TITLE PAGE

Protocol Title: The Clinical Effectiveness of Fluticasone Furoate/Umeclidinium Bromide/Vilanterol in a Single Inhaler (TRELEGYTM ELLIPTATM) when Compared with Non-ELLIPTA Multiple Inhaler Triple Therapies in COPD Patients within a Usual Care Setting.

Protocol Number: 206854/Amendment 02

Short Title: INTREPID: **IN**vestigation of **TR**ELEGY **E**ffectiveness: Usual **P**ract**I**ce **D**esign

Compound Number: GSK2834425(GSK573719+GW642444+GW685698)

Sponsor Name and Legal Registered Address:

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

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

Regulatory Agency Identifying Number(s): EudraCT number 2017-004369-29

Approval Date:28-SEP-2018

SPONSOR SIGNATORY:

PPD

28 SEP 2018

Chris Compton
Medical Affairs Lead, COPD

Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	28-Sep-2018
Amendment 1	15-Feb-2018
Original Protocol	06-Nov-2017

Amendment 2 28-SEP-2018

Overall Rationale for the Amendment 02:

The purpose of the amendment is to:

- Include wording for collection of a historical eosinophil count, whole blood count and % eosinophils, which will be used to provide further characterisation of the patient population enrolled in the study.
- Clarify information pertaining to the reporting of GSK Medical Device/Drug/Device combinations incidents.

Section # and Name	Description of Change	Brief Rationale
2 Schedule of activities	Addition of requirement to collect the most recent historical eosinophil count data.	There is increasing evidence to suggest that eosinophil levels are predictive of response to inhaled corticosteroids. Collection of eosinophil data will allow more complete characterisation of the patient population included in the study and support data interpretation.
3.2.1 and 3.2.2 Risk Mitigation	Changed source of safety information used by the Investigator for Trelegy from the Summary of patient characteristics to the Investigator Brochure.	To be consistent across the asset the decision was made to use the Investigator Brochure as the Reference Safety Information (RSI) as there are countries where Trelegy is still not licensed and are unable to use the SmPC as the RSI.
5.5 Data Collection	Addition of requirement to collect the most recent historical eosinophil count data	There is increasing evidence to suggest that eosinophil levels are predictive of response to inhaled corticosteroids. Collection of eosinophil data will allow more complete characterisation of the patient population included in the study and support data interpretation.
9.4	Rationale for collection of historical eosinophil counts, whole blood count and % eosinophils	There is increasing evidence to suggest that eosinophil levels are predictive of response to inhaled corticosteroids.
9.6 Treatment of overdose	Changed source of safety information used by the Investigator for Trelegy from the Summary of patient characteristics to the Investigator Brochure.	To be consistent across the asset the decision was made to use the Investigator Brochure as the Reference Safety Information (RSI) as there are countries where Trelegy is still not licensed and are unable to use the SmPC as the RSI.
9.7.1 GSK Medical Device GSK Drug/Device combinations	To provide clarity on the reporting requirements and what a drug/device combination is.	As this study is using commercial supply of investigational products, the reporting requirements around drug/device products is different from that of clinical supplies This has been clarified

Section # and Name	Description of Change	Brief Rationale
incidents		
7.6.1 Medications	Changed source of safety information used by the Investigator for Trelegy from the Summary of patient characteristics to the Investigator Brochure.	To be consistent across the asset the decision was made to use the Investigator Brochure as the Reference Safety Information (RSI) as there are countries where Trelegy is still not licensed and are unable to use the SmPC as the RSI.
References	Addition of references to provide background to eosinophil data collection	Provide reader with additional sources.

Overall Rationale for the Amendment 01: The purpose of the amendment is to include wording for reporting of unusual failure in efficacy for new drugs as required by the Canadian Marketed Health Products Directorate. This will permit the inclusion of Canada as a potential study country. Changes have also been made to enable collection of both pre- and post-bronchodilator FEV1 from the spirometry subgroup at baseline. This will permit reversibility assessment and definition of the study subpopulation.
A consenting visit has been added to the schedule of activities, this will allow sites who are assessing lung function to have more flexibility in scheduling.
Other protocol updates include guidance on recording participant participation in pulmonary rehabilitation; the reporting requirements for medical device incidents and inhaler malfunction; some editing for clarity/ consistency and corrections of typographical errors.

Section # and Name	**Description of Change**	**Brief Rationale**
12.3.1 Additional Adverse Event (AE) Reporting Requirements for Canadian investigators	Addition of Health Canada requirements for reporting of unusual failure in efficacy for new drugs to the Marketed Health Products Directorate	Potential addition of Canada as a study country
9 Study Assessments and Procedures 9.1.2 Lung Function	Change to allow collection of both pre-and post-bronchodilator spirometry at Visit 1	Assessment of reversibility and definition of study population
7 Treatments 7.6 Concomitant Therapy	Collection of participant pulmonary rehabilitation programme details	Use of a pulmonary rehabilitation programme may impact the primary outcome. We will collect details of any pulmonary rehabilitation programme to permit analysis of this impact.
9.6 Safety Assessments	Wording added to describe the reporting requirements for medical devices and defective inhalers	To provide sites with clarity
2 Schedule of Activities	Consenting Visit 0 added The maximum time allowed between consent, screening and randomisation set to 6 weeks	To provide sites with flexibility, clarity and consistency
Throughout	Editing for clarity/ consistency and corrections of typographical errors.	Minor, therefore have not been summarised

TABLE OF CONTENTS

PAGE

1. SYNOPSIS

Protocol Title: The Clinical Effectiveness of Fluticasone Furoate/Umeclidinium Bromide/ Vilanterol in a Single Inhaler (TRELEGY™ ELLIPTA™) when Compared with Non-ELLIPTA Multiple Inhaler Triple Therapies in COPD Patients within a Usual Care Setting.

Short Title: INTREPID: **IN**vestigation of **TR**ELEGY **E**ffectiveness: usual **P**ract**I**ce **D**esign

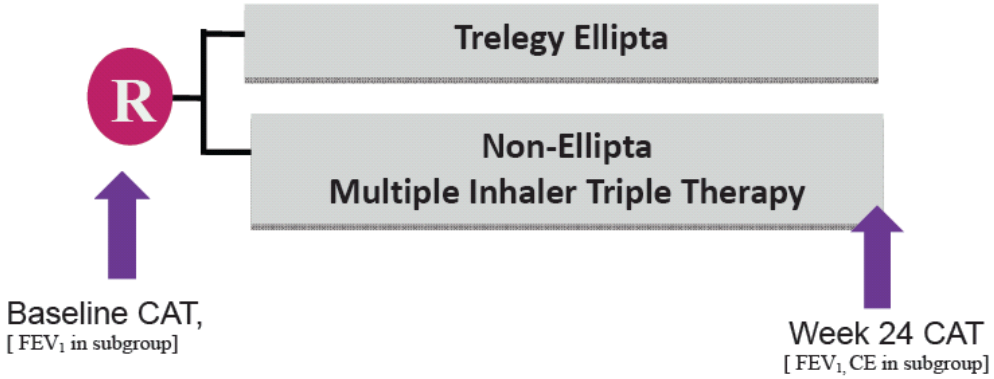
Rationale: The highly-controlled conditions of a randomised clinical trial (RCT) remove factors that influence and differentiate the use of medicines in everyday clinical practice. Effectiveness data generated in the broader population observed in an everyday clinical setting is increasingly being recognised as important in complementing data derived from the pivotal Phase III safety and efficacy studies.

The primary purpose of this study is to assess the effectiveness of TRELEGY ELLIPTA relative to non-ELLIPTA Multiple Inhaler Triple Therapies (MITT) for Chronic Obstructive Pulmonary Disease (COPD) control within the usual clinical practice setting. The study will be conducted once TRELEGY ELLIPTA has been approved in the countries in which the study will be conducted and is available commercially.

Objectives and Primary and Secondary Outcomes:

Objective	Outcome
Primary	
To compare the effectiveness of TRELEGY ELLIPTA with non-ELLIPTA MITT for the impact of COPD on wellbeing and daily life after 24 weeks' treatment.	Proportion of responders based on the COPD Assessment Test (CAT) at week 24. Response defined as change from baseline of CAT score ≥2 at 24 weeks.
Secondary (subgroup of participants)	
To compare the effectiveness of TRELEGY ELLIPTA with non-ELLIPTA MITT on lung function after 24 weeks' treatment.	Change from baseline in Forced Expiratory Volume in one second (FEV_1) at 24 weeks (subgroup of participants).
To compare critical errors made by study participants using the ELLIPTA inhaler with participants using selected non-ELLIPTA MITT after 24 weeks' treatment.	Percentage of participants making at least 1 critical error in inhalation technique at 24 weeks. (subgroup of participants)

Overall Design:



This is a randomised, open-label, effectiveness, phase IV study of 24 weeks' duration in COPD patients to evaluate TRELEGY ELLIPTA [FF/UMEC/VI: 100mcg/62.5mcg/25mcg] inhalation powder taken once daily using a single ELLIPTA inhaler compared with any non-ELLIPTA MITT in the usual care setting.

To reflect usual care as closely as possible, only 2 study visits are required: these are at screening/randomisation (Visit 1) and at the end of the study after 24 weeks of treatment (Visit 2) or at early withdrawal (EW). At the investigators discretion, it is acceptable to invite the participant to a consenting visit (Visit 0) prior to Visit 1.

During the 24-week treatment period (between the two study visits), participants should receive usual clinical care, according to physician's discretion, in line with local COPD care guidelines. After starting a new treatment, the physician should, at their discretion, ascertain participant well-being within a time-frame acceptable for the participants needs.

The participants will complete the COPD Assessment Test (CAT; V1 and Visit 2/EW Visit), a Health-Related Quality of Life Questionnaire (HRQoL; V1 and Visit 2/EW Visit) and a Participant Treatment and Study Satisfaction Questionnaire (Visit 2/EW Visit). A subgroup will be assessed for lung function and for inhaler error assessment.

The investigator will record serious adverse events (SAEs), study treatment related adverse events (AEs) and AEs that lead to withdrawal from study treatment. The investigator will also record moderate and severe exacerbation events, COPD related healthcare resource use, change in medication since the last scheduled or unscheduled visit/contact, historical eosinophil counts, whole blood count and % eosinophils.

Eligibility

Patients enrolled into the study must have the following

- A clinical diagnosis of COPD with a score of ≥10 on the CAT prior to randomisation.

- At least one moderate or severe exacerbation during the 3 years prior to randomisation, documented in medical notes.
- Continuous use of non-ELLIPTA MITT or dual therapy prior to randomisation. Continuous use is defined as at least 60 days' prescription cover during the prior 16 weeks.
  Dual therapy is defined as:
    - Long-acting β2-agonist used in combination with long-acting muscarinic antagonist (LABA/LAMA)

      or

    - Inhaled corticosteroid used in combination with long-acting β2-agonist (ICS/LABA).

NOTE: Patients who are currently receiving dual therapy must be considered by their physician to require a step-up to triple therapy. The reason for the physician decision to step-up to triple therapy must be documented.

Study Treatment

- Patients who consent to join the study and who meet eligibility criteria will be randomised to receive 24 weeks' prescription cover for one of the following:
    - TRELEGY ELLIPTA
    - non-ELLIPTA MITT.
- Randomisation will be stratified by prior therapy.
- For the duration of the study, participants should remain on the treatment to which they are randomised. If this is not possible, then at the investigator's discretion, the participant may change treatment to a preferred alternative treatment. If the preferred alternative treatment is, in the opinion of the treating physician, unsuitable for the participant, then treatment can be changed to a non-preferred alternative. A change in study treatment should not result in withdrawal from the study. All participants should remain in the study and complete the 24-week Visit. If this is not possible then an EW visit should be completed.
- In line with usual care, physicians will ensure that participants receive training on the correct use of COPD maintenance treatment inhaler(s) at randomisation and whenever a treatment change is prescribed.

Number of Participants:

The target enrolment is 3000 participants randomised equally between the two treatment arms. It is estimated that approximately 3400 participants will be screened in order to randomise 3000.

2. SCHEDULE OF ACTIVITIES (SOA)

PROCEDURE *		**TREATMENT PERIOD**				**NOTES**
	VISIT 0 **Consenting**	**VISIT 1** **Screening & Randomisation**	**Usual care / contact for COPD related event or serious adverse event**	**Early Withdrawal (EW) Visit**	**VISIT 2**	The following sequence of events must be followed 1.ICF, 2. Screening, 3. Randomisation. All three may occur on the same day with no more than 6 weeks between ICF and screening and no more than 6 weeks between screening and randomisation.
Study week		1	After week 1 and before Visit 2	After week 1 and before Visit 2	24 (±21 days)	EW Visit should only be conducted if the participant discontinues from participating in the study. Participants withdrawing from study treatment but remaining in the study should continue to Visit 2.
Informed consent form (ICF)	X					ICF must be signed before any study procedures/ assessments
Inclusion and exclusion criteria		X				Recheck clinical status before randomisation and/or 1st prescription for study treatment
Demography		X				
Height and weight		X				
Medical history: past and current medical conditions		X				This includes family history of premature CV disease.

PROCEDURE *		**TREATMENT PERIOD**				**NOTES**
	VISIT 0 **Consenting**	**VISIT 1** **Screening & Randomisation**	**Usual care / contact for COPD related event or serious adverse event**	**Early Withdrawal (EW) Visit**	**VISIT 2**	The following sequence of events must be followed 1.ICF, 2. Screening, 3. Randomisation. All three may occur on the same day with no more than 6 weeks between ICF and screening and no more than 6 weeks between screening and randomisation.
Study week		1	After week 1 and before Visit 2	After week 1 and before Visit 2	24 (±21 days)	EW Visit should only be conducted if the participant discontinues from participating in the study. Participants withdrawing from study treatment but remaining in the study should continue to Visit 2.
Historical eosinophil count. whole blood count, % eosinophils	X	X				Most recent historical eosinophil measure taken within the **previous** 36 months prior to patients consenting visit. (Visit 1 or Visit 0 whichever is applicable) o An absolute number of eosinophils and the % of eosinophils out of the total WBC o White Blood Cell count (WBC)
Chronic Obstructive Pulmonary Disease (COPD) and Exacerbation history		X				The number of moderate/ severe exacerbations in the 12 months prior to V1 will be collected.
Randomisation		X				

PROCEDURE *		**TREATMENT PERIOD**				**NOTES**
	VISIT 0 **Consenting**	**VISIT 1** **Screening & Randomisation**	**Usual care / contact for COPD related event or serious adverse event**	**Early Withdrawal (EW) Visit**	**VISIT 2**	The following sequence of events must be followed 1.ICF, 2. Screening, 3. Randomisation. All three may occur on the same day with no more than 6 weeks between ICF and screening and no more than 6 weeks between screening and randomisation.
Study week		1	After week 1 and before Visit 2	After week 1 and before Visit 2	24 (±21 days)	EW Visit should only be conducted if the participant discontinues from participating in the study. Participants withdrawing from study treatment but remaining in the study should continue to Visit 2.
COPD assessment test (CAT)		X		X	X	CAT must be completed prior to randomization and prior to any other study procedures. Participants who have changed or discontinued treatment will remain in the study and complete CAT assessment at the Visit 2/EW Visit.
COPD Exacerbation assessment			X	X	X	Moderate and severe exacerbations that occur between V1 and V2 will be recorded.
COPD related healthcare resource use assessment			X	X	X	Details of primary healthcare contacts, known secondary care contacts and all COPD related medication use that occurs between V1 and V2 will be recorded in the eCRF.
Assessment of inhaler errors (subgroup only)				X	X	

PROCEDURE *		**TREATMENT PERIOD**				**NOTES**
	VISIT 0 **Consenting**	**VISIT 1** **Screening & Randomisation**	**Usual care / contact for COPD related event or serious adverse event**	**Early Withdrawal (EW) Visit**	**VISIT 2**	The following sequence of events must be followed 1.ICF, 2. Screening, 3. Randomisation. All three may occur on the same day with no more than 6 weeks between ICF and screening and no more than 6 weeks between screening and randomisation.
Study week		1	After week 1 and before Visit 2	After week 1 and before Visit 2	24 (±21 days)	EW Visit should only be conducted if the participant discontinues from participating in the study. Participants withdrawing from study treatment but remaining in the study should continue to Visit 2.
Spirometry for lung function (subgroup only)		X		X	X	Spirometry should be performed before the day's dose of usual care or study medication. The assessment is pre-and post-salbutamol at Visit 1 and pre-salbutamol at Visit 2 /EW Visit. It should be started between approximately 6:00 am and 12:00 pm The most recent use of COPD maintenance inhaler/ study treatment should be noted.
Participant treatment & study satisfaction questionnaire				X	X	
Health Related Quality of Life Questionnaire (HRQoL)		X		X	X	

PROCEDURE *		TREATMENT PERIOD				NOTES
	VISIT 0 **Consenting**	**VISIT 1** **Screening & Randomisation**	**Usual care / contact for COPD related event or serious adverse event**	**Early Withdrawal (EW) Visit**	**VISIT 2**	The following sequence of events must be followed 1.ICF, 2. Screening, 3. Randomisation. All three may occur on the same day with no more than 6 weeks between ICF and screening and no more than 6 weeks between screening and randomisation.
Study week		1	After week 1 and before Visit 2	After week 1 and before Visit 2	24 (±21 days)	EW Visit should only be conducted if the participant discontinues from participating in the study. Participants withdrawing from study treatment but remaining in the study should continue to Visit 2.
Review of study treatment related Adverse Events (AE)		X	X	X	X	Clinical judgment should be used to determine whether there is a relationship between study treatment and each occurrence of each AE/SAE. Study treatment related adverse events must be recorded from V1. Where a causality relationship is determined, this must be recorded as a study treatment related AE. **AEs not related to either study treatment or withdrawal from study treatment are not recorded, unless classified as serious adverse events.** Refer to Appendix 3 for definitions of AEs, SAEs and guidelines on assessment of causality by investigator

PROCEDURE *		**TREATMENT PERIOD**				**NOTES**
	VISIT 0 **Consenting**	**VISIT 1** **Screening & Randomisation**	**Usual care / contact for COPD related event or serious adverse event**	**Early Withdrawal (EW) Visit**	**VISIT 2**	The following sequence of events must be followed 1.ICF, 2. Screening, 3. Randomisation. All three may occur on the same day with no more than 6 weeks between ICF and screening and no more than 6 weeks between screening and randomisation.
Study week		1	After week 1 and before Visit 2	After week 1 and before Visit 2	24 (±21 days)	EW Visit should only be conducted if the participant discontinues from participating in the study. Participants withdrawing from study treatment but remaining in the study should continue to Visit 2.
Review of Adverse Events (AE) that lead to withdrawal from study treatment		X	X	X	X	All AEs that lead to withdrawal from study treatment, whether judged related to study treatment or not, should be recorded. The participant should be encouraged to remain in the study for collection of effectiveness and safety data. All AEs that lead to withdrawal from the study whilst the participant is on study treatment, **whether judged related to study treatment or not**, should be recorded.

PROCEDURE *		TREATMENT PERIOD				NOTES
	VISIT 0 **Consenting**	**VISIT 1** **Screening & Randomisation**	**Usual care / contact for COPD related event or serious adverse event**	**Early Withdrawal (EW) Visit**	**VISIT 2**	The following sequence of events must be followed 1.ICF, 2. Screening, 3. Randomisation. All three may occur on the same day with no more than 6 weeks between ICF and screening and no more than 6 weeks between screening and randomisation.
Study week		1	After week 1 and before Visit 2	After week 1 and before Visit 2	24 (±21 days)	EW Visit should only be conducted if the participant discontinues from participating in the study. Participants withdrawing from study treatment but remaining in the study should continue to Visit 2.
SAE review	X	X	X	X	X	SAEs that are related to study participation or to GSK products are collected from the time of consent to randomisation. All other SAEs are recorded from the time of randomisation. Clinical judgment should be used to determine the relationship between study treatment and each occurrence of each AE/SAE. Where a causality relationship is determined, this must be recorded as a study treatment related SAE. Refer to Appendix 3 for definitions of AEs, SAEs and guidelines on assessment of causality by investigator.
Details of randomised study treatment and any study treatment changes		X	X	X	X	Reason for change in treatment, details and date of new treatment should be recorded.

PROCEDURE *		**TREATMENT PERIOD**				**NOTES**
	VISIT 0 **Consenting**	**VISIT 1** **Screening & Randomisation**	**Usual care / contact for COPD related event or serious adverse event**	**Early Withdrawal (EW) Visit**	**VISIT 2**	The following sequence of events must be followed 1.ICF, 2. Screening, 3. Randomisation. All three may occur on the same day with no more than 6 weeks between ICF and screening and no more than 6 weeks between screening and randomisation.
Study week		1	After week 1 and before Visit 2	After week 1 and before Visit 2	24 (±21 days)	EW Visit should only be conducted if the participant discontinues from participating in the study. Participants withdrawing from study treatment but remaining in the study should continue to Visit 2.
Details of medicine and therapy taken for respiratory and other selected conditions		X	X	X	X	
	* The timing and number of planned study assessments, including assessments may be altered during the study based on newly available data.					

3. INTRODUCTION

3.1. Background and Rationale

COPD guidelines advocate the use of one or more long-acting bronchodilators (long-acting muscarinic receptor antagonists (LAMA) or long-acting β_2-adrenergic receptor agonists (LABA) in addition to inhaled corticosteroids (ICS) for patients who continue to have advanced COPD with significant symptoms and are at a high risk of exacerbations [GOLD, 2013]. Population based studies of COPD treatment patterns demonstrate that Multiple Inhaler Triple Therapy (MITT), an ICS/LAMA/LABA combination, is already widely used in the clinical management of COPD [Price, 2014, Landis, 2017].

GlaxoSmithKline (GSK) has developed a once-daily triple therapy [Fluticasone Furoate (FF)/ Umeclidinium (UMEC)/ Vilanterol (VI) (100mcg/62.5mcg/25mcg)] in a single inhaler (TRELEGY ELLIPTA). TRELEGY ELLIPTA provides a new treatment option for the management of patients with advanced COPD with the aim of reducing exacerbation frequency and burden of polypharmacy, improving lung function, health related quality of life and symptom control, while providing a more convenient treatment option for patients compared with established dual/monotherapies.

It is acknowledged that double-blind randomised clinical trials (RCT) conducted for registration purposes enrol a more selected patient population than is expected to be prescribed the medication post-approval and treated in normal clinical practice. Traditional, randomised controlled trials often exclude or withdraw participants who do not achieve a certain level of compliance with the investigational product. Participants may also be excluded because of their age, the severity of their disease, or the presence of comorbidities which would exclude them from entry to registration trials [Herland, 2005]. The highly-controlled conditions of an RCT remove factors that influence and differentiate the use of medicines in everyday clinical practice. Thus, safety and effectiveness data generated in the broader population observed in an everyday clinical setting are increasingly being recognised as important in complementing data derived from the pivotal Phase III safety and efficacy studies [Kardos, 2016]. The Salford Lung Study (SLS) was designed to evaluate the effectiveness and safety of the once-daily inhaled combination of fluticasone furoate and vilanterol (fluticasone furoate–vilanterol) as compared with existing maintenance therapy in a broad population of patients with COPD receiving usual care [Vestbo, 2016]. This study will build on the learnings from SLS to permit the unobtrusive assessment of effectiveness outcomes and safety monitoring, blended into routine clinical care.

The primary purpose of this study is to meet this need by assessing the effectiveness of TRELEGY ELLIPTA relative to non-ELLIPTA MITT within the usual clinical practice setting. The study will be conducted once TRELEGY ELLIPTA has been approved in the countries in which the study will be conducted and is available commercially.

3.2. Benefit/Risk Assessment

3.2.1. Risk Assessment

TRELEGY ELLIPTA

More detailed information about the known and expected risks and reasonably expected adverse events of TRELEGY ELLIPTA are described in the Investigator Brochure. To supplement this, the study risk assessment is outlined in Appendix 6 and the following section outlines the risk mitigation strategy for this study.

Multiple Inhaler Triple Therapy (MITT)
In this study, MITT will be used in line with the recommendations provided in the product label. The most common drug-related adverse reactions for the components of MITT are associated with anti-cholinergic therapy, β_2-agonists and inhaled corticosteroids. These are of the same drug class as TRELEGY ELLIPTA and so have a similar profile of undesirable effects (see Appendix 6). Please refer to the package insert for precise information on the risks of using the individual components of MITT.

Other COPD Maintenance Therapy
If other COPD maintenance therapy is prescribed at the physician's direction, these should be used in line with the recommendations provided in the product label. Please refer to the package insert for precise information on the risks of using the individual components.

3.2.2. Risk Mitigation

TRELEGY ELLIPTA and MITT

- Investigators are informed of the risks for Trelegy in the Investigator Brochure.
- Patients with known hypersensitivity to the study treatment, excipients or components will be excluded from the study.

3.2.3. 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, 2017].

Benefits of MITT have been shown in published studies which assessed the use of MITT in moderate-severe COPD patients. These studies reported improvements in lung function, health related quality of life, hospitalisation rates and rescue medication use, compared to dual therapy (ICS/LABA) or LAMA alone [Lipson, 2017, Aaron, 2007, Cazzola, 2007, Hanania, 2012, Jung, 2012, Welte, 2009]. These studies also showed that the number and type of reported AEs were generally similar with administration of dual or monotherapy doses for periods of up to one year, and were mostly related to their pharmacological mode of action.

Patients enrolled in this study will receive either TRELEGY ELLIPTA or a non-ELLIPTA MITT. Based on available data with the components ICS, LAMA and LABA,

it is expected that patients will potentially derive clinical benefit from this combination of study treatments.
In a disease where polypharmacy is common, the TRELEGY ELLIPTA, once-daily combination has the potential to optimise bronchodilator therapy, improve patient adherence to therapy and, as a result, improve overall disease management in COPD patients.

3.2.4. Overall Benefit: Risk Conclusion

The clinical development programmes for TRELEGY ELLIPTA demonstrated a favourable benefit/risk for patients with COPD. This has led to approval and marketing of TRELEGY ELLIPTA for a COPD indication in a number of countries around the world.

Current risks that have been identified for these therapeutic classes are based on the known pharmacology of the individual components: ICS, LAMA and LABA. These include key risks of pneumonia and bone disorders/fractures from ICS-containing combinations, and the risk of adverse cardiovascular effects from LAMA/LABA-containing combinations. However, the associated benefit/risk profiles for both arms of the study are similar because the three active components are of the same therapeutic class.

Participants enrolled onto the study will be receiving medication of therapeutic classes which are available for prescription. At enrolment, the treating physician has already made the decision that the benefit/risk for this triple combination therapy is appropriate for these patients.

Participants will be monitored according to usual care at their physician's discretion with adverse events recorded as described in Section 9.5. The potential benefit of this new therapy in patients with moderate to severe COPD supports the conduct of this study to collect effectiveness data from a clinical practice setting.

4. OBJECTIVES AND OUTCOMES

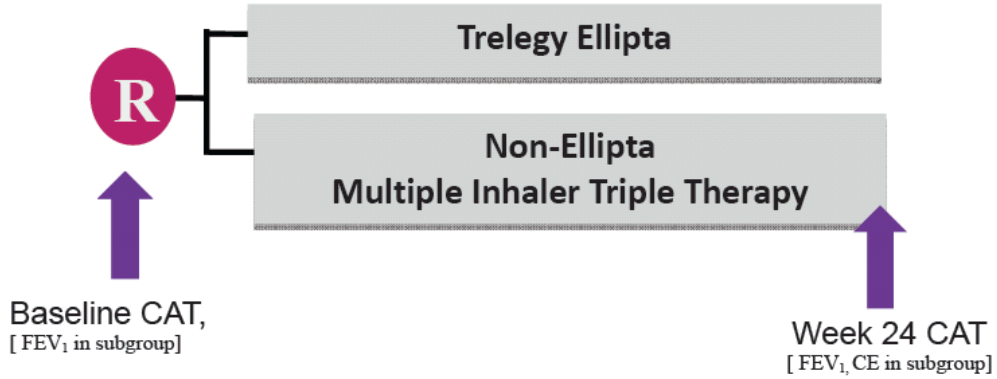
Objectives	Outcomes
Primary	
To compare the effectiveness of TRELEGY ELLIPTA with non-ELLIPTA MITT for the impact of COPD on wellbeing and daily life after 24 weeks' treatment.	Proportion of responders based on the COPD Assessment Test (CAT) at week 24. Response defined as change from baseline of CAT score ≥2 at 24 weeks.
Secondary	
To compare the effectiveness of TRELEGY ELLIPTA with non-ELLIPTA MITT on lung function after 24 weeks' treatment.	Change from baseline in FEV_1 at 24 weeks (in a subset of participants).
To compare critical errors (CE) made by study participants using the ELLIPTA inhaler with participants using selected non-ELLIPTA MITT after 24 weeks' treatment.	Percentage of participants making at least 1 critical error in inhalation technique at 24 weeks (in a subset of participants).
Other	
To compare TRELEGY ELLIPTA with inhaled non-ELLIPTA MITT for a clinically important deterioration (CID)	Proportion of responders who experience CID. CID is a composite outcome defined as any one of the following events: • 100 mL reduction from baseline in FEV_1 at 24 weeks. • An exacerbation (requiring treatment with antibiotics and/or systemic steroids or hospitalisation) • 2 units change (increase) from baseline in CAT score at 24 weeks.

Objectives	Outcomes
To quantify the incidence, rate and time to first moderate/severe COPD exacerbation for study participants on TRELEGY ELLIPTA compared with participants on non-ELLIPTA MITT.	• Annualised rate of moderate/severe exacerbations (defined as: requiring treatment with antibiotics and/or systemic steroids or hospitalisation). • Time to first moderate /severe exacerbation (defined as: requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalisation).
To compare the effectiveness of TRELEGY ELLIPTA with non-ELLIPTA MITT for COPD-related Healthcare Resource Utilisation (HCRU).	The frequency of COPD related HCRU including: • Primary healthcare contacts. • COPD related medication. • Hospital admissions, outpatient appointments and A&E attendances. **Exploratory:** frequency of HCRU assessed using electronic health records.
Exploratory	
To assess the data for correlation between critical errors and clinical outcomes	Numerical correlation of CE with CAT, moderate/ severe exacerbations and FEV_1.
To describe the patient study experience	Participant Treatment and Study Satisfaction Questionnaire at 24 weeks/ EW Visit.
To describe the change from baseline in patient Health Related Quality of Life	Health Related Quality of Life Questionnaire

Objectives	Outcomes
Safety	
To compare safety for study participants using the ELLIPTA inhaler with participants using non-ELLIPTA MITT after 24 weeks' treatment.	▪ All serious adverse events ▪ Study treatment related adverse events ▪ Adverse events that lead to withdrawal from study treatment

5. STUDY DESIGN

Figure 1 Study Schematic



This is a randomised, open-label, effectiveness, phase IV study of 24 weeks' duration in COPD patients to evaluate TRELEGY ELLIPTA [FF/UMEC/VI: 100mcg/62.5mcg/25mcg] inhalation powder taken once daily using a single ELLIPTA inhaler compared with any non-ELLIPTA MITT in the usual care setting.

Patients who meet the study entry criteria will be invited to join the study by their physician. Those who give their informed consent will be assessed for eligibility.

5.1. Eligibility criteria

Patients enrolled into the study must have the following.

- A clinical diagnosis of COPD with a score of ≥10 on the COPD Assessment Test (CAT) prior to randomisation.
- At least one moderate or severe exacerbation during the 3 years prior to randomisation, documented in medical notes.
- Continuous use of non-ELLIPTA MITT or dual therapy prior to randomisation. Continuous use is defined as at least 60 days' prescription cover during the prior 16 weeks.

Dual therapy is defined as:

- Long-acting β2-agonist used in combination with long-acting muscarinic antagonist (LABA/LAMA).

  or

- Inhaled corticosteroid used in combination with long-acting β2-agonist (ICS/LABA)

NOTE: Patients who are currently receiving dual therapy must be considered by their physician to require a step- up to triple therapy. The reason for the physician decision to step-up to triple therapy must be documented.

Full details of inclusion/ exclusion criteria are listed in Section 6.

5.1.1. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are never subsequently randomised. The reason for screen failure will be recorded in the electronic case report form (eCRF).

5.2. Study Treatment

- Study treatment is defined as the COPD maintenance therapy that the patient is prescribed whilst enrolled in the study from randomisation to the Visit 2 /EW visit.
- Patients meeting eligibility criteria will be randomised to receive 24 weeks' prescription cover for one of the following:
  - TRELEGY ELLIPTA
  - non-ELLIPTA MITT
- Participants should remain on the treatment to which they are randomised.
- However, the prescribed COPD maintenance therapy (i.e. study treatment) may change for an individual participant as described in Section 5.2.1.
- In line with usual care, physicians should ensure that participants receive training on the correct use of COPD maintenance treatment inhalers at randomisation and whenever there is a study treatment change.

5.2.1. Treatment Change

For the duration of the study, participants should remain on the treatment to which they are randomised. If this is not possible, then at physician's discretion, they may change treatment to a preferred alternative treatment.

- The preferred alternative treatment for patients randomised to TRELEGY ELLIPTA is any MITT or any single inhaler triple therapy.
- The preferred alternative treatment for patients randomised to non-ELLIPTA MITT is an alternative non-ELIPTA MITT or any other non-ELLIPTA COPD maintenance therapy.

If the preferred alternative treatment is, in the opinion of the treating physician, unsuitable for the participant, then treatment can be changed to a non-preferred alternative.

Any change in study treatment must be recorded. The reason for this change should also be recorded.

A change in COPD maintenance treatment should not result in withdrawal from the study. All participants should remain in the study and complete Visit 2. If this is not possible then an early withdrawal visit should be completed.

5.3. Study Visits and Usual Care

To reflect usual care as closely as possible, only 2 study visits are required: these are at screening/randomisation (Visit 1) and at the end of the study after 24 weeks of treatment or at early withdrawal (Visit 2/EW Visit). At the investigators discretion, it is acceptable to invite the participant to a consenting visit (Visit 0) prior to Visit 1. The gaps between each activity must be no more than 6 weeks.

During the 24-week treatment period (between the two study visits), participants should receive usual clinical care, according to physician's discretion, in line with local COPD care guidelines. After starting a new treatment, the physician should, at their discretion, ascertain participant well-being within a time-frame acceptable for the participants needs.

The participants will complete the CAT (V1 and Visit 2/EW Visit), a Health-Related Quality of Life Questionnaire (V1 and Visit 2/EW Visit) and a Participant Treatment and Study Satisfaction Questionnaire (Visit 2/EW Visit). A subgroup will be assessed for lung function and for inhaler error assessment.

The investigator will record moderate and severe COPD exacerbation events (on the exacerbation page of the eCRF). With respect to COPD exacerbation SAEs, only a subset of these will be collected (on the SAE page of the eCRF; see Section 9.5.7).

5.4. Study Procedures

Full details of study procedures are given Section 9: Study Assessments and Procedures

5.4.1. COPD Assessment Test (CAT)

CAT should be completed prior to randomisation and at Visit 2 /EW Visit. The CAT is required for all participants. It is a simple 8-item validated questionnaire to assess the impact of COPD on wellbeing and daily life.

If a participant does not present as expected for their final study visit (on study completion or withdrawal), every attempt should be made to encourage them to attend as soon as possible.

In very exceptional circumstances, when the participant is not able to attend for a Visit 2/EW Visit, the CAT assessment, together with a safety assessment may be carried out

via a domiciliary visit/telephone call within 21 days of final study/early withdrawal visit date. The type of contact used for the CAT assessment must be recorded.

5.4.2. Spirometry

In a subgroup of approximately 1520 participants, spirometry will be measured at randomisation and at the Visit 2/EW Visit. If, in the opinion of the investigator, a participant has a pre-existing condition that makes them unable to perform spirometry, then this should be clearly documented.

5.4.3. Assessment of Errors in the Use of Study Treatment Inhalers

In line with usual care, at the start of the study, and whenever participants are issued with a prescription for a new study COPD maintenance treatment, the physician (or delegate) should, at their discretion, train the participant on the correct use of their inhaler(s).

All participants who are offered spirometry should also have an assessment of inhaler errors provided that an appropriate error checklist is available for the study medication they are using for COPD maintenance therapy at Visit 2/EW. A critical error (CE) is defined as an error that is most likely to result in no, or significantly reduced, medication being inhaled. If participants are unable to perform spirometry they may still participate in the CE assessment.

5.4.4. Participant Treatment and Study Satisfaction Questionnaire

At Visit 2/EW Visit, participants will complete a short treatment and study satisfaction questionnaire.

5.4.5. Health Related Quality of Life Questionnaire

At enrolment and at Week 24/EW Visit, participants will complete a short HRQoL questionnaire.

5.5. Data Collection

In addition to the details of study procedures and patient reported outcomes, data collection in the study eCRF will include the following

- All SAEs.
- Study treatment related AEs (see Appendix 3 for guidelines on assessment of causality by investigator).
- AEs which lead to withdrawal from study treatment.
- Details of moderate and severe COPD exacerbation events including medications given.
- Reason for change in study treatment
- Healthcare resource use associated with COPD related medical encounters including medication prescribed for treatment of respiratory conditions.
- Historical blood eosinophils

5.5.1. Exploratory Electronic Health Record (EHR) Data Collection

Following patient consent, in some countries which have suitable systems, healthcare resource utilisation data will be electronically transmitted from electronic health records to a third party who will transfer anonymised data to GSK for exploratory analysis.

Data captured from electronic health records will be considered exploratory only and is not intended to be relied upon in assessing the study outcomes or for monitoring or otherwise managing the participant's care.

Data sources and data flow will be clearly defined in the Data Management Plan. The data collected will be the subject of a supplementary analysis plan.

5.6. Number of Participants

The target enrolment is 3000 participants randomised equally between the two treatment arms. This assumes a study drop-out rate of 13.5% i.e., the study will have 2594 participants who attend the Visit 2 and are still on their initially randomised treatment (1297 per arm). It is estimated that approximately 3400 participants will be screened in order to randomise 3000.

5.7. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit at Week 24.

The end of the study is defined as the date of the last visit of the last participant in the study.

5.8. Scientific Rationale for Study Design

Although the intention of this study is to assess TRELEGY ELLIPTA in a minimally interventional routine clinical care setting, a randomised parallel group design has been chosen to provide the most robust evidence of clinical effectiveness.

Randomisation provides some control for potential bias, e.g. time (disease progression) and study effects. A study effect was observed in the usual care arm of the triple therapy subgroup within the Salford Lung Study (SLS); annualised exacerbation rates decreased substantially following randomisation although the patient's treatment remained unchanged [Vestbo, 2016].

Comparison of randomised parallel groups will enable a fair assessment of the effectiveness of TRELEGY ELLIPTA relative to non-ELLIPTA MITT.

The study population is intended to be broad and reflect COPD patients with advanced symptomatic disease who their physician may consider to be suitable for triple therapy.

The primary focus of this study is COPD control measured by the CAT questionnaire which is recommended in the most recent Global COPD Strategy Document for assessment of COPD health status impairment [GOLD, 2017]. CAT is meaningful to

patients as a patient-reported outcome measure which assesses the impact of COPD on their daily lives and helpful to Health Care Professionals (HCPs) to inform patient management. It has also been shown to be of significant interest and relevance to payers in recent (unpublished) research conducted by GSK. CAT is a minimally interventional measure which will be assessed only at randomisation, and at the end of study (Visit 2/EW Visit).

The CAT data will be supported by secondary outcomes of lung function and inhaler error use errors in a subgroup of patients, but no additional study visits have been included to support these outcomes: thus, maintaining the routine-care nature of the study. Exacerbations and healthcare resource use data is of key interest to payers and will be included in the study as descriptive outcomes.

The duration of the study is 24 weeks, when all primary and secondary outcomes can be assessed adequately and there is less potential for treatment switching than in a longer study. Maintenance of the patient's randomised treatment regimen during the study is at the discretion of the treating physician. Change in COPD maintenance treatment represents a potential challenge to the assessment of the true treatment effect. This is because the decision to change treatment could be directly influenced by the patient's outcome. The study will collect outcomes relating to treatment changes in order to better understand switch patterns and reasons for treatment changes.

There will be no protocol defined study visits other than at the start and finish of the 24-week treatment period in order to minimise study effects and create conditions which are as similar as possible to everyday clinical practice. Study visits and non-routine clinic assessments have a potential impact on factors which can differentiate treatments in usual clinical practice, e.g. treatment adherence [Chen, 2015].

The minimal patient assessment and monitoring planned for this study is suitable for investigation of this approved medicine, which has been in clinical use for some time as two separate inhalers containing the same medicines.

5.9. Dose Justification

The FF/UMEC/VI (100/62.5/25mcg) dose was studied in the phase III clinical trial programme and is the licensed dose in the countries in which the study will be conducted. The dose of the non-ELLIPTA MITT and all other COPD medications will be prescribed as the approved doses within the licence.

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

1. **Informed Consent:** Capable of giving signed informed consent as described in Appendix 2 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. **COPD Diagnosis**: Patients with a documented physician diagnosis of COPD.
3. **Severity of COPD symptoms:** A score of ≥10 on the COPD Assessment Test (CAT) at screening.
4. **History of Exacerbations**. Patients who have a history of treatment with systemic/oral corticosteroids, antibiotics and/or hospitalisation for at least one COPD exacerbation in the 3 years prior to randomisation. This will be captured through patient recall and/or medical records and must be documented in patients notes.

   Prior use of systemic/oral corticosteroids and/or antibiotics alone does not qualify as an exacerbation history unless the use was associated with treatment of worsening symptoms of COPD.
5. **Existing COPD Maintenance Treatment**. Patients currently receiving one of the non-ELLIPTA maintenance therapies listed below who have been prescribed it continually for at least 16 weeks prior to randomisation.

   Continuous prescription is defined as a minimum of 60 days' prescription cover during the prior 16 weeks.

   The non -ELLIPTA maintenance therapy must be one of the following

   - ICS in combination with LAMA and LABA (MITT)
   - LAMA and LABA used in combination as a dual therapy
   - LABA and ICS used in combination as a dual therapy

   NOTE: patients who are currently on a dual maintenance therapy for COPD must be considered by their physician to require a step-up to triple therapy. The reason for the physician decision to step-up must be documented.

   Patients who are receiving only COPD medication on an 'as required' basis are not eligible.
6. **Age and Sex:** Participants must be aged ≥40 years of age at the time of signing the informed consent.

6.2. Exclusion Criteria

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

1. **Women of child bearing potential** as defined in Appendix 4. This includes women who are pregnant or lactating or are planning on becoming pregnant during the study.

2. **Medical Conditions:** Patients with any life-threatening condition i.e. low probability, in the opinion of the investigator, of 6-month survival due to severity of COPD or co-morbid condition.
3. **Patients with unstable COPD**. Patients with resolution of an exacerbation less than 2 weeks prior to Visit 1, must not be randomised. Patients may be rescreened 2 weeks after resolution of exacerbation (exacerbation is defined as: requiring treatment with antibiotics and/or systemic steroids or hospitalisation).
4. **Other diseases/abnormalities**: Patients with historical or current evidence of uncontrolled or clinically significant disease. 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 effectiveness or safety analysis if the disease/condition exacerbated during the study
5. **Hypersensitivity:** 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.
6. **Prior/Concomitant Therapy with Oral Corticosteroid.** Patients who, in the opinion of the treating investigator, are chronic users of oral corticosteroids for respiratory or other indications (if unsure discuss with the medical monitor prior to screening).
   Chronic use is defined as more than 14 days' continuous use during the 12 weeks prior to Visit 1.

7. **Participants currently participating in any interventional clinical study.**
   Participants taking any investigational drug treatment within 30 days prior to Visit 1 or within five half-lives ($t_{½}$) of the prior investigational study (whichever is the longer of the two).

6.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised to study treatment. 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 and screen failure details.

Individuals who do not initially meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new subject number.

7. TREATMENTS

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

7.1. Treatments Administered

All study treatments will be sourced from commercial supply. Participants randomised to TRELEGY ELLIPTA will receive the following investigational product (see Table 1) and should inhale once from the ELLIPTA at the same time each day for the duration of the 24-week treatment period:

Table 1 Description of Inhalation Powder in TRELEGY ELLIPTA

TRELEGY ELLIPTA Dry Powder Inhaler (DPI)		
FF/UMEC/VI	**First strip**	**Second strip**
	GW685698 (FF) blended with lactose	GW642444 (VI) and GSK573719 (UMEC) blended with lactose and magnesium stearate
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	100 mcg 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	

Participants randomised to non-ELLIPTA MITT will receive the ICS/LAMA/LABA products and dosing regimens as prescribed by their physician.

Study treatment may be augmented with other prescribed COPD medications such as including rescue medications, which will be prescribed and obtained according to usual practice.

At the physician's discretion, participants recruited into the study will be instructed on the proper use of the inhaler(s) to which they have been randomised.

7.2. Method of Treatment Assignment

A participant will be assigned a subject number at the time the informed consent is signed. Once a subject number is assigned to a participant it cannot be reassigned to any other participant in the study.

All participants will be centrally randomised using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each site. Once a randomisation number is assigned to a participant it cannot be reassigned to any other participant in the study.

A country based randomisation schedule will be generated by Clinical Statistics, prior to the start of the study and using validated internal software.

Participants will be randomised (1:1) to receive a prescription for one of the following study treatment regimens:

- TRELEGY ELLIPTA once daily in the morning
  or
- Non- ELLIPTA MITT twice daily treatment

The randomisation will be stratified based on previous treatment (ICS/LABA or LABA/LAMA or ICS/LAMA/LABA). The recruitment of ICS/LABA and LABA/LAMA will be capped at a combined total of approximately 50% at a country level.

The duration of treatment for each participant is 24 weeks.

7.3. Blinding

Blinding procedures will not be used in this open label study

7.4. Preparation/Handling/Storage/Accountability

Study treatment will be prescribed to the participant by the site as a licensed product. Handling and storage will be as per normal pharmacy practice. No study treatment accountability will be performed.

7.5. Treatment Compliance

No measures, outside of usual care, will be taken to ensure and document treatment compliance.

7.6. Concomitant Therapy

Any medication or vaccine for the treatment of a respiratory condition that the participant receives at the time of consent or receives during the study should be recorded along with:

- dates of administration including start and end dates

- dosage information including dose and frequency

7.6.1. Medications

There are no prohibited medications. Participants should be prescribed medications at the physician's discretion according to usual care, with reference to the Investigator Brochure for potential interactions.

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

Treatment for COPD

COPD exacerbations should be treated at physician's discretion as per usual practice. Medications used may include:

- Antibiotics prescribed for an exacerbation.
- Treatment with systemic corticosteroid (tablets, suspension or injection) for a limited period as described in Appendix 5.
- A physician-advised change in SABA use (i.e. routinely scheduled versus as needed use).
- Leukotriene receptor antagonists (LTRAs) and leukotriene modifiers.
- Oral theophylline.
- Mucolytics such as Acetylcysteine.
- Any COPD medication deemed medically necessary for the short-term treatment (≤14days) of a moderate/severe COPD exacerbation or pneumonia

Guidance / caution is provided in relation to use of the following:

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

- Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs): Administer with extreme caution as they may potentiate the effects of beta-agonists on the cardiovascular system, including QTc prolongation.

- Diuretics: Caution is advised in the co-administration of beta-agonists with non-potassium sparing diuretics as this may result in hypokalemia and/or ECG changes.

- CYP3A4 inhibitors: Caution should be exercised when considering the coadministration of long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin,

voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.

7.6.2. Non-Drug Therapies

Pulmonary Rehabilitation

At physician's discretion, it is preferable to defer starting a course of pulmonary rehabilitation until after the end of the study.

Details of any pulmonary rehabilitation programme which starts or stops either during the 8 weeks prior to Visit 1 or during the study should be captured in the eCRF.

Oxygen therapy is permitted.

Continuous Positive Airway Pressure (CPAP)

At the physician's discretion, it is preferable to defer commencing CPAP for the treatment of obstructive sleep apnoea during the 6 weeks prior to enrolment.

Details of CPAP treatment should be captured in the eCRF.

7.7. Treatment after the End of the Study

There is no plan to continue to provide study treatment following the end of the study. At the end of the study, the choice of COPD maintenance treatment is at the discretion and clinical judgment of the physician.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study

- GSK reserves the right to suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues. For multicentre studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly

inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.

- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the Independent Review Board/Independent Ethics Committee (IRB/IEC) promptly and provide the reason for the suspension or premature discontinuation.
- Participants who are found to be pregnant during the conduct of the study should be withdrawn from the study.

8.2. Discontinuation of Study Treatment

For the duration of the study, participants should remain on the treatment to which they are randomised.

If deemed necessary by the treating physician, the participant may change to a preferred alternative COPD maintenance therapy as listed in Table 2.

Table 2 Preferred Alternative COPD maintenance therapy

Note: alternatives treatment should only be prescribed when participant cannot continue the treatment to which they were randomised at Visit 1.

Treatment at randomisation	Permitted Treatment change
TRELEGY ELLIPTA	Any therapy for COPD including 1.any MITT 2.any single inhaler triple therapy
Any non-ELLIPTA MITT	1.Any non-ELLIPTA MITT 2. Any non-ELLIPTA therapy for COPD, **excluding single inhaler triple therapy**

Participants who are prescribed a preferred alternative COPD maintenance treatment should still be encouraged to continue in the study to collect all data including at Visit 2. Those who discontinue from the study should complete the EW Visit.

Participants who are prescribed COPD maintenance treatment which is **not** a preferred alternative should still be encouraged to continue in the study to collect all data including at Visit 2. Those who discontinue from the study should complete the EW visit.

8.3. Withdrawal from the Study

- **Participants that permanently stop study treatment are not required to withdraw from the study.** If for any reason a participant must permanently stop

their study treatment, every effort should be made by the Investigator/delegate to keep the participant in the study to collect important effectiveness and safety data. Alternative treatment options are described in Section 8.2, Table 2

- 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 administrative reasons.
- Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.4. Lost to Follow Up

A participant will be considered lost to follow-up if he or she fails to return for the Visit 2 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 the Visit 2:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible.
- Before a participant is deemed lost to follow up, the investigator/ delegate 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.
- If a participant is unable to attend for the end of study visit or EW visit, the CAT assessment may be carried out via a telephone call from the study site within 21 days of the planned study visit.
- Should the participant be completely unreachable, 21 days after the planned study visit, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- 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 treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of ICF may be utilised for screening or baseline purposes provided the procedure met the protocol-specified definition.

9.1. Effectiveness Assessments

9.1.1. The COPD Assessment Test (CAT):

The CAT questionnaire should be completed prior to randomisation and before any procedures or assessments are performed to avoid influencing the participant's response. To avoid biasing responses, the participant should not be told the results of any diagnostic tests prior to completing the CAT questionnaire. It is recommended that the questionnaires be administered at the same time of day at both Visit 1 and 2.

The CAT will be completed by participants on paper prior to randomisation (Visit 1) and at Visit 2 before any other scheduled assessments.

In very exceptional circumstances, when the participant is not able to attend for a Visit 2, the CAT assessment, together with a safety assessment may be carried out via a domiciliary visit/telephone call within 21 days of final study visit date. This must be noted in the eCRF.

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

Adequate time must be allowed to complete all items on the questionnaires; the questionnaires must be reviewed for completeness and, if necessary, the participant should be encouraged to complete any missing assessments or items.

Further instructions for completing the questionnaires can be found in the Study Reference Manual (SRM).

9.1.2. Lung Function

Lung function will be obtained using spirometry equipment that meets or exceeds the minimal performance recommendations of the ATS [Miller, 2005]. All sites will use standardised spirometry equipment provided by an external vendor.

For FEV1 and FVC determination, 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 artefacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons [Miller, 2005].

To facilitate pre-dose spirometry, participants should be encouraged to time their COPD maintenance therapy so that they are due for their next dose at the time of the study visit, which should be in the morning.

At Visit 1 and 2, Spirometry, should be measured prior to the day's dose of usual care/ study treatment. At Visit 1 pre- and post-salbutamol spirometry should be measured to assess reversibility (see Section 9.1.2.1). At Visit 2/ EW Visit, only pre-salbutamol spirometry will be measured.

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

Spirometry should be performed as follows:

- Started between approximately 6:00am and 12:00pm.
- After completing the CAT.
- Before the assessment of inhaler errors (critical errors).
- After withholding short-acting beta-agonists/anti-cholinergic for 4 hours
- At Visit 1 before the morning dose of usual COPD medication.
- At Visit 2/ EW Visit before the morning dose of study COPD maintenance treatment.
- The participant's position during spirometry measurements (sitting or standing) should be consistent for both study visits.

If it is not possible to withhold usual care/study treatment and/or short-acting beta-agonists or anti-cholinergic for ≥4 hours, then spirometry will still be measured and recorded. The most recent use of COPD maintenance treatment/ study treatment should be recorded.

The spirometry equipment must be used according to vendor guidelines. Further details regarding the spirometry procedures are provided in the SRM and the manual provided by the spirometry vendor.

Participants who are unable to perform spirometry may still have an inhaler error assessment and will not be excluded from the study.

9.1.2.1. Reversibility Testing

Reversibility testing should be completed as follows: Following pre-salbutamol spirometry (three acceptable spirometry efforts), the participant should self-administer salbutamol. Three acceptable spirometry efforts should be obtained approximately 10 to 15 minutes after salbutamol administration.

9.1.3. Assessment of Errors in the Use of Inhaler(s)

At the start of the study, and whenever participants are issued with a prescription for a new COPD maintenance therapy, the physician (or delegate) will, at their discretion, train the participant on the correct use of their inhaler(s).

All participants who have spirometry measured should also have an assessment of inhaler errors performed where an appropriate error checklist is available for the study treatment they are using at Visit 2/EW Visit. If participants are unable to perform spirometry they may still participate in the inhaler errors assessment.

The errors listed will be aligned with the correct use information from the respective Patient Information Leaflets (PILs), in a checklist for each inhaler and these will be provided to investigators for scoring errors during the assessment.

The critical and overall errors per inhaler and how these have been defined are described in Appendix 7. If a suitable checklist is not available for study treatment, the participant will not have an error assessment. For participants who are on multiple inhaler therapy, checklists must be available for both inhalers in order for error assessment to proceed.

The errors made during the demonstration by participants are defined as “noncritical”, when the dose may not be affected, but the participant has demonstrated improper use of their inhaler, as per the checklist. A critical error is defined as an error that is most likely to result in no or significantly reduced medication being inhaled.

Assessment of Inhaler Error in Use
For the assessment, participants will be asked to demonstrate inhaler use when taking their regular dose of medication. Participants who have not withheld prescribed study medication must not perform an inhaler error assessment. Any errors (critical or non-critical) made by the participant while using the inhaler will be recorded by the investigator or delegate during the assessment on the checklist provided. If the participant makes no errors, this will also be recorded by the investigator/delegate.

If the participant makes any error in the use of the inhaler, the investigator/delegate will provide instruction in the correct use to the participant.

Where applicable, participants who use multiple inhalers should be tested on each inhaler consecutively according to their usual practice.

The checklists will be provided in the Study Reference Manual.

9.2. Other Assessments

9.2.1. Clinically Important Deterioration

CID is a composite outcome which assesses individual deteriorations in lung function and CAT (as defined by the accepted minimal clinically important difference) as well as the incidence of exacerbation (requiring treatment with antibiotics and/or systemic steroids or hospitalisation). For this study, it will be defined as follows:

- 100 mL reduction from baseline in FEV1 at 24 weeks.
- An exacerbation (requiring treatment with antibiotics and/or systemic steroids or hospitalisation)
- 2 units change (increase) from baseline in CAT score at 24 weeks.

9.2.2. COPD Exacerbations

Moderate and severe COPD exacerbation data will be collected from medical records and patient recall in the eCRF by the investigator and study-site personnel for all participants. A moderate or severe exacerbation is defined as worsening COPD symptoms that required systemic corticosteroids and/or antibiotics or hospitalisation. Use of antibiotics alone does not qualify as an exacerbation unless the use is associated with treatment of worsening symptoms of COPD, such as increased dyspnoea, sputum volume, or sputum purulence (colour). See Appendix 5 for Exacerbation Identification, Categorisation and Treatment Guidelines.

9.2.3. Healthcare Resource Utilisation

Primary and available secondary healthcare resource utilisation data including prescriptions associated with COPD related medical encounters will be collected in the eCRF by the investigator and study-site personnel for all participants.

In addition, visits and contacts that are due to a moderate or severe COPD exacerbation will be assessed and recorded.

The data collected will include:

- Primary healthcare contacts for COPD related care and treatment
- Medication for COPD related treatment.
- Hospital admissions, outpatient appointments and A&E attendances relating to COPD care.

Protocol-mandated procedures, tests, and encounters are excluded.

9.3. Exploratory Assessments

9.3.1. Participant Treatment and Study Satisfaction Questionnaire

A short questionnaire will be provided to the participant on paper for completion. This will then be transferred by site staff or the investigator into the eCRF.

9.3.2. Health Related Quality of Life Questionnaire

A short HRQoL questionnaire will be provided to the participant on paper for completion. This will then be transferred by site staff or the investigator into the eCRF.

9.4. Other

Eosinophil count

Eosinophils are increasingly being recognised as important biomarkers to predict which patients with COPD may respond to inhaled steroids. There is growing evidence, (Pascoe, 2018, Greulich, 2018, Brusselle, 2018) that patients with higher eosinophils have a better response to inhaled steroids (ICS) and this may be incorporated in guidelines about who should receive ICS in the near future. Gathering eosinophil data for subjects taking part in this study will help to further define the study COPD patient population, whether they would meet future guideline recommendations for ICS and also offers the opportunity to gain this information in normal clinical practice.

A new blood test is not required on patients entering the study, as the intention is to keep interventions to a minimum, in this clinical effectiveness study. It is likely that most patients will have had a full blood count in the last three years, which will have included eosinophil measurement. Where available, peripheral blood eosinophil levels/percentage of count and WBC counts will be collected using the historical value closest to the patients consenting visit, (V0/V1) and no later than 36 months prior to the patients first study visit.

9.5. Adverse Events

At scheduled and unscheduled visits for COPD related care, the following information will be collected and recorded in the eCRF:

- All SAEs
- Treatment related AEs
- AEs that lead to withdrawal from study treatment.

The definitions of an AE or SAE can be found in Appendix 3.

In addition, from the above safety data, the investigator will be instructed to fill the eCRF for Cardiovascular effects events and Pneumonia events (see Section 9.5.5 and Section 9.5.6).

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

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.**

Canadian Specific Reporting Requirements

In order for GSK to comply with Health Canada requirement, Canadian investigators are required to record drug related lack of efficacy events. A lack of efficacy is the failure to produce expected benefits.

Lack of efficacy" or "failure of expected pharmacological action" will be reported on a paper form as an AE or SAE as described in Section 12.3.1: Additional AE reporting requirements for Canadian Investigators.

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

- All SAEs that are considered related to study participation or considered related to any GSK product will be collected from the signing of the ICF until randomisation.
- All other SAEs will be collected from randomisation until completion of the Visit 2/EW Visit at the time points specified in the SoA (Section 2).
- All study treatment related AEs and AEs that lead to withdrawal from study treatment will be collected from randomisation until completion of the Visit 2/EW Visit at the time points specified in the SoA (Section 2).
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours of the investigator becoming aware of the event, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants, after the study end. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

- 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 3.

9.5.2. Method of Detecting AEs and SAEs

Care must 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.

9.5.3. Follow-up of AEs and SAEs

After the initial SAE, study treatment related AE or AE leading to withdrawal report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs which are study treatment related, will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.4). Further information on follow-up procedures is given in Appendix 3.

9.5.4. Regulatory Reporting Requirements for SAEs

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

9.5.5. Cardiovascular and Death Events

For all SAEs, deaths, treatment related AEs and AEs that lead to withdrawal from study drug, the cardiovascular events detailed in Appendix 3 must be reported. For these events the specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be

recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

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

9.5.6. Pneumonia

For all pneumonia events, which are SAEs, treatment related AEs or AEs that lead to withdrawal from study treatment, the pneumonia section of the eCRF should be completed with the details that are available to the investigator.

The investigators and site staff should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD receiving ICS/LABA include current smokers, patients with a history of prior pneumonia, patients with a body mass index < 25 kg/m^2 and patients with an FEV1 < 50% predicted.

For all suspected cases of pneumonia, Investigators are strongly encouraged to confirm the diagnosis (this includes obtaining a chest x-ray) and to initiate appropriate therapy as promptly as possible.

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

COPD Exacerbation is a disease related events (DREs), common in participants with COPD and can be serious/life threatening.

Moderate and severe COPD exacerbation events will be recorded on the Exacerbation page in the participant's eCRF.

Because exacerbations are typically associated with the disease under study, an exacerbation will not be reported according to the standard process for expedited reporting of SAEs to GSK unless the event meets the following criteria:

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or
- The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product. Please refer to Appendix 3 for guidelines on assessment of causality by investigator

NOTE: If either of the above conditions apply, then the event must be recorded and reported as an SAE in addition to reporting as an exacerbation.

9.5.8. Pregnancy

Women of Child Bearing Potential are excluded from this study. If a female participant becomes pregnant whilst enrolled in the study, the participant must withdraw from the study and should be followed up until the pregnancy outcome. Refer to Appendix 4 for further detail.

9.6. Treatment of Overdose

An overdose is defined as a dose greater than the total doses which results in clinical signs and symptoms. These should be recorded by the investigator on the AE/SAE pages. In the event of an overdose of study 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, AEs, and other significant data pertaining to the study treatment being used in this study. Such documents may include, but not be limited to, the PIL/Investigator Brochure or equivalent document. In the event of an overdose, the treating investigator should:

- Contact the medical monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically.
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

9.7. Safety Assessments

All SAEs that are considered related to study participation or considered related to a GSK product will be collected from the time of consent.

All other SAEs, treatment related AEs and AEs that lead to withdrawal from study drug will be collected from randomisation. These events will be collected, where available, during the 24-week period of usual care when the participant is seen for COPD related usual care visits. This information may be supplemented from available medical records and patient recall.

Planned time points for safety assessments are provided in the SoA.

9.7.1. Medical Devices

A medical device is any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for any of the following:

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

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means (Medical Device Definition from European Union Council Directive 007/47/EC dated 5 Sept 2007).

Medical devices approved for use in Europe bear a European Conformity (CE) mark; otherwise, they are considered investigational devices.

Examples of GSK medical devices include, but are not limited to: metered dose inhaler, auto-injector, **inhalation spacers**, measuring cups, measuring spoons, paediatric oral syringes, dry powder inhalers

Medical devices (spacers/holding chambers) are being provided by GSK for use in this study by a subgroup of participants.

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

GSK medical device incidents, including those resulting from malfunctions of the device, must be reported.

9.7.2. Drug/Device Combination Products

Not all delivery systems are considered “medical devices”. However, some GSK investigational products are considered “drug/device combination products” and incidents of device malfunction must be reported to GSK from the investigative site. Examples of GSK drug/device combination products include, but are not limited to: albiglutide lyophylized pen injector, albiglutide liquid autoinjector, **ELLIPTA (nDPI)** inhaler, and **Breezhaler inhaler.**

GSK must be notified if any GSK device or Drug/Device combination product fails to function properly. Incidents should be reported as a device malfunction and not as a safety event.
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 9.5

If a device malfunction is reported to the investigator site, the following process should be followed:

- report the malfunction
- as this study uses commercial supply, the GSK Customer Complaints Form will be used.
- arrange for a new device to be provided if not already done so by a pharmacy/ prescription

Non-GSK medical device incidents should be reported to the appropriate manufacturer as per usual local practice.

9.8. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

9.9. Pharmacodynamics

Pharmacodynamics parameters are not evaluated in this study.

9.10. Genetics

Genetics are not evaluated in this study.

9.11. Biomarkers

Biomarkers are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Hypotheses

The primary objective of this study is to evaluate the effectiveness of TRELEGY ELLIPTA versus non-ELLIPTA MITT in COPD patients in a pragmatic setting over 24 weeks. The study will provide evidence to support HCP and payer discussions that TRELEGY ELLIPTA is more effective on CAT improvement than non-ELLIPTA MITT in a patient population representative of everyday clinical practice.

The primary effectiveness outcome is the proportion of CAT responders at Visit 2 and the primary treatment comparison is TRELEGY ELLIPTA versus non-ELLIPTA MITT for all participants.

In addition, other exploratory treatment comparisons of TRELEGY ELLIPTA with non-ELLIPTA MITT will be performed for the prior treatment stratification levels of ICS/LABA/LAMA, ICS/LABA and LABA/LAMA separately for the primary outcome only.

The null hypothesis is that there is no difference in the proportion of CAT responders at Visit 2 between TRELEGY ELLIPTA and non-ELLIPTA MITT:

H_0: $T_1 - T_2 = 0$

The alternative hypothesis is that there is a difference between treatment groups:

H_1: $T_1 - T_2 \neq 0$

where T_1 and T_2 are, the treatment means for TRELEGY ELLIPTA and non-ELLIPTA MITT respectively.

10.2. Sample Size Determination

10.2.1. Primary Outcome

The sample size is based on the proportion of CAT responders for the comparison of TRELEGY ELLIPTA with non-ELLIPTA MITT.

A recent effectiveness study conducted by GSK (HZC115151) included a cohort of participants who were on triple (ICS+LABA+LAMA) therapy at baseline, who were subsequently randomised to continue with this therapy ('usual care') or to switch to FF/VI + LAMA therapy. The proportion of CAT responders at 12 months in the 'usual care' arm was 35% and the odds ratio for being a responder vs. a non-responder for FF/VI+LAMA vs. usual care was 1.68.
CAT and St George's Respiratory Questionnaire (SGRQ) responder data from a RCT of FF/UMEC/VI generally demonstrated lower odds ratios for triple vs. dual therapy and in addition some participants will be stepping up from ICS/LABA or LABA/LAMA, so a lower value of 1.3 has been assumed for sample size calculations.
For the sample size calculation for this study, the proportion of CAT responders in the non-ELLIPTA MITT arm at Visit 2 is assumed to be 35%. Assuming the true odds ratio between treatments is 1.3 (i.e. proportion of responders on FF/UMEC/VI is 41%), a sample size of 1297 participants per arm would provide 90% power to reject the null hypothesis at the two-sided 5% significance level. Calculation performed using PASS 12 sample size software [Hintze, 2013].

In the HZC115151 study, 88% of participants were included in the analysis of CAT responders at 12 months, and RCT data from a recently completed study with FF/UMEC/VI indicated low levels of dropout between 6 and 12 months [Lipson, 2017]. For some estimands missing data may be treated as missing, and hence assuming a similar level of dropout (13.5%), a total of 3000 participants are required to be randomised. Missing assumptions will be explored within the estimand framework which will be provided in more detail in the Reporting & Analysis Plan (RAP).

Participants will be randomised in a 1:1 proportion to the TRELEGY ELLIPTA and non-ELLIPTA MITT arms, respectively.

The randomisation schedule will be stratified based on previous treatment. The stratification levels will be one of ICS/LABA, LABA/LAMA or ICS/LAMA/LABA.

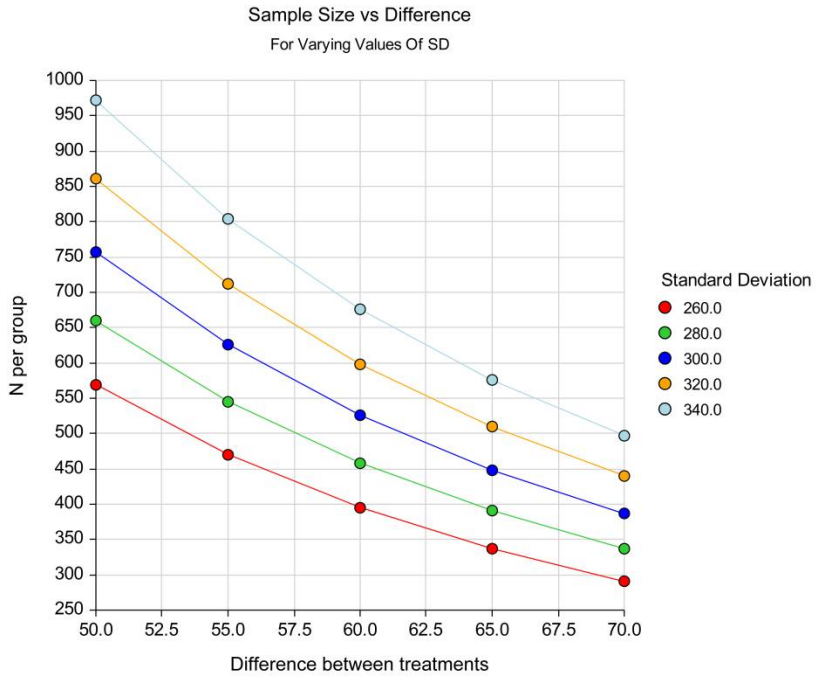
10.2.2. Secondary Outcomes

10.2.2.1. FEV1

Estimated values for the residual standard deviation (SD) for trough FEV1 observed in RCTs have been around 250 ml. As this study is a pragmatic study with minimal intervention carried out in normal clinical practice and participants may not be able to provide a true trough FEV1 measurement it is expected that the variability of the data will be higher.

Using an estimated residual SD of 300 mL, a two-sided significance threshold of 5% and 90% power, and assuming a true treatment difference of 50mL, the study would need to obtain FEV1 data for a minimum of 757 participants per treatment arm to detect a statistically significant difference between TRELEGY ELLIPTA and non-ELLIPTA MITT Figure 2.

Figure 2 FEV1 Sample Size vs Assumed True Treatment Difference



10.2.2.2. Critical Errors

There is limited data available on CEs made by patients following 24 weeks of inhaler use.

A range of CE rates (participants with at least one CE) were explored for each of the treatment groups. Using conservative rates of 10% on ELLIPTA and 20% on non-ELLIPTA MITT 266 participants in each treatment group would be required to provide 90% power to reject the null hypothesis at a two-sided 5% significance level. The CE rate within the non-ELLIPTA MITT treatment group would include participants who had an error on one inhaler only as well as those who had an error on both inhalers.

Given that not all participants in the non-ELLIPTA MITT arm may be on inhaler combinations for which error checklists in both inhalers are available, there may be fewer participants in the non-ELLIPTA MITT arm and thus more than 266 participants may be assessed in the ELLIPTA treatment arm in order to ensure we have 266 participants in the non-ELLIPTA MITT arm.

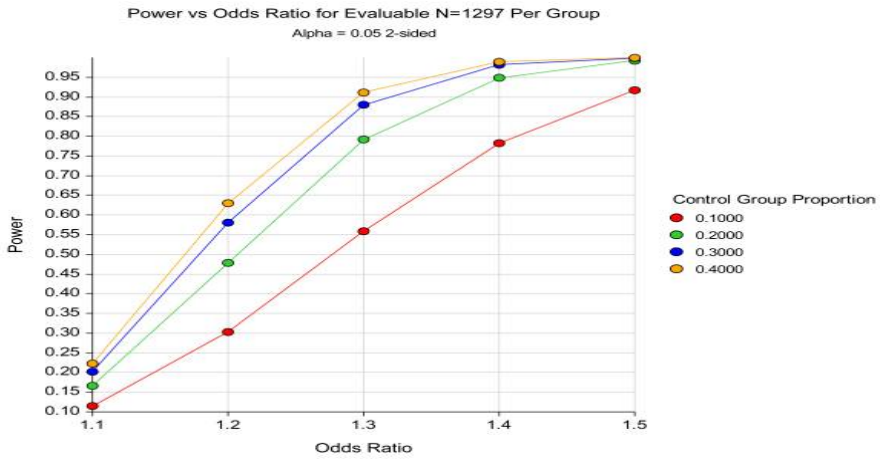
Additionally, in order to enable further exploratory treatment comparisons between specific inhalers, the aim will be to obtain at least 500 participants per treatment arm with error assessments performed.

10.2.3. Sample Size Sensitivity

If the CAT response rate in the non-ELLIPTA MITT treatment arm is different from the value of 35% or the assumed true odds ratio used in the sample size calculation, the power to detect a difference in the response rates between the treatment arms will be affected.

Figure 3 illustrates the effect on power for varying non-ELLIPTA MITT CAT response rate assumptions and odds ratio values for the comparison. The sample size and two-sided significance threshold of 5% remain fixed.

Figure 3 CAT Power and Odds Ratio



It should be noted that a trial can run to its conclusion and deliver a significant p-value for an effect smaller than the one we nominally powered for (assuming the assumptions underlying the sample size calculation are correct). In this case, based on a nominal true odds ratio of 1.3, a response rate of 35% on the non-ELLIPTA MITT arm and a sample size of 1297 evaluable participants per arm, we would see a p=0.05 with an odds ratio of 1.172 and p<0.05 for odds ratios >1.172.

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined in Table 3.

Table 3 Definitions of Analysis Populations

Population	Definition / Criteria
All Subjects Enrolled (ASE)	All participants for whom a record exists in the study database, including screen failures.
Intent-to-treat (ITT)	All randomised participants, excluding those who were randomised in error. A participant who is recorded as a screen failure and also randomised will be considered to be randomised in error. Any other participant who receives a randomisation number will be considered to have been randomised. Displays will be based on the treatment to which the participant was randomised unless otherwise stated.
FEV1 Population	All members of the ITT population for whom an FEV1 assessment was planned.

Population	Definition / Criteria
CE Population	All members of the ITT population for whom a CE assessment was planned. Note that participants within selected centres performing inhaler assessments who are not on an inhaler for which an error checklist is available will not be included in this population.

10.4. Statistical Analyses

10.4.1. Effectiveness Analyses

The primary comparison of interest for the all effectiveness outcomes is TRELEGY ELLIPTA compared to non-ELLIPTA MITT. However, for each outcome, different estimands may be explored depending on the scientific question of interest. These will be detailed in the RAP.

Table 4 Statistical Analysis Methods for key Outcomes

Outcome	Statistical Analysis Methods
Primary	The primary outcome of proportion of CAT responders at Visit 2 will be analysed for the ITT population using a logistic regression model with treatment as an explanatory variable and baseline CAT score, number of exacerbations in the prior year, prior medication use strata and country included as covariates. All recorded data up to the time of study withdrawal will be included in analysis. The primary estimand of interest will be defined in the RAP. Consideration will be given on how to handle participants in the analysis who discontinue study medication, receive alternative medications, who fail to provide a CAT response or who discontinue from the study. In some of these scenarios participants may provide data after these events, in others subsequent data may be missing. These situations will be further investigated using sensitivity analysis to the primary estimand of interest or using alternative estimands on the primary outcome. Further details will be provided in the RAP.
Secondary	Inference will only be made on the secondary outcomes if the primary analysis achieves significance. Otherwise results will be for descriptive purposes only. **FEV1:** FEV1 will only be collected at a subset of centres. The secondary outcome of change from baseline in FEV1 at Visit 2 will

Outcome	Statistical Analysis Methods
	be analysed for the ITT population using an analysis of covariance model with treatment as an explanatory variable and baseline FEV1, prior medication use strata and country included as covariates. **Critical Errors:** Inhaler error assessments will only be performed at a subset of centres. The secondary outcome of percentage of participants making at least one CE at Visit 2 will be analysed for the ITT population using a logistic regression model with treatment as an explanatory variable. Country and prior medication use strata will be included in the model if possible. The odds ratio, 95% CI and p-value will be presented for the comparison between TRELEGY ELLIPTA and non-ELLIPTA MITT. It will be based on a two-sided hypothesis testing approach of superiority. For the non-ELLIPTA MITT arm all inhalers for which error checklists are available will be considered. Any participant in the non-ELLLIPTA MITT arm using an inhaler for which no error checklist is available will not be considered for CE assessment. Estimands may be defined in order to take into account participants who have changed their study treatment during the study. These will be detailed further in the RAP.
Exploratory	Exploratory analyses relating to HCRU outcomes obtained from the EHR database will be described in a supplementary RAP and reported independently of the main RAP.

Full details of the analyses to be performed on the primary and other effectiveness outcomes will be given in the RAP.

10.4.2. Safety Analyses

SAEs will be coded using the standard GSK dictionary, MedDRA, and grouped by system organ class. The number and percentage of participants experiencing at least one SAE of any type, SAEs within each system organ class and SAEs within each preferred term will be presented for each treatment group. Separate summaries will be provided for all SAEs, study treatment related SAEs, fatal SAEs and SAEs leading to withdrawal. Deaths and SAEs will be documented in case narrative format.

All safety analyses will be performed on the ITT population. Further consideration may be given to cases where participants have changed treatment.

Similar summaries will be performed for Adverse Drug Reactions (ADRs).

10.4.3. Other Analyses

All other analyses will be described in the RAP.

10.4.4. Interim Analyses

No interim analyses are planned.

11. REFERENCES

Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in Combination with Placebo, Salmeterol, or Fluticasone–Salmeterol for Treatment of Chronic Obstructive Pulmonary Disease A Randomised Trial. Ann Intern Med. 2007.146:545-555.

Brusselle G, Pavord ID, Landis S, Pascoe S, Lettis S, Morjaria N, Barnes N, Hilton E, Blood eosinophil levels as a biomarker in COPD, Respiratory Medicine (2018), doi: 10.1016/j.rmed.2018.03.016

Cazzola M, Ando F, Santus P, Ruggeri P, Marco F, Sanduzzi A, Smato M. A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe to-very severe COPD. Pul. Pharm. & Therapeu. 2007. 20:556–561.

Chen LF, Vander Weg MW, Hofmann DA, Reisinger HS. The Hawthorne Effect in Infection Prevention and Epidemiology. Infect Control Hosp Epidemiol. 2015. 36(12):1444-50.

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

Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org.

Greulich T, Franz Vogelmeier C. The Lancet Respiratory Medicine. Blood eosinophils as a marker of eosinophilic exacerbations in COPD 2018: doi: 10.1016/S2213-2600(18)30095-X.

Hanania NA, Crater GD, Morris AN, Emmett AH, O'Dell DM, Niewoehner DE. Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. Respir Med. 2012;106(1):91-101.

Herland K, Akselsen JP, Skjønsberg OH, Bjermer L.How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease? Respir Med. 2005 Jan; 99(1):11-9.

Hintze, J. PASS 12. NCSS, LLC. Kaysville, Utah, USA. 2013.www.ncss.com.

International Conference of Harmonisation [ICH] of Technical Requirements for Registration of Pharmaceuticals for Human Use 2009. Guidance on nonclinical safetystudies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2).

Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009. 34(3):648-54.

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

Jung KS, Park HY, Park SY, Kim SK, Kim YK, Shim JJ et al. Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: A randomised controlled study. Resp. Med. .2012. 106: 382-389. doi:10.1016/j.rmed.2011.09.004.

Kardos P, Worsley S, Singh D, Román-Rodríguez M, Newby DE, Müllerová H. Randomised controlled trials and real-world observational studies in evaluating cardiovascular safety of inhaled bronchodilator therapy in COPD. International Journal of Chronic Obstructive Pulmonary Disease. 2016. 11(1) Pages 2885—2895 https://doi.org/10.2147/COPD.S118867

Landis SH, Wurst K, Le HV, Bonar K, Punekar YS. Can Assessment of Disease Burden Prior to Changes in Initial COPD Maintenance Treatment Provide Insight into Remaining Unmet Needs? A Retrospective Database Study in UK Primary Care. COPD. 2017. 14(1):80-85.

Lipson DA; Barnacle H, Birk R, Brealey N, Locantore N, Lomas DA, Ludwig-Sengpiel A , Mohindra R, Tabberer M, Zhu C_Q, and Pascoe SJ. FULFIL Trial: Once-Daily Triple Therapy in Patients with Chronic Obstructive Pulmonary Disease. American Journal of Respiratory and Critical Care Medicine 2017. 196(4):438-446. https://doi.org/10.1164/rccm.201703-0449OC

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

Price D, West D, Bruseelle G, Gruffydd-Jones, K, Jones, R, Miravitlles M, Rossi A, Hutton, C, Ashton V, Stewart R, Bichel, K, Management of COPD in the UK primary-care setting: an analysis of real-life prescribing patterns. International Journal of COPD 2014. 9 889–905

Pascoe S, Pavord I, Hinds D, Locantore N, Barnes N. The association between blood eosinophils and risk and treatment outcome in COPD is not dichotomised. The Lancet Respiratory Medicine. 2018: doi: 10.1016/S2213-2600(18)30137-1.

Vestbo,J, Leather, D, Diar Bakerly, N, New, J, Gibson, M, McCorkindale, S, Collier, S, Crawford, J, Frith, L Harvey, C, Svedsater, H, Woodcock, A Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice. N Engl J Med 2016. 375:1253-1260 September 29, 2016 DOI: 10.1056/NEJMoa1608033

Welte, T Miravitlles M, Hernandez P, Eriksson G, Peterson S, Polanowski T, Kessler R. Efficacy and Tolerability of Budesonide/Formoterol Added to Tiotropium in Patients with Chronic Obstructive Pulmonary Disease. Am. J. Respir. Crit.Care Med. 2009.180:741–750.

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATS	American Thoracic Society
CAT	COPD Assessment Test
CE	Critical Errors
CFR	Code of Federal Regulation
CI	Confidence Intervals
CID	Clinically Important Deterioration
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CSR	Clinical Study Report
CV	Cardiovascular
DRE	Disease Related Events
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EHR	Electronic Health Record
EW	Early Withdrawal
EXT	Extension
FEV1	Forced Expiratory Volume in One Second
FF	Fluticasone Furoate
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
GSK573719	Umeclidinium (UMEC)
GW642444	Vilanterol Trifenatate (VI)
GW685698	Fluticasone Furoate (FF)
HCP	Health Care Provider
HCRU	Health Care Resource Use
HIPPA	Health Insurance Portability and Accountability Act
HR	Heart Rate
HRQoL	Health Related Quality of Life
ICF	Informed Consent Form
ICH	International Conference of Harmonization
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IRB	Independent Review Board

IRT	Interactive Response Technology
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine System
LABA	Long-acting β2 Agonist
LAMA	Long-acting Muscarinic Receptor Antagonist
LRTI	Lower Respiratory Tract Infection
LTRA	Leukotriene Receptor Antagonists
MACE	Major Adverse Cardiac Event
MAO	Monoamine Oxidase Inhibitors
mcg	Microgram
MedDRA	Medical dictionary for Regulatory Activities
MHDP	Marketed Health Products Directorate
MITT	Multiple Inhaler Triple Therapy
MMRM	Mixed Models Repeated Measures
MSDS	Material Safety Data Sheet
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PRAC	Pharmacovigilance Risk Assessment Committee
prn	As required
RAP	Reporting and Analysis Plan
RAMOS NG	Participant Randomisation & Dispensing IT System
RCT	Randomised Clinical Trial
SABA	Short-acting β2-adrenergic receptor agonist
SAE	Serious Adverse Event
SD	Standard Deviation
SGRQ	St Georges Respiratory Questionnaire
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TOC	Table of Contents
UFIE	Unusual Failure in Efficacy
UMEC	Umeclidinium
VI	Vilanterol Trifenatate
WOCBP	Woman of Childbearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ELLIPTA
TRELEGY

Trademarks not owned by the GlaxoSmithKline group of companies
SAS

12.2. Appendix 2: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines [ICH, 2009]
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, 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 IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - 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), and all other applicable local regulations

Financial Disclosure

If required, 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.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations,

ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

Data Protection

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

Publication Policy

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

Dissemination of Clinical Study Data

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

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

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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

Data Quality Assurance

- Participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., EHR). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final 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.

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 can be found in the SRM.

Study and Site Closure

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

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

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

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

12.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

SAEs, study treatment related AEs and AEs that lead to withdrawal from study treatment will be reported in this study.

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events Meeting the AE Definition
Study treatment related events or AEs that lead to withdrawal from study treatment will be reported if they meet the following definition • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram (ECG), radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. (Refer to Section 12.3.1 for specific requirements for Canadian investigators)

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (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.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the investigator's office or outpatient setting. Complications that occur during hospitalisation are AE. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred, or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, 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:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

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

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs that satisfy the criteria in Section 9.2.

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

Recording 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 in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised 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 one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment

administration will be considered and investigated.

- The investigator will also consult the 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 HCPs.
- If a participant dies during participation in the study or during a recognised follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology, if any.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within

the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **medical monitor**
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

12.3.1. Additional Adverse Event (AE) Reporting Requirements for Canadian investigators

Health Canada requires pharmaceutical manufacturers to expeditiously report domestic cases of unusual failure in efficacy (UFIE) for new drugs to the Marketed Health Products Directorate (MHPD) within 15 days of first notification. This regulation applies to marketed drugs, and used as directed per the Canadian prescribing information, including those drugs used in Phase IV (non-CTA filed) clinical trials.

In order for GSK to comply with this Health Canada requirement, Canadian investigators are required to record drug related lack of efficacy events. A lack of efficacy is the failure to produce expected benefits.

Lack of efficacy" or "failure of expected pharmacological action" will be reported on a paper form as an AE or SAE as described in Table 5.

All paper forms are required to be faxed to GSK Canada's Drug Safety department at PPD PPD within 24 hrs of first awareness.

Table 5 CANADA ONLY: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Event

1.Adverse Event criteria	**2.All countries including Canada: Electronic case record form (eCRF) only**	**3.Canada only: Paper form only**	**4.Canada only: Electronic case record form (eCRF) AND Paper form**
Non-serious	AEs considered related to study treatment and AEs leading to withdrawal from the study or from treatment	Drug related lack of efficacy reports **without** associated signs or symptoms or clinical sequelae.	Drug related lack of efficacy **with** associated signs or symptoms or clinical sequelae
Serious	All SAEs	Drug related lack of efficacy reports **without** associated signs or symptoms or clinical sequelae.	Drug related lack of efficacy reports **with** associated signs or symptoms or clinical sequelae

12.4. Appendix 4: Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- Females on HRT must have physician confirmation of postmenopausal status prior to study enrolment.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK.
- Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 3. 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 will be withdrawn from the study.

12.5. Appendix 5 COPD Exacerbation Identification, Categorisation and Treatment Guidelines

12.5.1. Guidelines for Identifying COPD Exacerbations

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

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

- Dyspnea
- Sputum volume
- Sputum purulence (colour)

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 might choose one of the following courses of action:

- Use prescribed medication (rescue pack) and inform their physician or study investigator at the next health care contact.
- Contact a health care provider for COPD related care.
- Participants with worsening respiratory symptoms will be classified as having:

  A mild/moderate/severe exacerbation and/or pneumonia

OR

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

12.5.2. COPD Exacerbation Severity

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

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

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

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.

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

12.5.3. Treatment of COPD Exacerbations

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

12.5.4. Guidelines for Treatment with Corticosteroids

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

12.5.5. Guidelines for Treatment with Antibiotics

- Use of antibiotics for the treatment of upper or lower respiratory tract infections is not considered a COPD exacerbation unless the participant experiences worsening of symptoms of COPD.

12.5.6. Onset and Resolution of COPD Exacerbations

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

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

The date of resolution should be based on when the treating investigator or participant determines that the COPD symptoms have returned to pre-exacerbation levels or to a new baseline. In determining this resolution date, consideration should be given to participant valuation.

12.5.7. Guideline for assessing multiple exacerbations

Two 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.

12.5.8. Guideline for assessing exacerbations that increase in severity

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

12.6. Appendix 6: Summary of Risks

	Summary of Data/Rationale for Risk for FF/UMEC/VI
Identified risk of clinical significance	
Pneumonia in patients with COPD Pneumonia is a class concern for any ICS-containing product for the treatment of COPD	In a study (CTT116853) in 1810 randomised COPD patients treated with FF/UMEC/VI or budesonide/formoterol (BUD/FOR) for up to 24 weeks (ITT population), or up to 52 weeks (subset of 430 patients; extension (EXT) population), the incidence of events in the pneumonia adverse event of special interest (AESI) group was 2.2% and 0.8% for FF/UMEC/VI and BUD/FOR respectively in the ITT population, and 1.9% and 1.8% for FF/UMEC/VI and BUD/FOR respectively in the EXT population. There was one fatal case of pneumonia in a patient who received FF/UMEC/VI. The incidence of pneumonia with FF/UMEC/VI in this study was in line with the incidence of pneumonia seen in 24 week studies with FF/VI (<1-2% with FF/VI 100/25) and less than that observed in 52 week exacerbation studies with FF/VI (6% with FF/VI 100/25) [Dransfield, 2013]. Similarly, the incidence of pneumonia with FF/UMEC/VI was less than that observed in a 12-month exacerbation trial with BUD/FOR (6.4%) [Sharafkhaneh, 2012]. Prior studies with FF/VI have demonstrated risk factors associated with a higher risk of pneumonia in patients with COPD (e.g., advanced age, poor lung function, low BMI, current smoking, and a prior history of pneumonia) [Crim, 2009]. These risk factors were present in some patients with pneumonia in study CTT116853 with FF/UMEC/VI, however, the low number of pneumonia events reported in the study precludes drawing any definite conclusions about risk factors. These risk factors should be taken into consideration when using an ICS in patients with COPD. Pneumonia risk will be important in the benefit-risk assessment for FF/UMEC/VI in COPD patients, hence a robust risk mitigation strategy is being proposed. The Pharmacovigilance Risk Assessment Committee (PRAC) recently conducted an Article 31 review to evaluate the risk of pneumonia with use of ICSs in patients with COPD. The PRAC review confirmed that COPD patients treated with inhaled corticosteroids are at increased risk of pneumonia; however, the Committee's view was that the benefits of ICSs continue to outweigh their risks. The PRAC also looked whether there were any differences in the risk of pneumonia between these products, and did not find conclusive evidence

	Summary of Data/Rationale for Risk for FF/UMEC/VI
	of such difference
Potential risk of clinical significance	
Decreased bone mineral density and associated fractures. Reduction in bone density, and the subsequent risk of fractures, is a known potential risk with corticosteroids.	There may be a modest increase in risk of fracture among patients with COPD treated with ICS; but, the results are not consistent across individual studies [Christensson, 2008, Lehouck, 2011, Weldon, 2009]. In study CTT116853, the incidence of events in the decreased bone mineral density and associated fractures AESI group was low, with an incidence of 0.4% and 0.7% in the FF/UMEC/VI and BUD/FOR treatment groups respectively in the ITT population up to 24 weeks, and 0.5% in both treatment groups in the EXT Population up to 52 weeks. The majority of the fractures in both treatment groups were traumatic in nature.
Serious Cardiovascular effects on heart rate (HR), blood pressure, QT interval, potentially leading to cardiac arrhythmia 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 CTT116853, approximately two-thirds of all participants reported CV risk factors at baseline. In this study, cardiovascular effects were the most frequently reported AESI, with a similar incidence between FF/UMEC/VI and BUD/FOR treatment groups in the ITT population up to 24 weeks (4.3% and 5.2% respectively) and the EXT population up 52 weeks (8.6% and 10% respectively). Within subgroups of cardiovascular effects, hypertension was reported most frequently and with a numerically higher incidence with BUD/FOR (2.3%) compared with FF/UMEC/VI (1.3%) in the ITT population up to 24 weeks, but with a similar incidence in the EXT population up to 52 weeks (0.9 to 1.0% across treatment groups). Cardiac arrhythmias were reported the next most frequently and occurred with an incidence of 1.2% in both treatment groups in the ITT Population up to 24 weeks, and with an incidence of 1.9% and 3.6% in the FF/UMEC/VI and BUD/FOR groups in the EXT population up to 52 weeks. The incidence of serious events in the cardiovascular effects AESI was low, with an incidence of 1.0% and 1.1% in the FF/UMEC/VI and BUD/FOR groups respectively in the ITT population to 24 weeks, and 2.9% and 1.4% in the FF/UMEC/VI and BUD/FOR groups respectively in the EXT population to 52 weeks. The absolute numbers of fatal events in cardiovascular effects AESI was low in the study, despite the study enrolling participants with a number of CV comorbidities at baseline.

	Summary of Data/Rationale for Risk for FF/UMEC/VI
	A pre-specified Major Adverse Cardiac Event (MACE) analysis was conducted in CTT116853, with broad MACE defined as: Ischemic Heart Disease SMQ excluding fatalities, plus Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ excluding fatalities, plus adjudicated cardiovascular deaths. The narrow MACE definition included only the preferred terms of Myocardial ischaemia and Acute myocardial infarction in place of the Ischaemic Heart Disease SMQ. Overall, the absolute number of MACE events using either the broad or narrow definition was low both in the ITT population up to 24 weeks and EXT population up to 52 weeks. No clinically relevant differences were observed between FF/UMEC/VI and BUD/FOR based on narrow and broad MACE analysis both in the ITT population to 24 weeks and EXT population to 52 weeks. In study CTT116853, there were no emerging number of CV comorbidities at baseline. A pre-specified Major Adverse Cardiac Event (MACE) analysis was conducted in CTT116853, with broad MACE defined as: Ischemic Heart Disease SMQ excluding fatalities, plus Central Nervous System Haemorrhages and Cerebrovascular Conditions SMQ excluding fatalities, plus adjudicated cardiovascular deaths. The narrow MACE definition included only the preferred terms of Myocardial ischaemia and Acute myocardial infarction in place of the Ischaemic Heart Disease SMQ. Overall, the absolute number of MACE events using either the broad or narrow definition was low both in the ITT population up to 24 weeks and EXT population up to 52 weeks. No clinically relevant differences were observed between FF/UMEC/VI and BUD/FOR based on narrow and broad MACE analysis both in the ITT population to 24 weeks and EXT population to 52 weeks. In study CTT116853, there were no emerging signals from vital signs, ECGs, or Holter data.
Missing information	
Safety in pregnancy and lactation	There is a low incidence of pregnancy in the COPD population due to their age. There were no reports of pregnancy in the COPD patients enrolled in the CTT116853 and 200109/200110 studies with FF/UMEC/VI. Due to the high risk to the foetus of uncontrolled COPD in pregnant women, a discussion on the benefit of continuing therapy will need to occur with the patient and the prescribing

	Summary of Data/Rationale for Risk for FF/UMEC/VI
	physician.
Safety in severe hepatic impairment	Patients with severe hepatic impairment were studied as part of FF/VI development program but not in the UMEC/VI development program. It was agreed with European Medicines Agency (EMA; Follow-up Scientific Advice meeting) that no additional/repeat studies in subjects with hepatic impairment would be required as part of FF/UMEC/VI development program. Due to lack of data with UMEC in severe hepatic impairment, safety in this subgroup of subjects would be included as missing information in this FF/UMEC/VI Risk Management Plan.

References

Brusselle G, Pavord ID, Landis S, Pascoe S, Lettis S, Morjaria N, Barnes N, Hilton E, Blood eosinophil levels as a biomarker in COPD, Respiratory Medicine (2018), doi: 10.1016/j.rmed.2018.03.016

Christensson C, Thoren A, Lindberg B. Safety of inhaled budesonide: clinical manifestations of systemic corticosteroid-related adverse effects. *Drug Safety.* 2008;31:965-988.

Crim C, Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *EUR Respier J* 2009;34(2):641-647.

De Bisschop MB, Bellou A. Anaphylaxis. *Current Opinion in Critical Care. 2012;18(4):308-317.*

Dransfield MT, Bourbeau J, Jones PW, Hanania NA, Mahler DA, Vestbo J, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med 2013;1:210-223.*

Lehouck A, Boonen S, Decramer M, Janssens W. COPD, bone metabolism, and osteoporosis. *Chest.* 2011;139:648-657.

Niggemann B, Beyer K. Factors augmenting allergic reactions. *Allergy.* 2014;69(12):1582-1587.

Packe GE, Cayton RM, Mashhoudi N. Nebulised ipratropium bromide and salbutamol causing closed-angle glaucoma. *Lancet*. 1984;22:691.

Sharafkhaneh A, Southard JG, Goldman M, Uryniak T, Martin UJ. Effect of budesonide/formorterol pMDI on COPD exacerbations: A double-blind, randomised study. *Respir Med* 2012;106(2):257-268.

Steve Pascoe, Ian Pavord, David Hinds, Nicolas Locantore, Neil Barnes. The association between blood eosinophils and risk and treatment outcome in COPD is not dichotomised The Lancet Respiratory Medicine. 2018: doi: 10.1016/S2213-2600(18)30137-1.

Timm Greulich, Claus Franz Vogelmeier. Blood eosinophils as a marker of eosinophilic exacerbations in COPD. The Lancet Respiratory Medicine. 2018: doi: 10.1016/S2213-2600(18)30095-X.

Weldon D. The effects of corticosteroids on bone growth and bone density. *Ann. Allergy Asthma Immunol.* 2009;103:3-11.

12.7. Appendix 7: Inhaler Specific Errors

There are no universally agreed checklists that define CEs and over all errors for specific inhalers. The checklist and identification of CEs have been developed by GSK based upon:

- A review of the PIL for each inhaler and the steps defined therein for correct use.
- The available literature which is exhaustive for a number of the commonly used inhalers.
- Review of these errors with a group of external inhaler experts.

The CE checklists are therefore, as robust as possible. Furthermore, GSK uses selected sites with trained assessors to ensure as much consistency as possible in the valuation of errors in study participants.

Checklist of instructions for correct use will be based on the steps listed in the PIL/package insert for each inhaler. Some of the steps outlined in the PILs/package inserts require several actions to be identified and checked by the investigator.

CEs are identified as underlined in the list below. A CE is defined as an error that is most likely to result in no or significantly reduced medication being inhaled. These errors will be captured in a checklist provided for assessment of inhaler use.

Note: Checklists which may be used to assess inhaler errors are listed below. These checklists may be updated as new information becomes available using the stringent procedure described above. New checklists may be utilised in the study as and when they are developed for use, with appropriate training material available.

Inhaler Errors Checklist: ELLIPTA

PIL Step	PIL Wording (ELLIPTA June 2016)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
2	**Prepare a dose** Wait to open the cover until you are ready to take your dose. Do not shake the inhaler. • Slide the cover down until you hear a click.	Failed to open cover	☐	☐
		Shook the device after dose preparation	☐	☐
3	**Inhale your medicine** • While holding the inhaler away from your mouth, breathe out as far as is comfortable. Do not breathe out into the inhaler.	No exhalation before an inhalation	☐	☐
		Exhaled directly into mouthpiece	☐	☐

PIL Step	PIL Wording (ELLIPTA June 2016)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
	• Put the mouthpiece between your lips, and close your lips firmly around it. Do not block the air vent with your fingers. • Take one long, steady, deep breath in. Hold this breath for as long as possible (at least 3-4 seconds). • Remove the inhaler from your mouth. • Breathe out slowly and gently.	No seal by the lips round the mouthpiece during the inhalation	☐	☐
		Inhalation manoeuvre **was not**: - long - steady - deep	☐	☐
		Blocked air inlet during inhalation manoeuvre	☐	☐
		Did not hold breath	☐	☐
4	• Close the inhaler	Did not close the device (Note: this is an error but one which does not affect the medication that is inhaled)	☐	☐
Other comments:				

Inhaler Errors Checklist: Generic MDI

PIL Step	PIL Wording (Generic MDI March 2015)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
2	• Remove the mouthpiece cover/cap	Failed to remove cap.	☐	☐
3	Shake the inhaler 4-5 times to ensure that: • Any loose objects are removed • The contents of the inhaler are evenly mixed	Did not shake the device.	☐	☐
4	• Hold the inhaler upright with your thumb on the base, below the mouthpiece. • Breathe out as far as is comfortable. • Do not breathe in again yet.	Did not inhale within 5 seconds of shaking the device.	☐	☐
		No exhalation before inhalation.	☐	☐
5	• Place the mouthpiece in your mouth between your teeth. •Close your lips around it. •Do not bite.	Failed to place device in mouth.	☐	☐
6	• Breathe in through your mouth. • Just after starting to breathe in, press down on the top of the canister to release a puff of medicine. • Do this while still breathing in slowly and deeply.	Inhalation manoeuvre **was not**: - slow - deep (Note: if it lasts for <2 seconds, then it is too fast)	☐	☐
		No dose actuated during an inhalation manoeuvre.	☐	☐
		Dose coordination so poor that patient is likely to have received no dose or only received minimal dose.	☐	☐

PIL Step	PIL Wording (Generic MDI March 2015)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
		Dose coordination was sup-optimal but patient likely to have received some dose.	☐	☐
7	• Hold your breath, take the inhaler from your mouth and your finger from the top of the inhaler. •Continue holding your breath for a few seconds, or as long as is comfortable.	Did not hold breath	☐	☐
8	• If your doctor has told you to take two puffs, wait about half a minute before taking another puff by repeating steps 3 to 7	More than one dose actuation during inhalation procedure	☐	☐
9	• After use always replace the mouthpiece cover straight away to keep dust out. Replace the cover by firmly pushing and clicking into position		NOT REQUIRED	
Other comments:				

Inhaler Errors Checklist: Seebri Breezhaler

PIL Step	PIL Wording (Seebri Breezhaler October 2015)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
1	**Remove the cap**		NOT REQUIRED	
2	**Open inhaler** •Hold the base of the inhaler firmly and tilt the mouthpiece. This opens the inhaler		NOT REQUIRED	
3	**Prepare capsule** • Separate one of the blisters from the blister card by tearing along the perforation. Take one blister and peel away the protective backing to expose the capsule. •Do not push capsule through foil.		NOT REQUIRED	
4	**Remove a capsule** • Capsules should always be stored in the blister and only removed immediately before use. With dry hands, remove capsule from the blister. • Do not swallow the capsule.	Failed to remove capsule	☐	☐
5	**Insert capsule** • Place the capsule into the capsule chamber. • Never place a capsule directly into the mouthpiece.	Failed to insert capsule into the chamber	☐	☐
6	**Close the Inhaler** • Close the inhaler until you hear a "**click**".	Did not completely close device capsule chamber (heard click when satisfactory)	☐	☐

PIL Step	PIL Wording **(Seebri Breezhaler October 2015)**	Error **(Underlined text indicates a critical error)**	Completed Correctly	Not Completed Correctly
7	**Pierce the capsule:** • Hold the inhaler upright with the mouthpiece pointing up. • Pierce the capsule by firmly pressing together both side buttons at the same time. **Do this only once.** • You should hear a "**click**" as the capsule is being pierced.	Did not pierce the capsule and failed to release piercing buttons fully before inhalation (HCP to check that capsule was pierced and that piercing buttons were released)	☐	☐
8	**Release the side buttons fully,**	Shook the device after dose preparation	☐	☐
9	**Breathe out:** • Before placing the mouthpiece in your mouth, breathe out fully **Do not blow into the mouthpiece**	Exhaled directly into the mouthpiece	☐	☐
10	**Inhale the medicine:** • To breathe the medicine deeply into your airways: • Hold the inhaler as shown in the picture. The side buttons should be facing left and right. Do not press the side buttons. • Place the mouthpiece in your mouth and close your lips firmly around it. • Breathe in rapidly but steadily, as deeply as you can. **Do not press the side buttons.**	No seal by the lips round the mouthpiece during the inhalation	☐	☐
		Inhalation manoeuvre **was not:** -Rapid -Steady -Deep	☐	☐
11	**If you do not hear a whirring noise**: The capsule may be stuck in the capsule chamber. If this happens: • Open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. **Do not press the side buttons.**	Capsule did not rattle	☐	☐
		Blocked air inlet during inhalation manoeuvre	☐	☐

PIL Step	PIL Wording **(Seebri Breezhaler October 2015)**	Error **(Underlined text indicates a critical error)**	Completed Correctly	Not Completed Correctly
	• Inhale the medicine again by repeating steps 9 and 10.			
12	**Hold breath:** **After you have inhaled the medicine:** • Hold your breath for at least 5-10 seconds or as long as you comfortably can while taking the inhaler out of your mouth. • Then breathe out. • Open the inhaler to see if any powder is left in the capsule.	Did not hold breath	☐	☐
13	**If there is powder left in the capsule**: • Close the inhaler. • Repeat steps 9 to 12.	Did not check inside the capsule chamber if powder was left / did not make a second inhalation	☐	☐
Other comments:				

Inhaler Errors Checklist: Seretide Diskus

PIL Step	PIL Wording (Seretide DISKUS March 2015)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
1	• Hold the outer case in one hand and put thumb of your other hand on the thumbgrip. • Push your thumb away from you as far as it will go • You will hear a click. This will open a small hole in the mouthpiece	Failed to open cover	☐	☐
2	• Hold your inhaler with the mouthpiece towards you (you can hold it in either your right or left hand). • Slide the lever away from you as far as it will go (you will hear a click). This places dose in the mouthpiece.	Lever is not pushed back	☐	☐
		Shook the device after dose preparation	☐	☐
3	• Hold the inhaler away from your mouth, breathe out as far as is comfortable. • Do not breathe into the inhaler.	No exhalation before an inhalation	☐	☐
		Exhaled directly into mouthpiece	☐	☐
4	• Put the mouthpiece between your lips. • Breathe in, steadily and deeply through the inhaler, not through your nose. • Remove the inhaler from your mouth. • Hold your breath for about 10 seconds or for as long as is comfortable • Breathe out slowly.	No seal by the lips round the mouthpiece during the inhalation	☐	☐
		Inhalation manoeuvre **was not**: - steady - deep	☐	☐
		Did not hold breath	☐	☐
5	After use, rinse your mouth with water and spit it out, and/or brush your teeth.		NOT REQUIRED	
6	• To close the inhaler, slide the thumbgrip back towards you, as far as it will go. You will hear a click.	Did not close the device (Note: this is an error but one which does not affect the medication that is inhaled)	☐	☐

PIL Step	PIL Wording (Seretide DISKUS March 2015)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
Other comments:				

Inhaler Errors Checklist: Spiriva Handihaler

PIL Step	PIL Wording (Spiriva HandiHaler November 2014)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
3	• Remove capsule from blister pack (only immediately before use, see blister handling) and place it in the centre chamber, as illustrated. It does not matter which way the capsule is placed in the chamber.	Failed to remove capsule	☐	☐
		Failed to insert capsule into the chamber	☐	☐
4	• Close the mouthpiece firmly until you hear a click, leaving the dust cap open.	Did not completely close device capsule chamber (heard click when satisfactory)	☐	☐
5	• Hold the inhaler device with the mouthpiece upwards and press the piercing button completely in only once, and release This makes holes in the capsule and allows the medication to be released when you breathe in.	Did not pierce the capsule (HCP should check capsule was pierced)	☐	☐
		Shook the device after dose preparation	☐	☐
6	• Breathe out completely. • Please avoid breathing into the mouthpiece at any time	No exhalation before an inhalation	☐	☐
		Exhaled directly into mouthpiece	☐	☐
7	• Raise the inhaler to your mouth and close your lips tightly around the mouthpiece. • Keep your head in an upright position and breathe in slowly and deeply but at a rate sufficient to hear or feel the capsule vibrate. • Breathe until your lungs are full; then hold your breath as long as comfortable and at the same time take the inhaler out of your mouth. • Resume normal breathing. Repeat steps 6 and 7 once, in order to empty capsule completely.	No seal by the lips round the mouthpiece during the inhalation	☐	☐
		Inhalation manoeuvre **was not**: - slow - deep	☐	☐
		Capsule did not rattle	☐	☐
		Blocked air inlet during inhalation manoeuvre	☐	☐
		Did not hold breath	☐	☐
		Did not check inside the capsule chamber if powder was left/ did	☐	☐

PIL Step	PIL Wording (Spiriva HandiHaler November 2014)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
		not make second inhalation		

Other Comments:

Inhaler Errors Checklist: Symbicort Turbohaler

PIL Step	PIL Wording (Symbicort Turbuhaler October 2015)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
1	• Unscrew the cover and lift it off. You may hear a rattling sound	Failed to remove cap	☐	☐
2	• Hold your Inhaler upright with the red grip at the bottom.	Did not hold device upright (± 45° OK) during dose preparation	☐	☐
3	• Do not hold the mouthpiece when you load your inhaler. To load your inhaler with a dose, turn the red grip as far as it will go in one direction. Then turn it as far as it will go in the other direction (it does not matter which way you turn it first). • You should hear a click sound. Your inhaler is now loaded and ready to use. Only load your inhaler when you need to use it.	Base not twisted fully backwards and forwards, no click heard	☐	☐
		Device tipped downwards after dose preparation	☐	☐
		Shook the device after dose preparation	☐	☐
4	• Hold your inhaler away from your mouth. Breathe out gently (as far as is comfortable). • Do not breathe out through your inhaler	No exhalation before inhalation	☐	☐
		Exhaled directly into mouthpiece	☐	☐
5	• Place the mouthpiece gently between your teeth. Close your lips. • Breathe in as deeply and as hard as you can through your mouth. Do not chew or bite on the mouthpiece.	No seal by the lips round the mouthpiece during inhalation	☐	☐
		Inhalation manoeuvre **was not**: - forceful - deep *Note to HCP: it is important that the inhalation is forceful and deep from the start for this inhaler*	☐	☐
		Blocked air inlet during inhalation manoeuvre	☐	☐

PIL Step	PIL Wording (Symbicort Turbuhaler October 2015)	Error (Underlined text indicates a critical error)	Completed Correctly	Not Completed Correctly
6	• Remove the inhaler from your mouth. • Breathe out gently. The amount of medicine that is inhaled is very small. This means you may not be able to taste it after inhalation. If you have followed instructions, you can still be confident that you have inhaled the dose and the medicine is now in your lungs.	Did not hold breath	☐	☐
7	• If you are to take a second inhalation, repeat steps 2 to 6.		NOT REQUIRED	
8 + 9	• Replace cover tightly after use	Did not close the device (Note: this is an error but one which does not affect the medication that is inhaled)	☐	☐
Other comments:				

12.8. 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).

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 2	*28-Sep-2018*
Amendment 1	*15-Feb-2018*
Original Protocol	*06-Nov-2017*