Protocol Amendment 1

Study ID: 217658

Official Title of Study: A 12-week, Prospective, Open Label, Single Cohort Study to Evaluate the Real-world Effectiveness of Fluticasone Furoate/ Umeclidinium Bromide/Vilanterol in a Single Inhaler (Trelegy Ellipta) in Symptomatic Chronic Obstructive Pulmonary Disease (COPD) Patients

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CLINICAL STUDY PROTOCOL

UNIQUE IDENTIFIER	217658
TITLE	A 12-week, prospective, open label, single cohort study to evaluate the real-world effectiveness of Fluticasone Furoate/Umeclidinium Bromide/Vilanterol in a single inhaler (Trelegy Ellipta) in symptomatic chronic obstructive pulmonary disease (COPD) patients.
STUDY ACCOUNTABLE PERSON	PPD
CONTRIBUTING AUTHORS	PPD
ASSET ID	GSK2834425
GSK ASSET	Trelegy Ellipta
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PHASE OF DEVELOPMENT	Phase IV

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Approval Date: 27 Jan 2023

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 1	27 Jan 2023	TMF-15637673
Original Protocol	02 February 2022.	TMF-14425986

Amendment 1:

This amendment is considered non-substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union.

Overall Rationale for Amendment 1: The protocol is amended mainly to 1) add an additional analysis for license renewal to have the flexibility to provide data as a supporting document to agency to meet Trelegy licence renewal timeline, 2) eligibility criteria are adjusted to reflect real world clinical practice and add flexibility in recruitment, 3) inverse-probability weighted mixed model for repeated measures will be employed in the primary analysis, 4) others include correcting typo errors and inconsistencies. Protocol changes are described in the table below.

Section # and Name	**Description of Change**	**Brief Rationale**
Title	Correct the spelling error of 'Trelegy'	Correction
Study accountable person	PPD is taking the role of Study accountable person and replaces PPD PPD	personnel change
Contributing authors	PPD is taking the role of study statistician and replaces PPD	Personnel change

Section # and Name	Description of Change	Brief Rationale
Section 2: objective	Add 'to evaluate the proportion of patients achieving health status response with Trelegy.' as the third secondary objective Add an additional secondary outcome to see CAT score change at week 4	Align with study endpoints Align with study objectives
Section 3.2.1. Withdrawal from Trelegy or the Study	Add 'Any female participant who becomes pregnant while participating will be withdrawn from the study.'	For clarification
Section 3.3 study population	Update study site to 30 Replace 'Based on local market research data, the proportion of participants taking free combination of triple therapy and with LAMA/LABA at baseline will be no more than 25% of all enrolled participants to reflect the real-world status of COPD maintenance treatment pattern in China.' with 'Based on local market research data, the proportion of participants with different baseline maintenance treatments in this study may be adjusted during enrolment stage to reflect the real-world status of COPD maintenance treatment pattern in China.'	Update. Remove threshold for baseline pre-existing treatment to add flexibility in recruitment.
Section 3.4.1 inclusion criteria	replace 'who have been prescribed it continually for at least 12 weeks' with 'with no minimum treatment duration'	To accommodate to real world clinical practice and add flexibility in recruitment
Section 3.4.2: Exclusion criteria	Modify exclusion criteria 2 to 'Treated with Trelegy within 3 months prior to screening (Visit 1).' Replace 'prescribed' to 'treated' Reduce the timeframe to 3 months	To ensure the alignment with inclusion criteria 6 and avoid confusion. To reduce the timeframe to 3 months to add flexibility in recruitment.

Section # and Name	Description of Change	Brief Rationale
Section 3.4.2: Exclusion criteria	Remove original exclusion criteria 10	Not applicable based on current China COVID-19 management policy.
Section 3.6.1.3: Pulmonary function test (spirometry) for Pre-dose FEV_1, FVC, FEF_{25-75}, IC	Remove 'Participants who are unable to perform spirometry could still have an inhaler error assessment and are not excluded from the study.'	Not applicable in the study.
Section 3.6.2.4: Electrocardiogram	Remove 'and a repeated recording used for analysis'	Correction. No recording will be used for analysis in this study.
Section 3.7.2: Sample size consideration	Change Table 2 to Table 3	Correction.
Section 5.2: Reporting of pregnancy exposures	Remove 'and/ or GSK medical affairs'	Correction. No GSK medical affairs will be involved in this procedure.
Section 3.8.2.1 Primary endpoint/ estimand	Primary analysis will be conducted using an inverse-probability weighted mixed model for repeated measures (MMRM) for the change from baseline in CAT score under the missing at random assumption to handle missingness which may occur during the data collection.	The MMRM may provide additional insights to the primary endpoint.
Section 3.8.3: Additional analysis for license renewal	Add section of additional analysis for license renewal	To add flexibility to provide data for license renewal.
Section 6	Add 'whole study'	For clarification. Whole study data will be reported. (rather than after the additional analysis for license renewal)
Throughout	Minor editorial and document formatting revisions	Minor therefore have not been summarized.

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ABBREVIATIONS AND TRADEMARK INFORMATION

AE	Adverse Event
CAT	COPD Assessment Test
CDE	Center for Drug Evaluation in China
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COPD	chronic obstructive pulmonary disease
CRA	clinical research assistant
CSR	clinical study report
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
E.D.	early discontinuation / withdrawal
EHR	Electronic Health Records
FAS	Full Analysis Set
FEF_{25-75}	Forced Expiratory Flow at the 25 and 75%
FEV_1	Forced expiratory volume in 1 second
FF	fluticasone furoate
FVC	Forced Vital Capacity
GCP	Good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health related quality of life
IC	Inspiratory Capacity
ICF	informed consent form

ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
LABA	Long-Acting Beta-2-Agonists
LAMA	Long-Acting Muscarinic Antagonist
MCID	minimum clinical meaningful difference
MedDRA	Medicinal Dictionary for Regulatory Activities
mMRC	Modified Medical Research Council
NDA	New Drug Application
PK	Pharmacokinetic
PFT	Pulmonary function test
RCT	Randomized controlled trial
SAE	Serious Adverse Event
SD	standard deviation
SMPC	Summary of Product Characteristics
SoA	Schedule of Activities
SRM	Study Reference Manual
WOCBP	Woman of Childbearing Potential
UMEC	umeclidinium
VI	vilanterol

Trademark Information

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Trelegy

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NONE

1. BACKGROUND AND RATIONALE

Trelegy [fluticasone furoate (FF)/ umeclidinium (UMEC)/ vilanterol (VI) (100 µg/62.5 µg/25 µg)] in a single inhaler (TRELEGY ELLIPTA) provides a recently approved treatment option for the management of patients with advanced Chronic obstructive pulmonary disease (COPD) the aim of reducing exacerbation frequency and burden of polypharmacy, improving lung function, health related quality of life (HRQoL) and symptom control, while providing a more convenient treatment option for patients compared with established dual/monotherapies.

Trelegy 100/62.5/25 µg was approved in China on 04 November 2019 for a maintenance treatment in adult patients with COPD. Data from two phase III studies and one Pharmacokinetic (PK) study supported the New Drug Application (NDA) approval in China. In the two phase III studies [Lipson, 2018; Lipson, 2017], Trelegy showed significantly better improvement in the primary and secondary endpoints, including Forced expiratory volume in 1 second (FEV_1), exacerbation reduction and symptoms compared with Inhaled Corticosteroids (ICS)/ Long-Acting Beta-2-Agonists (LABA) or Long-Acting Muscarinic Antagonist (LAMA)/LABA in the overall population.

CCI

[redacted]

COPD refers to a progressive deterioration of lung function and a series of mental and physical comorbidities. It is one of the leading causes of morbidity and mortality worldwide, inducing substantial economic, social, and health-care burden [GOLD, 2021]. COPD is the fifth leading cause of death in China with a reported prevalence of 13.7% in people aged 40 years or older [GBD, 2017]. It is essential to provide appropriate treatments for COPD patients according to guidelines.

GOLD guideline recommends one of the goals of treatment of stable COPD is the reduction of symptoms which includes three components, i.e., to reduce symptoms, improve exercise tolerance and improve health status [GOLD, 2021]. Triple therapy (ICS/LABA/LAMA) is recommended as step-up therapy in patients with COPD whose symptoms or exacerbations are not controlled by ICS/LABA or LAMA/LABA, or with high level of blood eosinophils or comorbid with asthma [GOLD, 2021].

As high symptom burden is one of the key unmet medical needs for COPD patients even among those under the treatment of maintenance therapies, the main goal of this single-armed study is to collect the real-life effectiveness data focusing on symptoms of COPD in patients treated with Trelegy for 12 weeks, by comparison to baseline data which can reflect the benefits of patients who remain symptomatic with their prior maintenance treatment and switch to Trelegy under the discretion of their physicians. Based on previous results [Marth, 2021; Bansal, 2021], a decrease over 2 unit [minimum clinical meaningful difference (MCID)] of COPD Assessment Test (CAT) score and MCID change (over 100 ml) of forced expiratory volume in one second (FEV1) were observed

for triple therapy after 12-week treatment. Therefore, a 12-week duration is considered to be enough to observe a clinical meaningful change from baseline of the study outcomes, i.e., CAT and FEV_1.

The CAT score is defined as primary outcome because it is recommended by guideline [GOLD, 2021] as the tool for assessment of disease severity and usually leveraged by physicians in daily practice to evaluate the patient's response to treatment. A decrease of 2 unit compared to baseline is considered as the MCID [Kon, 2014]. Other outcomes including lung function and dyspnea can provide data from different dimensions on effectiveness which are also clinically relevant to the evaluation of the response of patients to treatment.

2. OBJECTIVES

Primary Objective	**Primary Outcome**
The primary objective of this study is to evaluate the effectiveness of Trelegy on health status in patients with symptomatic COPD at week 12.	• Change from baseline of CAT score at week 12
Secondary Objectives	**Secondary Outcomes**
to evaluate the effectiveness of Trelegy on dyspnea in patients with symptomatic COPD at week 12. to evaluate the effectiveness of Trelegy on lung function in patients with symptomatic COPD at week 12. to evaluate the proportion of patients achieving health status response with Trelegy. to evaluate the effectiveness of Trelegy on health status in patients with symptomatic COPD at week 4.	• Change from baseline of Modified Medical Research Council (mMRC) at week 12 • Change from baseline of pre-dose FEV_1 at week 12 • Proportion of CAT responder (defined as ≥ 2 unit decrease from baseline) at week 12 • Change from baseline of CAT score at week 4
Exploratory Objectives	**Exploratory Outcomes**
to evaluate the effectiveness of Trelegy on lung function in patients with symptomatic COPD	• Change from baseline of Forced Vital Capacity (FVC), Forced Expiratory Flow at the 25 and 75% (FEF_{25-75}) , Inspiratory Capacity (IC) at week 12
Safety Objective	**Safety Outcomes**
The safety objective is to collect the safety information of participants using Trelegy.	• Trelegy related AEs • SAEs • AEs that lead to the discontinuation of Trelegy

3. RESEARCH METHODOLOGY

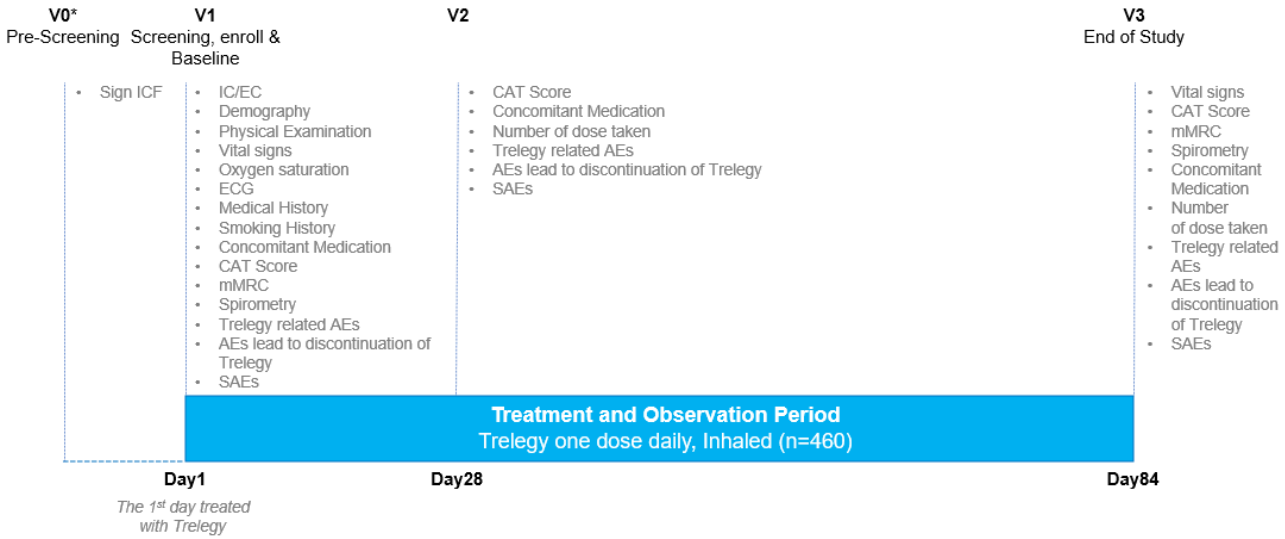
3.1. Study Design

This is a 12-week, prospective, open label, single cohort study. The enrolled participants will be those who are symptomatic under COPD maintenance treatments, and newly prescribed with Trelegy under the discretion by clinical physicians.

The study applies a single cohort design to evaluate the effectiveness following 12-week treatment with Trelegy by comparison to baseline data, which can reflect the benefits (i.e., CAT score and FEV_1, etc.) of patients who remain symptomatic with their prior maintenance treatment. The decision to prescribe Trelegy shall be independent to the study with medical records providing documentation of a Trelegy prescription.

The prospective data collection starts from Visit 1 when Trelegy is taken by patients for the first dose (see Figure 1 below). The participants will complete the CAT score at Visit 1, Visit 2 and Visit 3 or early discontinuation/withdrawal visit (E.D.), and the mMRC at Visit 1 and Visit 3 or E.D. The participants' pulmonary function test will be assessed at Visit 1 and Visit 3 or E.D.. The investigators will record Trelegy-related adverse events (AEs), serious adverse events (SAEs) and AEs that lead to withdrawal from Trelegy.

Figure 1 The Schematic diagram for this study



* : V0 and V1 could occur on the same day, and V1 should be completed ≤7 days after V0.

3.2. Data Source / Data Collection

The investigators will enroll participants by assessing the inclusion/exclusion criteria. The patients will be enrolled at visit 1 and will be followed up prospectively for 12 weeks.

During this trial the following information and measurements will be collected, and the details are listed in Table 1:

To be completed at Visit 1:

- Patient demographics (including sex, age, height, weight)
- Patient past medical history and co-morbid diseases
- Patient smoking history [never a smoker, former smoker (previously smoked ≥10 pack year and has not smoked for at least 6 months prior to Visit 1), current smoker (10 pack year and smoked within 6 months prior to Visit 1); the number of pack years for former smoker and current smoker should be calculated (round up to the nearest integer)]
- Patient concomitant medication
- Pregnancy status
- Oxygen saturation
- Patient vital signs and Electrocardiogram (ECG)
- CAT score
- mMRC
- Pulmonary function test (spirometry): pre-dose FEV1, FVC, $FEF_{25–75}$ and IC
- Trelegy related AEs
- AEs that lead to the discontinuation of Trelegy
- SAEs

To be completed at Visit 2:

- Patient concomitant medication
- Pregnancy status
- Number of doses of Trelegy taken
- CAT score
- Trelegy related AEs
- AEs that lead to the discontinuation of Trelegy
- SAEs

To be completed at Visit 3 or E.D.:

- Patient concomitant medication
- Pregnancy status
- Number of doses of Trelegy taken
- Patient vital signs
- CAT score
- mMRC
- Pulmonary function test (spirometry): Pre-dosed FEV_1, FVC, $FEF_{25–75}$ and IC
- Trelegy related AEs
- AEs that lead to the discontinuation of Trelegy
- SAEs

Table 1 Visit flow chart and data collection schedule

Procedure	**Consenting**	**Treatment and Observation Period (Days)**				**Notes** **E.D. = early discontinuation / withdrawal (within 7 days of study discontinuation)**
Study visit	**V0[1]** **Pre-Screening**	**V1** **Screen, enroll & baseline** **(Day 1)**	**V2** **(Day 28)**	**V3** **End of Study** **(Day 84)**	**E.D.**	
Time Window Allowed (days)			**±7**	**±10**		
Informed consent[2]	X					
Inclusion / exclusion criteria		X				
Demography		X				
Full physical examination including height and weight		X				
Smoking History		X				

Procedure	Consenting	Treatment and Observation Period (Days)				Notes E.D. = early discontinuation / withdrawal (within 7 days of study discontinuation)
Medical history: past and current medical conditions		X				
Vital signs		X		X	X	
Oxygen saturation		X				
ECG		X				
Trelegy Taken worksheet			X	X	X	Number of doses of Trelegy taken should be documented weekly by the patients, and the investigators will review and record in EDC
CAT score[2]		X	X	X	X	
mMRC[3]		X		X	X	
Spirometry[4]		X		X	X	

Procedure	Consenting	Treatment and Observation Period (Days)				Notes E.D. = early discontinuation / withdrawal (within 7 days of study discontinuation)
Review of Study treatment related AEs		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 discontinuation from study treatment are not recorded, unless classified as SAE.
Review of AEs that lead to the discontinuation of Trelegy		X	X	X	X	All AEs that lead to discontinuation from study treatment, whether judged related to study treatment or not, should be recorded. 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	Consenting	Treatment and Observation Period (Days)				Notes E.D. = early discontinuation / withdrawal (within 7 days of study discontinuation)
SAEs review		X	X	X	X	All SAEs are recorded from the start of using Trelegy. 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.
Pregnancy status		X	X	X	X	
Concomitant medication review		X	X	X	X	

1. V0 and V1 could occur on the same day, and V1 should be completed ≤7 days after V0.
2. If a participant is unable to attend to the clinic for Visit 2 under certain situation (e.g. COVID-19 impact or lockdown), it's acceptable to carry out the CAT assessment by telephone or other remote approaches.
3. mMRC: assessed by both patients and physicians will be collected, refers to 3.6.1.2.
4. Pre-dose FEV_1 , FVC, FEF_{25-75} and IC will be entered into eCRF.

3.2.1. Withdrawal from Trelegy or the Study

Participants that permanently stop Trelegy are not required to withdraw from the study. If for any reason a participant must permanently stop Trelegy, every effort should be made by the Investigator/delegate to keep the participant in the study to collect all the effectiveness and safety data of the subsequent visits per the Schedule of Activities (SoA) after the Trelegy discontinuation.

Any female participant who becomes pregnant while participating will be withdrawn from the study.

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or administrative reasons. If a participant withdraw from the study, he/she has to complete the E.D. visit per SoA (Table 1), and no more extra data will be collected after E.D. visit.

3.2.2. Lost to Follow Up

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

If a participant fails to return to the clinic for Visit 2 or Visit 3, the site should attempt to contact 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) and reschedule the missed visit as soon as possible. If a participant is completely unreachable, they are considered to have withdrawn from the study with a primary reason of lost to follow-up.

3.3. Study Population

This study plans to enrol 460 patients with symptomatic COPD (details in sample size estimation in Section 3.7). In this study, patients will be recruited from approximately 30 centres in China. The study sites will be selected from different regions and tiers of hospitals around China to ensure the patients could be representative. Based on local market research data, the proportion of participants with different baseline maintenance treatments in this study may be adjusted during enrolment stage to reflect the real-world status of COPD maintenance treatment pattern in China.

3.4. Eligibility Criteria

3.4.1. Inclusion Criteria

AGE
1. Participant must be 40 years or above of age inclusive, at the time of signing the informed consent.
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Participants with a documented physician diagnosis of COPD;

3. CAT ≥ 10;

4. Existing COPD Maintenance Treatment. Patients currently receiving one of the maintenance therapies listed below with no minimum treatment duration prior to screening (Visit 1):

- ICS/LABA (single or multiple inhalers)
- LAMA/LABA (single or multiple inhalers)
- Free combination of ICS, LAMA, LABA

5. Current or former cigarette smokers with a history of cigarette smoking history≥10 pack-years at screening.

6. Trelegy is prescribed under the discretion of clinical physicians with medical records providing documentation of a Trelegy prescription in daily practice.

INFORMED CONSENT
7. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

3.4.2. Exclusion Criteria

Women of childbearing potential
1. Women who are pregnant or lactating or are planning on becoming pregnant during the study.

PRIOR/CONCOMITANT THERAPY
2. Treated with Trelegy within 3 months prior to screening (Visit 1). 3. 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.

MEDICAL CONDITIONS
4. Patients with any life-threatening condition i.e. low probability, in the opinion of the investigator, of 3-month survival due to severity of COPD or comorbid condition.

MEDICAL CONDITIONS
5. Patients with unstable COPD. Patients with resolution of an exacerbation less than 2 weeks prior to Visit 1. Patients may be rescreened 2 weeks after resolution of exacerbation (exacerbation is defined as: requiring treatment with antibiotics and/or systemic steroids or hospitalisation; resolution is defined as: 2 weeks after all symptoms have resolved and any medicines to treat the exacerbation have finished). 6. Patients who need more than 3 L/min supplemental oxygen at rest at screening. 7. 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 efficacy or safety analysis if the disease/condition exacerbated during the study.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE
8. Participation received any investigational drug in other clinical trial within four weeks or 5 half-lives prior to this study whichever is longer.

OTHER EXCLUSIONS
9. Any conditions or illnesses listed in the section of contraindications in the Summary of Product Characteristics (SmPC) of Trelegy, i.e., hypersensitivity to the active substances of Trelegy Ellipta; 10. Inability to read: In the opinion of the Investigator, any participant who is unable to read and/or would not be able to complete study related materials.

3.5. Treatment

3.5.1. Treatment Administered

All patients will receive Trelegy (FF/UMEC/VI ELLIPTA 100/62.5/25 µg) according to the local SmPC. Participants are expected to inhale one dose in the morning from the Trelegy Ellipta at approximately the same time each day for 12 weeks after enrolment.

3.5.2. 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

3.6. Study Assessments and Procedures

3.6.1. Effectiveness Assessments

3.6.1.1. The COPD Assessment Test (CAT)

The COPD Assessment Test (CAT) is a validated 8-item questionnaire developed for use in routine clinical practice to measure the health status of patients with COPD [Jones, 2009; Jones, 2012]. Participants rate their experience on a 6-point scale (Protocol 8.1 Appendix 1-1), ranging from 0 (no impairment) to 5 (maximum impairment) with a scoring range of 0-40. Higher scores indicated greater disease impact.

The questionnaire is completed on paper prior to the study treatment and before any procedures or assessments are performed (to avoid influencing the participant's response). To avoid biasing responses, the participant is not to be told the results of any diagnostic tests prior to completing the CAT questionnaire. Questionnaires are to be administered at Visit 1, Visit 2 and Visit 3/E.D.

A change of 2 unit compared to baseline is considered as the MCID [Jones, 2012].

3.6.1.2. Modified Medical Research Council (mMRC)

The mMRC was developed in 1960 [Behrman S, 1960], and it's considered adequate for assessment of symptoms, as it relates well to other measures of health status and predicts future mortality risk [GOLD, 2021].

The mMRC (Patient Version and Physician Version) will be used to assess the breathlessness state of the patient before and after the treatment (Protocol 8.2 Appendix 1-2). With it, patients are scored on a scale of 0-4 depending on their disability due to shortness of breath from 0 (no impact) to 4 (worst possible impact).

The mMRC (Patient Version) will be completed by each patient firstly, without supervision, after CAT. The investigator should check whether the patient has completed the mMRC adequately but cannot assist in completing it. Then, the investigators will finish the mMRC (Physician Version) through their observation.

3.6.1.3. Pulmonary function test (spirometry) for Pre-dose FEV_1, FVC, FEF_{25-75}, IC

Pre-dose FEV_1, FVC, FEF_{25-75} and IC are all measured through a pulmonary function test (spirometry). Pre-dose FEV1 and FVC are basic items of COPD's pulmonary function test (PFT). FEV % of predicted value is a good indicator to assess moderate to severe airflow limitation [GOLD, 2021]. It's used clinically as a predictor of exacerbation or mortality in patients with COPD [CMA, 2018]. FEF_{25-75} is one of the standard results provided in spirometry reports too, low FEF_{25-75} is well known indicator of small airway obstruction [GOLD, 2021]. IC is measured as you exhale casually followed by a maximal inhalation. The calculation for IC is tidal volume plus inspiratory reserve volume. The decrease of IC is associated with an increase at the end of expiration, it can be used as a simple assessment of lung volume changes in COPD [GOLD, 2021].

Spirometry for assessment of pulmonary function is to be performed as described in Table 1 in all participants at Visit 1and Visit 3/E.D.

All sites will use their own spirometry equipments for pulmonary function test. For Pre-dose FEV_1, FVC, FEF_{25-75} and IC determination, at least 3 acceptable spirometry efforts (no more than 8) need to be obtained. To facilitate pre-dose spirometry, participants are 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.

Each spirometry should be performed prior to the day's dose of usual care/ study treatment. The largest Pre-dose FEV_1 , FVC, FEF_{25-75} and IC from the 3 acceptable efforts are recorded, even if not from the same effort. If it is not possible to withhold usual care/study treatment and/or short-acting beta-agonists or anti-cholinergic for ≥4 hours, spirometry is still measured and recorded along with the most recent use of COPD maintenance treatment/ study treatment.

3.6.2 Safety Assessments

The following safety events will be collected during the study:

- All Trelegy related AEs

- All SAEs

- AEs that lead to the discontinuation of Trelegy

COPD exacerbation is a disease-related event. Because exacerbations are typically associated with the disease under study, an exacerbation will not to be reported as an SAE unless, in the investigator's opinion, the event is of greater intensity, frequency, or duration than expected for the individual participant, or the investigator considered that there is a reasonable possibility that event is related to study treatment.

The investigator or site staff are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. The following information on AEs will be obtained:

- Patient's coded data
- Treatment's data
- Reporter's data
- Duration (start and stop dates).
- Severity (mild, moderate, severe).
- Causality (reasonable possibility yes/no).
- Actions taken and outcome.

The detailed definitions and procedures for recording, evaluating, follow-up, and reporting of the AEs, study treatment related AEs and SAEs are listed in APPENDIX 3.

3.6.2.1 Physical examination

A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

3.6.2.2 Vital signs

Vital signs (Body Temperature, Pulse Rate, Blood Pressure) will be performed at the time points specified in Visit 1 and Visit 3/E.D. prior to conducting spirometry and prior to taking the morning dose of study treatment. Blood pressure (systolic and diastolic) and pulse rate will be measured in the sitting position after approximately 5 minutes rest. A single set of values will be collected and recorded in the source documentation and eCRF.

3.6.2.3 Oxygen saturation

The oxygen saturation of participants is evaluated by pulse oximetry, to ensure whether they need supplemental oxygen or not. Patients who need more than 3 L/min supplemental oxygen at rest at screening are excluded.

3.6.2.4 Electrocardiogram

12-lead resting ECG will be conducted at Visit 1. All ECG measurements will be made with the participant in a supine position having rested in this position for approximately 5 minutes before each reading. The investigator or a designee will evaluate whether the ECG is normal or abnormal. ECGs may be repeated for quality reasons . Dated and signed printouts of ECG with findings should be documented in patient's medical record.

3.7 Sample Size Calculations

3.7.1 Statistical assumptions

INTREPID study [study 206854 China CSR GSK Document Number 2019N418769_00] showed that in the real world setting 19% participants had early withdrawn from the Trelegy treatment prior to week 24. Considering the difference in the China clinical practice and study designs, it is assumed that 79% enrolled participants would complete 12 weeks of Trelegy treatment with no intercurrent events, 20% would have the intercurrent event of receiving a new COPD maintenance therapy, 1% would have the intercurrent event of treatment discontinuation.

Based on results from a few studies, i.e., IMPACT [Lipson, 2018; study CTT116855 China CSR GSK Document Number 2018N356723_00], INTREPID [study 206854 China CSR GSK Document Number 2019N418769_00] and one randomized controlled trial (RCT) [Bansal, 2021], it is assumed that a decrease of 2 in the primary endpoint at week 12 will be observed in this study with a common standard deviation of 7 (Table 2).

Table 2 Assumptions for the primary endpoint

Proportion of each type of participants		Primary endpoint	
		Mean	Standard deviation
Participants with no intercurrent events	79%	-2	7
Participants receiving other COPD maintenance therapy	20%	-2	7
Participants with treatment discontinuation	1%	0	7
Total	100%	-1.98	7.003

3.7.2 Sample size consideration

A sample size of 460 is planned. With the aforementioned assumptions in Table 1, the sample size would be able to provide a half-width ranging from 0.64 to 0.73 for the 95% confidence interval (CI) of the inverse probability weighted mean of the change from baseline in CAT score at week 12 in the primary analysis under different missingness scenarios (Table 3).

3.7.3 Sensitivity assessments

The half-width of confidence interval are assessed when the sample size varies under different missingness scenarios (Table 3). Scenario 1 is the ideal situation where no missingness occurs, which results a half-width of 0.64 for the 95% confidence interval for the inverse probability weighted mean of the primary endpoint with the sample size of 460. Scenario 2 represents a situation with the moderate missingness, which results a

half-width of 0.69 for the 95% confidence interval of the primary endpoint with the sample size of 460. Scenario 3 represents the worst missingness situation, which results a half-width of 0.73 for the 95% confidence interval of the primary endpoint with the sample size of 460.

Table 3 Sample size versus the half-width of the 95% CI for the primary endpoint

Sample size	Data availability status	Proportion of missing data at week 12			Expected inverse probability weighted mean	Half width of 95% CI
		Participants with no intercurrent events	Participants receiving other COPD maintenance therapy	Participants with treatment discontinuation		
280	Scenario 1	No missing	No missing	No missing	-1.98	0.82
	Scenario 2	5% missing	30% missing	50% missing	-1.98	0.87
	Scenario 3	10% missing	50% missing	70% missing	-1.98	0.94
340	Scenario 1	No missing	No missing	No missing	-1.98	0.74
	Scenario 2	5% missing	30% missing	50% missing	-1.98	0.79
	Scenario 3	10% missing	50% missing	70% missing	-1.98	0.85
400	Scenario 1	No missing	No missing	No missing	-1.98	0.69
	Scenario 2	5% missing	30% missing	50% missing	-1.98	0.73
	Scenario 3	10% missing	50% missing	70% missing	-1.98	0.78
460	**Scenario 1**	**No missing**	**No missing**	**No missing**	**-1.98**	**0.64**
	Scenario 2	**5% missing**	**30% missing**	**50% missing**	**-1.98**	**0.69**
	Scenario 3	**10% missing**	**50% missing**	**70% missing**	**-1.98**	**0.73**

With the planned sample size of 460, the half-width of the 95% confidence interval for the inverse probability weighted mean for the primary endpoint is also assessed when the standard deviation varies (Table 4).

Table 4 The half-width of the 95% CI versus standard deviations when N=460

Standard deviation	Data availability status	Proportion of missing data at week 12			Expected inverse probability weighted mean	Half width of 95% CI
		Participants with no intercurrent events	Participants receiving other COPD maintenance therapy	Participants with treatment discontinuation		
6.5	Scenario 1	No missing	No missing	No missing	-1.98	0.60
	Scenario 2	5% missing	30% missing	50% missing	-1.98	0.64
	Scenario 3	10% missing	50% missing	70% missing	-1.98	0.68
7	**Scenario 1**	**No missing**	**No missing**	**No missing**	**-1.98**	**0.64**
	Scenario 2	**5% missing**	**30% missing**	**50% missing**	**-1.98**	**0.69**
	Scenario 3	**10% missing**	**50% missing**	**70% missing**	**-1.98**	**0.73**
7.5	Scenario 1	No missing	No missing	No missing	-1.98	0.69
	Scenario 2	5% missing	30% missing	50% missing	-1.98	0.73
	Scenario 3	10% missing	50% missing	70% missing	-1.98	0.79

3.8 Data Analysis Considerations

3.8.1 Population for Analysis

Full Analysis Set (FAS) The Full Analysis Set will consist all participants who enrol in the study and take at least one dose of Trelegy. Unless otherwise specified the data will be analysed based on the Full Analysis Set.

3.8.2 Statistical Analysis

3.8.2.1 Primary endpoint/estimand

Primary estimand

The primary clinical question of interest is: what is the change from baseline in CAT score at week 12, regardless of receiving a new COPD maintenance therapy or treatment discontinuation.

The estimand is described by the following attributes:

- Population: Symptomatic Chinese COPD participants who are receiving COPD maintenance treatment
- Treatment condition: Trelegy (FF/UMEC/VI ELLIPTA 100/62.5/25 μg) one dose daily, inhaled
- Variable: change from baseline of CAT score at week 12.
- Intercurrent events:

- Receiving other COPD maintenance therapy is addressed by the treatment policy strategy.
- Treatment discontinuation due to any reason is addressed by the treatment policy strategy.
- Summary measure: average change from baseline in CAT score at week 12.

Rationale: Interest lies in the treatment effect at week 12 in the real-world setting, maybe confounded by other COPD maintenance therapies or the event of treatment discontinuation due to any reason. Therefore, treatment policy strategy is employed to handle the intercurrent events of receiving a new COPD maintenance therapy and treatment discontinuation due to any reason as it reflects the clinical practice.

Primary analysis

Primary analysis will be conducted using an inverse-probability weighted mixed model for repeated measures (MMRM) for the change from baseline in CAT score under the missing at random assumption to handle missingness which may occur during the data collection.

The missingness of the change from baseline in CAT score at week 12 will be modelled using a logistic regression model［Seaman SR and White IR, 2011], with the covariates of age, gender, years of COPD, smoker history, pre-dose FEV1 at baseline, COPD maintenance treatment at baseline, CAT score at baseline, the change from baseline in CAT score at week 4, intercurrent event status, duration of treatment exposure. The missingness of the change from baseline in CAT score at week 4 will be modelled analogously with the covariates collected before week 4.

The change from baseline in CAT score will be analysed using the MMRM model (in which each observation is weighted with the inverse probabilities derived from the above logistic regression models) with the covariates of smoking history, CAT score at baseline, visit, the interaction of CAT score at baseline*visit [Protocol No. CTT116855].

Sensitivity analysis will be conducted using the arithmetic mean. Missing data will be imputed using multiple imputation under missing at random assumption, for participants with no intercurrent events, receiving other COPD maintenance therapy, with treatment discontinuation, separately if data permits, otherwise may be imputed for the pooled groups.

Subgroup analyses of the primary endpoint will be further investigated across the CAT score at baseline: moderate impact [CAT 10-20], severe impact [CAT 21-30], very severe impact [31-40].

3.8.2.2 Secondary and exploratory endpoints/estimands

Similar estimands as the primary estimand will be employed for secondary endpoints and exploratory endpoints, except the variable is changed to the corresponding endpoint.

For the proportion of CAT responder at week 12, additional exceptions are:

- Summary measure is the proportion of participants having ≥ 2 unit decrease from baseline at week 12. The response status of a participant at a visit is set to missing if his/her CAT score at baseline or at the visit is missing.

The statistical analyses will be analogous to the primary endpoint.

Safety Analysis

AE terms will be coded using Medicinal Dictionary for Regulatory Activities (MedDRA) dictionary. The number and percentage of participants experiencing at least one Trelegy-related AE, SAEs, AE leading to discontinuation of Trelegy will be provided.

3.8.3 Additional Analysis for License Renewal

The study is designed to support the license renewal of Trelegy 100/62.5/25 μg in adult patients with COPD. If the study report is unlikely to be completed before the license renewal submission period due to the evolving COVID-19 situation and the competing enrolment environment, an additional analysis may be performed with the early available study data (i.e. the data in participants who are enrolled by 29 May 2023 and at the time when they all have completed the study or withdrawn from study). This analysis is exclusively for the license renewal purpose and will not have any impact on the study design and other study criteria. The whole study data will be analyzed when all the participants have completed the study or withdrawn from study.

4 LIMITATIONS

One main limitation arises from the single cohort design of this study with no control group and no blinding or randomisation, which may lead to difficulties to interpret the study results.

Another limitation could lie in the lack of representativeness of the enrolled patients to the overall COPD population treated with Trelegy in China. The study sites will be selected from different regions and tiers of hospitals around China to minimize this limitation although this could be influenced by a few factors, e.g., hospital listing status of Trelegy, willingness of participation in the study by sites and qualification of sites, etc.

5 STUDY CONDUCT, MANAGEMENT & ETHICS

This study will be conducted in accordance with GCP and all applicable legal requirements including subject privacy requirements. The investigator shall obtain proper consent from the study subjects which enables GSK's access and processing of the study data containing their personal information possibly for purpose of this study and shall ensure the protocol, the site's informed consent form, and any other information that will be presented to the study subjects are reviewed and approved by the appropriate Independent Ethics Committee (IEC). GSK will provide the investigator with needed documents for IEC. The detailed study governance considerations refer to Appendix 2.

All clinical safety data will be collected as outlined in the electronic Case Report Form (eCRF). Under ICH GCP and all applicable local regulations and legal requirements, the

Sponsor, is responsible for, and undertakes to, assess all clinical safety information arising during the Study (including, but not limited to, that listed in the APPENDIX 3 in order to generate all safety reports as required).

5.1 AEs, Study treatment related AEs and SAEs

All AEs and SAEs will be collected from the start of using Trelegy. For AEs/SAEs identified before study treatment discontinuation, it will be followed up. The subject should be followed until the event is resolved, stabilized with appropriate diagnostic evaluation or reasonably explained, or until the subject is lost to follow-up. Planned time points for safety assessments are provided in the Table 1.

5.2 Reporting of pregnancy exposures

To ensure subject safety, each pregnancy must be reported to the sponsor within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child, which must also be reported to the sponsor. Pregnancy complications and elective terminations for medical reasons must be reported.

Investigators will be provided with necessary “pregnancy exposure” and “pregnancy follow up” forms and supported by clinical research assistant (CRA) in complying with pregnancy reporting procedures. The Collection of Pregnancy Information is listed in Section 11 APPENDIX 4.

5.3 Medical Device

The definition of a Medical Device Deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.

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

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
- investigation, replacement or modification of the anatomy or of a physiological process;
- control of conception and which does not achieve its principle action in or on the human body by pharmacological, immunological or metabolic means, but may be assisted in its function by such means.

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.

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 (Dry Powder Inhaler, DPI) 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 5.1.

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

- report the malfunction.
- customer/consumer can call GSK hotline 400 991 1165 or mail to China Hub (cn.customer-relations@consumerrelations-mail.gsk.com) to report complaint, and China hub will log the complaint in system and assign to relevant department.
- Non-GSK medical device incidents should be reported to the appropriate manufacturer as per usual local practice.

6 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Any publication of the results from this study must be consistent with GSK’s publication policy and guided by Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE).

A publication would be generated once the whole study results are ready, and it will be submitted to the academic conferences and published in peer-reviewed journals.

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8 APPENDIX 1: QUESTIONNAIRES AND MEASURE

8.1 Appendix 1-1 CAT Assessment

Your name:_____

Today's date:_____

How is your COPD? Take the COPD Assessment Test™ (CAT)
This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy [0] [X] [2] [3] [4] [5] I am very sad

			SCORE
I never cough	[0] [1] [2] [3] [4] [5]	I cough all the time	☐
I have no phlegm (mucus) in my chest at all	[0] [1] [2] [3] [4] [5]	My chest is completely full of phlegm (mucus)	☐
My chest does not feel tight at all	[0] [1] [2] [3] [4] [5]	My chest feels very tight	☐
When I walk up a hill or one flight of stairs I am not breathless	[0] [1] [2] [3] [4] [5]	When I walk up a hill or one flight of stairs I am very breathless	☐
I am not limited doing any activities at home	[0] [1] [2] [3] [4] [5]	I am very limited doing activities at home	☐
I am confident leaving my home despite my lung condition	[0] [1] [2] [3] [4] [5]	I am not at all confident leaving my home because of my lung condition	☐
I sleep soundly	[0] [1] [2] [3] [4] [5]	I don't sleep soundly because of my lung condition	☐
I have lots of energy	[0] [1] [2] [3] [4] [5]	I have no energy at all	☐

TOTAL SCORE ☐☐

8.2 Appendix 1-2 The mMRC

The Modified Medical Research Council Grading System (mMRC)- Patient

Check the box that best describes how breathless you are:

- ☐ 0 "I only get breathless with strenuous exercise"
- ☐ 1 "I get short of breath when hurrying on the level or walking up a slight hill"
- ☐ 2 "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"
- ☐ 3 "I stop for breath after walking about 100 yards or after a few minutes on the level"
- ☐ 4 "I am too breathless to leave the house" or "I am breathless when dressing"

MODIFIED MEDICAL RESEARCH COUNCIL (mMRC) DYSPNEA SCALE – PHYSICIAN COMPLETED (OBSERVER)

Select the one best response to describe the patient's shortness of breath	
[0] ☐	Not troubled by breathlessness except with strenuous exercise
[1] ☐	Troubled by shortness of breath when hurrying on level ground or walking up a slight hill
[2] ☐	Walks slower than people of the same age on level ground because of breathlessness or has to stop for breath when walking at own pace on level ground
[3] ☐	Stops for breath after walking about 100 yards or after a few minutes on level ground
[4] ☐	Too breathless to leave the house or breathless when dressing or undressing

9 APPENDIX 2: STUDY GOVERNANCE CONSIDERATIONS

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, 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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

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., Electronic Health Records (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 Study Reference Manual (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

10 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.1 Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., 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). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/selfharming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. "Lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

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.

10.2 Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission of any infectious agent via an authorised medicinal product
g. Other situations: • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3 Definition of Study treatment related AEs

It may also be referred to as Adverse Drug Reaction (ADR).

Study treatment related AE Definition
A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

10.4 Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information. • It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
• The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.5 Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the [X/medical monitor/SAE coordinator] by telephone.
- Mail to Qwy11935@gsk.com to report SAE.

SAE Reporting to GSK via Paper Data Collection Tool

- • Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the [X/medical monitor or the SAE coordinator].
- • 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 data collection tool within the designated reporting time frames.
- • Mail to Qwy11935@gsk.com to report SAE

11 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 Section 5.2. 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.

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