and post-treatment AEs.

In addition, summary statistics for vital signs and their change from baseline at Day 85: heart rate, systolic blood pressure and diastolic blood pressure will be produced.

9.3.3. Other Analysis

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).

9.4. Interim Analysis

Interim analysis is not planned but will be conducted if requested by the regulatory authority.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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, IB, and other relevant documents (e.g., 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.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable),), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. 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.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants 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.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about FF/UMEC/VI or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have FF/UMEC/VI approved for medical use or approved for payment coverage.

10.1.4. 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 who will be required to give consent for their data to be used as described in the informed consent.
- 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.

10.1.5. 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 all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients' received. The investigator(s) is/are encouraged to share the summary results with the study subjects, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in a separate document.
- Quality tolerance limits (QTLs) will be pre-defined in a separate document to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- 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 (CSR)/ 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.

10.1.7. 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 reported on the CRF or 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.
- Definition of what constitutes source data and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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.

10.1.8. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study/Site Termination

GSK or 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate participant therapy and/or follow-up

10.1.9. 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.

10.2. Appendix 2: Contraceptive and Barrier Guidance

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 6.

Table 6 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:
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.
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 sourced locally and in accordance with instructions provided in its package insert
- **Any female participant who becomes pregnant while participating in the study will immediately discontinue study medication.**

10.3. Appendix 3: 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

Table 7 Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
Alanine Transaminase (ALT)-absolute	ALT ≥8x ULN
ALT Increase	ALT ≥5x ULN but <8x ULN persists for ≥2 weeks ALT ≥3x ULN but <5x ULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥3x ULN **and** bilirubin ≥2x ULN (>35 % direct bilirubin)
International Normalized Ratio (INR)[2]	ALT ≥3x ULN **and** INR >1.5, if INR measured
Cannot Monitor	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
Symptomatic[3]	ALT ≥3x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** of occurrence of the SAE per process provided in the Study Reference Manual (SRM)	• 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].

Liver Chemistry Stopping Criteria - Liver Stopping Event	
• 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 (see **MONITORING** below) • **Do not restart** 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**	• Blood sample for pharmacokinetic analysis, obtained within 72 hours after last dose[6] • 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]). • 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.

Liver Chemistry Stopping Criteria - Liver Stopping Event	
• Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	

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.

Table 8 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,	• 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

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
and who can be monitored weekly for 4 weeks.	• 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.

10.4. Appendix 4: Study Procedures during COVID-19 Pandemic

Overall Rationale for this Appendix

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

These measures will remain in place until the site is able to resume normal working activities.

Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrollment and treatment decisions for trial participants.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants.

- Clinical investigators should document in site files and in participant notes how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes, and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).
- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation. Visits that were conducted via the telephone will not be classified as missed visits, however missed assessments (e.g. spirometry) should be recorded as COVID-19 protocol deviations.

Protocol Defined Procedures/Visits:

- Study participants that are in screening should remain on their current COPD maintenance therapy until it is safe for participants to return to the clinic and enter the treatment phase.
- Study participants in the treatment phase of the study (Visit 2 to Visit 5) should be contacted by sites at each scheduled study visit to collect the following:
    - SAEs

- AEs
- COPD exacerbations
- Concomitant medication
- Compliance with study intervention

- **Note:** *The secondary objective of the study is to evaluate the effect of FF/UMEC/VI on lung function, after 12 weeks of treatment. It will not be possible for study participants to complete spirometry assessments at home, therefore the sample size may need to be increased, to ensure there are a sufficient number of evaluable participants with completed spirometry assessments.*
- For study participants that have completed the treatment phase and have only the safety follow-up visit (Visit 6) to complete, this visit can be completed via the telephone, as specified in the SoA.

Study Intervention(s)

- If allowed by country regulation/ethics, study intervention (including rescue study medication) can be shipped direct-to-patient (DTP) from the investigational site to the participant's home address. The process for this shipment must be agreed with GSK who will provide the relevant documentation and links to courier sites required to ensure shipments are adequately temperature controlled (if required) throughout transportation
- The Principal Investigator assumes Good Clinical Practice (GCP) responsibilities for IMP handling and the medical control for dispensing to patients. Site Staff should document the dispensing in the Dispensing/Accountability Logs adding a comment that this was a DTP dispensing.
- In some cases, trial participants who no longer have access to investigational product or the investigational site may need additional safety monitoring.

Data Management/Monitoring:

- If on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a patient and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure subject privacy.
- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing the applicable eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF

signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.

- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK

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

10.5.1. 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

10.5.2. 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.

10.5.3. 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.

10.5.4. 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

10.5.5. 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

10.5.6. 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.

10.5.7. Guideline for assessing multiple mild exacerbations

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

10.5.8. 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.

10.6. Appendix 6: AEs and SAEs, Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.6.1. 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 intervention, whether or not considered related to the study intervention. • 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 intervention.

Events Meeting the AE Definition
• 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 intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention 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.

Events NOT Meeting the AE Definition
• Any clinically significant 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 (e.g., 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.

10.6.2. Definition of SAE

An SAE is defined as any serious adverse event 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 admitted (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 or significant 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,

An SAE is defined as any serious adverse event that, at any dose:
diarrhea, influenza, and accidental trauma (e.g. 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: • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.6.3. Definition of Cardiovascular Events

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

10.6.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- 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 required form.
- 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 sufficient 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 intervention 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.

Assessment of Causality
• Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure (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. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to GSK within 24 hours of receipt / awareness of the information.

10.6.5. Reporting of SAE to GSK

SAE Reporting to GSK via Email
• The primary mechanism for reporting SAE to GSK will be Email. • The site will enter the SAE data into the electronic system as soon as it becomes available and report the event within 24 hours of SAE occurence to GSK by sending the PDF of the Electronic Case Report Form (eCRF) as defined in the Study Reference Manual for the study. • 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

SAE Reporting to GSK via Email
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 medical monitor/SAE coordinator by telephone. • Contacts for SAE reporting will be provided in the Study Reference Manual (SRM) for the study.

SAE Reporting to GSK via email
• Email transmission of the SAE via PDF copy of the CRO eCRF is the preferred method to transmit this information to the SAE contact. • Contacts for SAE reporting will be provided in the Study Reference Manual for the study.

10.7. Appendix 7: Abbreviations and Trademarks

AE	Adverse Event
AF	Atrial Fibrillation
ASE	All Subjects Enrolled
ATS	American Thoracic Society
BfS	Federal Office for Radiation Protection
BPM	Beats per minute
BMI	Body Mass Index
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
COVID-19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Database
CT	Computerized Tomography
CV	Cardiovascular
CYP	Cytochrome P450
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of study
EU	European Union
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FF	Fluticasone Furoate
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
HCP	Health Care Provider
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-Pituitary-Adrenal
HPLC	High-Performance Liquid Chromatography
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
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
MAR	Missing at random
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
MMRM	Mixed-Model Repeated Measures
mPP	Modified Per Protocol
MSDS	Material Safety Data Sheet
msec	Millisecond
NA	Not Applicable
NYHA	New York Heart Association
PCR	Polymerase chain reaction
PDE4	Phosphodiestrase 4 inhibitor
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
SAE	Serious Adverse Event
SD	Standard Deviation
SMQ	Standardised MedDRA Queries
SoA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reaction
TQT	Thorough QT
UK	United Kingdom
UMEC	Umeclidinium
USA	United States of America
VI	Vilanterol
VT	Ventricular Tachycardia
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
None

10.8. Appendix 8: Protocol Amendment History

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

Amendment 3 (date): 29 Nov 2022

Overall Rationale for the amendment

Based on feedback received from top pulmonologists, and review of similar studies conducted in India, the total number of at clinic visits is reduced from 4 to 3 and run-in period on existing COPD medication for 2 weeks has been removed. These changes are expected to simplify the study, reduce the patient burden participant drop-out rates without compromising the quality of the study.

Approximately 306 participants will be screened in order to enroll 229 to the study treatment phase (assuming 25% screen failure rate) and achieve 220 evaluable participants at the end of the study (assuming 4% withdrawal from study treatment).

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Secondary Endpoint: change from baseline and mean change from baseline in trough FEV1 on Day 84 removed Overall Design: Participants will enter run-in on their existing COPD medication for 2 weeks post screening removed. Updated Day 84 visit from physical visit to telephone visit Number of Participants: number of participants screening changed from 336 to 306. Intervention: Groups and Duration: The total duration of participant participation will be approximately 13 weeks. Information on prescription data from India to be used to cap the approximate number of patients enrolled on the most widely prescribed COPD medications is removed	These changes are expected to simplify the study, reduce the patient burden without compromising the quality of the study.

1.2 Study Design Schema	Updated Schema to reflect the proposed amendments	These changes are expected to simplify the study, reduce the patient burden without compromising the quality of the study.
1.3 Schedule of Activities (SoA)	Updated the following: Day 84 visit from physical to telephonic, activities and related instructions in footnote. Updated Day 85 clinic visit activities. Run-in on their existing COPD medication for 2 weeks post screening removed.	These changes are expected to simplify the study, reduce the patient burden without compromising the quality of the study.
3 Objectives and endpoints/Estimands	Secondary Endpoint: Change from baseline and mean change from baseline in trough FEV1 on Day 84 removed	Since, Day 84 visit is replaced to a telephonic visit for medication reminder and effect of FF/UMEC/VI on lung function is evaluated on Day 85
4.1 Overall Design	Updated Day 84 visit from physical visit to telephone visit Participants will enter run-in on their existing COPD medication for 2 weeks post screening removed. Number of participants screening changed from 336 to 306. Text pertaining to participants enrolled are representative of the population that may be eligible for SITT is removed	These changes are expected to simplify the study, reduce the patient burden without compromising the quality of the study.
5 Study Population,	5.1 Inclusion criteria #7 Patient with history of ≥2 moderate exacerbations or one severe (hospitalized) exacerbation in the previous 12 months, and with a score of ≥10 on the CAT eligible for the study treatment in the opinion of the investigator and	To ensure right participants are enrolled in the study.

	documented post salbutamol FEV1/FVC ratio of <0.70 #8 clarification Existing COPD maintenance treatment: To be eligible for the study treatment phase, participants must be compliant with their existing COPD maintenance therapy (in the opinion of the investigator) for the preceding two weeks prior to screening. Updated Section 5.2 Exclusion Criteria section to include Documented (medical records) evidence of reversibility. Participants who are non-compliant to their current COPD maintenance therapy for two weeks prior to screening (in the opinion of the investigator) will be excluded Update below exclusion criteria – removed reference to run-in and updated changes Pneumonia and/or moderate or severe COPD exacerbation that has not resolved at least 14 days prior to Screening and at least 30 days following the last dose of oral/systemic corticosteroids (if applicable). In addition, any participant that experiences pneumonia and/or moderate or severe COPD exacerbation within the preceding two weeks prior to screening will be excluded	
5.3 Treatment Phase Criteria	1. Compliance with current COPD maintenance therapy • Participants who are non-compliant to their current COPD maintenance therapy for two weeks	To ensure right patient is enrolled in the study

	prior to screening (in the opinion of the investigator) will be excluded 2. 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 and/or antibiotics (if applicable). In addition, any participant that experiences pneumonia and/or moderate or severe COPD exacerbation within the preceding two weeks prior to screening will be excluded.	
5.5 Screen Failures	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 and/or antibiotics (if applicable). In addition, any participant that experiences pneumonia and/or moderate or severe COPD exacerbation within the preceding two weeks prior to screening will be excluded and may not be rescreened. and may not be rescreened.	To ensure right patient/ participant is enrolled in the study
6.8 Concomitant Therapy	Removed text pertaining to run-in period.	These changes are expected to simplify the study, reduce the patient burden without compromising the quality of the study.
8.3 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting	Updated section to align with local regulatory safety reporting procedures inputs from Named Safety Contact Removed Sentinel events.	To align with local reporting procedures Sentinel Event Management process is now retired for studies
9.2 Sample Size Determination	Updated the total number of screened subjects in the study	Considering removal of run-in period, the sample size has been updated

9.3 Analysis sets	Updated text for Screened population and added Enrolled population definition	To align with GSK standard to present the subjects disposition data
9.4.1Efficacy analyses	Removed the change from baseline in trough FEV1 on Day 84 analysis	Since, Day 84 visit is replaced to a telephonic visit and effect of FF/UMEC/VI on lung function is evaluated on Day 85
All Relevant sections	All sections relevant to the key changes were updated	To align with the proposed changes to the protocol around. “run-in period” and Day 84 related schedule or assessments

Amendment 2 30-MAR-2021

Overall Rationale for the Amendment:

Based on feedback and recommendations from the Subject Expert Committee (SEC) in India, the sample size of the study has been increased from 115 to 229 participants, to increase the probability of observing adverse events that make up the well-established safety profile of FF/UMEC/VI. In addition, the increase in sample size improves the precision of the estimate of the lung function endpoint, which is a secondary objective of the study.

Approximately 306 participants will be screened in order to recruit 229 to the study treatment phase (assuming 25% screen failure rate) and achieve 220 evaluable participants at the end of the study (assuming 4% withdrawal from study treatment).

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	Removed blood pressure and temperature from footnote f. Removed exacerbation assessment from V1.	This was a duplication, blood pressure and temperature are included in the vital signs assessments (footnote g). This was included in error, exacerbation history is collected as V1.
3 Objectives and endpoints/Estimands	Removed below text change from baseline in trough FEV1 on Day 84 (trough FEV1 on Day 84 is defined as the mean of the FEV1 values obtained prior to dosing on Day 84) mean change from baseline in trough FEV1 on Day 84	Consistent with changes i.e. day 84 will now be telephone call
9.2 Sample Size Determination	The sample size text and associated probabilities table has been updated.	To reflect the increase in sample size.
10.5.6 Onset and Resolution of COPD Exacerbations	Reference to participant diaries has been removed.	This text was included in error.

Amendment 1: 17 Nov 2020

Overall Rationale for the Amendment:

Following review by and presentation of the protocol to the Subject Expert Committee (SEC) in India, the SEC confirmed that the primary reason for requesting that GSK conduct a study, is to provide safety data that is representative of the COPD population in India. For this reason, the primary objective of the study has been amended. The primary objective of the study is to evaluate the safety profile of FF/UMEC/VI over 12 weeks. Lung function objectives are now included in the secondary objectives and associated endpoints.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 2.1 Study Rational 4.2 Scientific Rationale for Study Design	Text has been updated to reflect that the collection of safety data is the primary reason for conducting the study.	To ensure provision of safety data representative of the COPD population in India in line with local regulations
1.1 Synopsis 3 Objectives and Endpoints/Estimands	The primary and secondary objectives and associated endpoints/estimands have been switched, to make safety the primary objective and efficacy (lung function) the secondary objective of the study.	To ensure provision of safety data representative of the COPD population in India in line with local regulations
9.1 Statistical Hypotheses	The primary and secondary objectives have been updated to reflect that the analysis of safety data is the primary objective and the analysis of lung function data is the secondary objective of the study.	Safety is now the primary objective of the study, and efficacy (lung function) is the secondary objective.
9.2 Sample Size Determination	This section has been updated to reflect that the sample size is now determined based on the calculation of the probability of observing an AE.	Safety is now the primary objective of the study, and so the sample size is determined by a safety endpoint.
9.4 Statistical Analyses	Section 9.4.1.and Section 9.4.2. have been updated to define the statistical analyses as efficacy (Section 9.4.1) and safety (Section 9.4.2) and to reflect that safety is the primary objective of the study.	Safety is now the primary objective of the study, and efficacy (lung function) is the secondary objective.

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