

TITLE PAGE

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Title:	Post-authorisation Safety (PAS) Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD Patients Using Inhaled UMEC/VI Combination or Inhaled UMEC versus Tiotropium (Study 201038).
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Author(s):



PASS information

Title	Post-authorisation Safety (PAS) Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD Patients Using Inhaled UMEC/VI Combination or Inhaled UMEC versus Tiotropium (Study 201038).
Protocol version identifier	Version 1
Date of last version of protocol	Draft 3 dated 23 FEB 2015
EU PAS register number	To be registered after Pharmacovigilance Risk Assessment Committee (PRAC) protocol approval
Active substances	Umeclidinium bromide (UMEC), vilanterol trifenate (VI), tiotropium
Medicinal products	UMEC (INCRUSE TM), UMEC/VI (ANORO TM , Laventair TM)
Product reference	Tiotropium
Procedure number	INCRUSE : EMEA/H/C/002809/0000 ANORO /Laventair : EMEA/H/C/002751/0000, EMEA/H/C/003754/0000
Marketing authorisation holder(s)	Glaxo Group Limited
Joint PASS	Yes

<p>Research question and objectives</p>	<p>The study will address the research question of whether the incidence rates of cardiovascular (CV) and cerebrovascular events differ for new users of umeclidinium bromide/vilanterol trifenate (UMEC/VI) combination or umeclidinium bromide (UMEC) compared with tiotropium in patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD).</p> <p>The primary objectives are:</p> <ol style="list-style-type: none"> 1. To demonstrate non-inferiority of UMEC/VI combination and UMEC to tiotropium for risk of myocardial infarction (MI), stroke and heart failure individually based on an analysis of time to first event. 2. To quantify the incidence rate and frequency of each of MI, stroke, and heart failure for new users of UMEC/VI combination, UMEC, and tiotropium. <p>The secondary objectives are:</p> <ol style="list-style-type: none"> 1. To compare UMEC/VI combination and UMEC to tiotropium for risk of the composite endpoint of MI, stroke, heart failure or sudden cardiac death based on an analysis of time to first event. 2. To quantify the incidence rate and frequency of the composite endpoint of MI, stroke, heart failure or sudden cardiac death for new users of UMEC/VI combination, UMEC, and tiotropium. 3. To quantify the incidence rate and frequency of serious pneumonia/ serious LRTI (composite endpoint) for new users of UMEC/VI combination, UMEC, and tiotropium. 4. To quantify the overall mortality rate, cardiovascular and non cardiovascular mortality rates for new users of UMEC/VI combination, UMEC, and tiotropium <p>Other objectives are:</p> <p>I. Safety</p> <ol style="list-style-type: none"> 1. To quantify the incidence rate and frequency of haemorrhagic stroke, ischaemic stroke and undefined stroke for new users of UMEC/VI combination, UMEC, and tiotropium.
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	<ol style="list-style-type: none">2. To quantify the incidence rate and frequency of hospitalisation for heart failure for new users of UMEC/VI combination, UMEC, and tiotropium3. To quantify the incidence rate and frequency of reported serious adverse events (SAEs) and drug-related adverse events (AEs) for new users of UMEC/VI combination, UMEC, and tiotropium.4. To quantify the incidence rate and frequency of serious CV events of special interest (CV AESIs), including transient ischaemic attacks and angina pectoris, cardiac arrhythmias (including Torsades de Pointe), acquired long QT, heart failure, cardiac ischaemia, and hypertension for new users of UMEC/VI combination, UMEC, and tiotropium. <p>II. Effectiveness</p> <ol style="list-style-type: none">1. To quantify persistence with study medication for new users of UMEC/VI combination, UMEC, and tiotropium.2. To quantify the incidence rate and frequency of moderate/severe COPD exacerbation (requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalisation) for new users of UMEC/VI combination, UMEC, and tiotropium.3. To quantify all-cause and COPD-related health-care utilisation for new users of UMEC/VI combination, UMEC, and tiotropium.
Country(ies) of study	Selected European Union (EU) Member States and other non EU countries.
Authors	

MARKETING AUTHORISATION HOLDER(S)

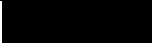
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1. LIST OF ABBREVIATIONS

ACOS	Asthma-COPD Overlap Syndrome
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine transaminase
ASAM	Average Standardized Absolute Mean
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CAT	COPD Assessment Test
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CRO	Contract Research Organisation
CV	Cardiovascular
DRE	Disease Related Event
EAC	Event Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
FEV ₁	Forced Expiratory Volume in one Second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GPP	Good Pharmacoepidemiology Practices
GSK	GlaxoSmithKline
GVP	Good Pharmacovigilance Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IPTW	Inverse Probability of Treatment Weighting
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LABA	Long-acting beta2-agonist
LAMA	Long-acting Muscarinic Antagonist
LRTI	Lower Respiratory Tract Infection
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MPR	Medication Possession Ratio
mMRC	Modified Medical Research Council

NI	Non-inferiority
NYHA	New York Heart Association
PAD	Peripheral Arterial Disease
PAS	Post-Authorisation Safety
PBRER	Periodic benefit-Risk Evaluation Report
PDC	Proportion of Days Covered
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient Reported Outcome
PS	Propensity Scores
PSUR	Periodic Safety Update Report
PT	Preferred Term
RCT	Randomised Controlled Trial
RWLPR	Real-World & Late Phase Research
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
SPM	Study Procedures Manual
SSC	Scientific Steering Committee
TIA	Transient Ischaemic Attack
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UK	United Kingdom
ULN	Upper Limit of Normal
UMEC	Umeclidinium bromide
UMEC/VI	Umeclidinium bromide/vilanterol trifenate
UPLIFT	Understanding Potential Long-Term Impacts on Function with Tiotropium
US	United States
VI	Vilanterol
WHO	World Health Organisation

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Xoterna

2. RESPONSIBLE PARTIES

Contact details and the list of all investigators are kept in a stand-alone document (listed in [ANNEX 1](#)) and will be available upon request.

Sponsor

The Marketing Authorisation Holder (MAH) will serve as the sponsor of this study. It is the responsibility of the MAH to ensure proper monitoring of the study and compliance with all applicable regulatory guidelines and laws.

Role/Title: Senior Director, Respiratory Therapeutic Group, Global Regulatory Affairs

Name: [REDACTED]

Address: GlaxoSmithKline Research & Development Ltd.

Study Coordination

The MAH has contracted with Quintiles Real-World & Late Phase Research (RWLPR), a contract research organisation (CRO) specialising in registries and observational post-market studies, to provide scientific leadership and to conduct the study. The CRO will conduct the study with review and input from the MAH. The approximate composition of the Scientific Steering Committee (SSC) is seven external members with relevant clinical and epidemiologic experience, as well as four GSK employees, and one representative from Quintiles. The SSC will provide expert medical and epidemiological input and advice, review the interim and final reports of safety data, and monitor the overall study progress through regular teleconferences and meetings. An Event Adjudication Committee (EAC) will be implemented to adjudicate cardiovascular (CV) and cerebrovascular events of interest in a blinded fashion continuously throughout the study. The EAC will include four independent medical specialists in cardiology and one neurologist who will conduct a blinded review of relevant data and documentation, and validate events as confirmed or unconfirmed based on predefined algorithms. The responsibilities of the SSC and EAC are further described in [Section 8.10.2](#).

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliated company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

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Regulatory Agency Identifying Number(s):

N/A

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

Investigator Signature

Date

3. ABSTRACT

Full Study Title: Post-authorisation Safety (PAS) Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD Patients with UMEC/VI Combination or UMEC versus Tiotropium (study 201038)

Protocol version: 1

Rationale and background: GlaxoSmithKline (GSK) has proposed a prospective observational study which aims to collect data reflecting the ‘real-world’ experience of Chronic Obstructive Pulmonary Disease (COPD) patients treated with either umeclidinium (UMEC; long-acting muscarinic antagonist [LAMA])/vilanterol (VI; long-acting beta₂ agonist [LABA]) combination product or UMEC in the post approval setting. The purpose of the study is to expand understanding of the potential cardiovascular (CV) and cerebrovascular risks of myocardial infarction (MI), stroke and new onset or acute worsening/decompensation heart failure of UMEC/VI and UMEC as compared to tiotropium. Tiotropium is a LAMA with a well established safety and efficacy profile. The Pharmacovigilance Risk Assessment Committee (PRAC) accepted the proposed study summary and the European Commission confirmed the obligation to perform the study as a condition of the European licenses for UMEC/VI and UMEC.

The overall study design is an observational cohort study of COPD patients designed to demonstrate non-inferiority for each of the three individual CV and cerebrovascular outcomes of MI, stroke and new onset, or acute worsening/decompensation heart failure. The analysis will compare new users of UMEC/VI with new users of tiotropium, and new users of UMEC with new users of tiotropium. These new treatments may be added on to existing therapies. Analyses will be based on the time to the first event of stroke, MI and heart failure individually and non-inferiority will be considered to be demonstrated if the upper bound of the 95% confidence interval around the hazard ratio is 2.0 or less. If the lower bound is greater than 1.0, non-inferiority will not be assumed.

Research question and objectives: The study will address the research question of whether the incidence rates of CV and cerebrovascular events differ among new users of UMEC/VI combination or UMEC compared with tiotropium in patients diagnosed with COPD.

The primary objectives are:

1. To demonstrate non-inferiority of UMEC/VI combination and UMEC to tiotropium for risk of MI, stroke and heart failure individually based on an analysis of time to first event.
2. To quantify the incidence rate and frequency of MI, stroke, and heart failure individually for new users of UMEC/VI combination, UMEC, and tiotropium.

The secondary objectives are:

1. To compare UMEC/VI combination and UMEC to tiotropium for risk of the composite endpoint of MI, stroke, heart failure or sudden cardiac death based on an analysis of time to first event.
2. To quantify the incidence rate and frequency of the composite endpoint of MI, stroke, heart failure or sudden cardiac death for new users of UMEC/VI combination, UMEC, and tiotropium.
3. To quantify the incidence rate and frequency of serious pneumonia/ serious lower respiratory tract infections (LRTI) (composite endpoint) for new users of UMEC/VI combination, UMEC, and tiotropium.
4. To quantify the overall mortality rate, cardiovascular and non cardiovascular mortality rates for new users of UMEC/VI combination, UMEC, and tiotropium

The other objectives are:

I Safety

1. To quantify the incidence rate and frequency of haemorrhagic stroke, ischaemic stroke and undefined stroke for new users of UMEC/VI combination, UMEC, and tiotropium.
2. To quantify the incidence rate and frequency of hospitalisation for heart failure for new users of UMEC/VI combination, UMEC, and tiotropium
3. To quantify the incidence rate and frequency of reported serious adverse events (SAEs) and drug-related adverse events (AEs) for new users of UMEC/VI combination, UMEC, and tiotropium.
4. To quantify the incidence rate and frequency of serious CV events of special interest (CV AESI), including transient ischaemic attacks and angina pectoris, cardiac arrhythmias (including Torsades de Pointes), acquired long QT, heart failure, cardiac ischaemia, and hypertension for new users of UMEC/VI combination, UMEC, and tiotropium.

II Effectiveness

1. To quantify persistence with study medication for new users of UMEC/VI combination, UMEC, and tiotropium.
2. To quantify the incidence rate and frequency of moderate/severe COPD exacerbation (requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalisation) for new users of UMEC/VI combination, UMEC, and tiotropium.
3. To quantify all-cause and COPD-related health-care utilisation for new users of UMEC/VI combination, UMEC, and tiotropium.

Study design: This will be a multinational, prospective, observational, non-randomised study, which will be carried out in several European Union (EU) and non-EU countries which will have UMEC/VI and UMEC and tiotropium available on prescription. COPD patients will be enrolled in the study at the time of a new UMEC/VI, UMEC or tiotropium prescription (new user design). These new therapies may be added on to existing treatments. All patients will have a diagnosis of COPD, with confirmation by current or historical spirometry and will be required to have no maintenance treatment with medications containing LAMA exceeding 60 days in the prior 12 months. Eligible patients will be enrolled by primary care physicians and pulmonologists. All patients will be assessed from the initiation of UMEC/VI, UMEC or tiotropium until the required number of events has been observed in the study population whilst on initially assigned treatment, and confirmed upon adjudication. Individual patients will be observed over at least a 24 month time frame, or until withdrawal of consent, loss to follow-up, or death. During this period, data will be collected at routine and unscheduled visits by their physician as they occur. Routine visits are expected to be at least twice yearly as part of normal care. Patients who are not seen for a period of 6 months will be contacted directly by their health care practice to collect minimal patient safety information, provided that this contact is considered by their physician to be within the standard of care for this patient. Hospital discharge summaries will also be collected. When the patient is enrolled into the study, the patient's prior and concurrent CV and cerebrovascular disease history and history of pneumonia and LRTIs as well as CV risk will be recorded. In addition, the patient will complete the modified Medical Research Council and COPD Assessment Tests. The decision to initiate use of UMEC/VI, UMEC, or tiotropium is to be made independently by the participant and their physician and is not mandated by the study design or protocol.

Population: The study will enrol an estimated 7,800 patients from a total of approximately 700 centres throughout selected EU and non EU countries over a four-year time period. This is an event driven study, required to observe at least 98 events for each of MI, stroke and heart failure in each pair of treatments. The number of patients required will be monitored and updated throughout the study based on observed data. Enrolment in non-EU countries will be capped at approximately 50%. Site selection criteria will include experience in treating patients with COPD, ability to prescribe the three treatments (UMEC/VI, UMEC, and tiotropium), access to the eligible patient population, ability to comply with study protocol procedures, and adequate site resources to meet study requirements.

Inclusion criteria

The following criteria must be met in order for a patient to be enrolled in the study:

- A clinical diagnosis of COPD verified by spirometry (defined as a post bronchodilator forced expiratory volume in one second/forced vital capacity [FEV1/FVC] ratio of <0.7). It is to be noted that at no point will any patients be requested to have spirometry solely for the purposes of participating in this study.
- Initiation of treatment with one of the three study treatments, UMEC/VI, UMEC, or tiotropium according to the decision of the treating physician (an index prescription may precede enrolment visit by up to seven days)

- Adult over 18 years of age who are willing and able to provide written informed consent
- Patient with medical records available for at least the 12 month period prior to enrolment.
- Patient able to read and write.

Exclusion criteria

Patients meeting the following criterion are not eligible for participation:

- Current participation in any interventional clinical trials in which treatment regimen and/or monitoring is dictated by a protocol
- Patients with hypersensitivity to UMEC, VI, tiotropium or excipients
- Maintenance treatment with a LAMA-containing medication during the 12 months prior to enrolment. Maintenance treatment is defined as 60 or more days of continuous use.

Variables:

Exposure

Three new user cohorts will be defined as follows:

1. New users of UMEC/VI
2. New users of UMEC
3. New users of tiotropium

For these three cohorts of new users all the following conditions will apply:

- New user is defined by the first prescription for the study medication.
- The date of the first prescription is the study start date. This is also described as prescription index date.
- No maintenance treatment with LAMA-containing medication in the 12 months prior to enrolment. Maintenance treatment is defined as 60 or more days of continuous use.
- NB: Reason for the choice of LAMA-containing medication prior to initial prescription index date will be recorded.

Patients will be classified as exposed to UMEC/VI, UMEC, or tiotropium from the prescription index date (at enrolment visit and including a maximum of 7 days prior to the enrolment) through to medication stop date plus 14 days. Patients will be followed up for a minimum of two years. Longest follow up time is expected to be approximately 5 years.

Exposure periods for COPD medication that are added on, or changes to different COPD medications (including UMEC/VI, UMEC, or tiotropium) will be recorded.

Baseline/Enrolment

Demographic characteristics, smoking history, CV, cerebrovascular and respiratory disease history and risk factors, and use of concomitant medications, will be collected for

patients at the time of the enrolment visit by the treating physician based on information documented in the medical records for all available past history. Clinical assessments including, but not limited to, weight and height, systolic and diastolic blood pressure, and New York Heart Association (NYHA) Heart Failure Class will also be recorded at enrolment. Patient reported outcome (PRO) assessments including the modified Medical Research Council (mMRC) dyspnoea scale and COPD Assessment Test (CAT) will be completed at enrolment.

Follow-up

Additional information including the use of the initiated study treatment and all other medication including other respiratory and CV medications will be captured at routine and unscheduled visits and/or through minimal direct contact with patients by their health care practice

Outcomes

Safety outcomes reported will include MI, stroke and new onset, or acute worsening/decompensation heart failure, sudden cardiac death, serious pneumonia/serious LRTI events, all-cause mortality, CV mortality and non-CV mortality, haemorrhagic stroke and ischaemic stroke, hospitalisation for heart failure, SAEs, all serious CV AESIs and all drug related AEs.

Treatment effectiveness outcomes recorded will include persistence with initiated medications, moderate/severe COPD exacerbations (requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalisation) and health care utilisation: all cause and COPD-related.

Data Sources: All data elements will be collected via electronic case report forms (eCRFs) from information routinely recorded in the medical record, or through patient self-report. Hospital discharge summaries will be requested by the investigator or site staff for all hospitalisations of enrolled patients. Data from these will be captured on the eCRF and also used for adjudication of CV and cerebrovascular events.

Information regarding the use of study medication and concomitant medication will be captured at routine and unscheduled visits. Event information, including MI, stroke and new onset, or acute worsening/decompensation heart failure, sudden cardiac death, all serious pneumonia/serious LRTI, CV mortality and non-CV mortality, all serious pneumonia/serious LRTI, haemorrhagic stroke, ischaemic stroke and undefined stroke, hospitalisation for heart failure, all SAEs, all CV AESI and all drug related AEs will be collected at routine and unscheduled visits and through minimal direct contact with patients by their health care practice.

Non-serious CV AESI and non-serious pneumonia/LRTI will also be captured by the investigator in the eCRF. All other non-serious events will be reported by the site investigator to GSK via national reporting systems.

Data collected for event adjudication will include, but is not limited to, medical records, death certificates, post mortems, and other sources as available and relevant to the event

of interest. This documentation will be used by the study Event Adjudication Committee (EAC) to classify the primary safety outcomes including MI, stroke, and new onset, or acute worsening/decompensation heart failure as “confirmed” or “unconfirmed” using predefined algorithms, and to determine CV versus non-CV death.

Study size: The estimated required number of events is intended to provide adequate power to demonstrate non-inferiority of UMEC/VI or UMEC, relative to tiotropium, for the risk of each primary endpoint based on an analysis of time to first event. The non-inferiority criterion will be the upper bound of the 95% CI around the hazard ratio not exceeding 2.0. If the lower bound of the 95% CI is above 1.0, non-inferiority will not be assumed. The primary endpoints will be the three individual CV and cerebrovascular endpoints of interest, namely MI, stroke, and new onset, or acute worsening/decompensation heart failure. Assumptions are as follows:

- One-sided alpha 2.5%
- 90% power
- Non-inferiority (NI) margin of 2.0
- 1:1 ratio of treatment groups to be compared
- Events must be confirmed on adjudication and occur while the subject is on the originally prescribed treatment (add-on treatments are permitted)

The sample size calculation is applied separately to each comparison (UMEC/VI vs. tiotropium or UMEC vs. tiotropium) and to each of MI, stroke and new onset, or acute worsening/decompensation heart failure. Based on these assumptions, it is estimated that for each comparison made for each endpoint 98 patients with an adjudicated event occurring on originally prescribed treatment are required to be observed. Patients will be recruited and continue to be followed until the required number of patients with adjudicated events for each of the primary endpoints (MI, stroke, and new onset, or acute worsening/decompensation heart failure) has been observed. In order to convert this to an approximate number of patients, the following assumptions have been used:

- Event rate per 100 person-years of 1.3 for MI, 3.4 for heart failure and 1.6 for stroke (Jara, 2012).
- Mean follow-up time (person-time) of 1.5 years.

Based on these assumptions, an estimated sample size of approximately 2,600 patients per treatment cohort is required for the primary endpoint analyses yielding a total required sample size of approximately 7,800 total patients. The actual number of subjects recruited will depend on the observed event rate, the proportion of events confirmed by adjudication, the average length of exposure to the indexed treatment, recruitment patterns and the similarity of subject characteristics between the treatment arms. This information will be monitored throughout the study and the number of patients required will be updated accordingly.

Multiplicity will be addressed by ensuring that there is sufficient power to demonstrate non-inferiority on all three primary endpoints (MI, stroke, and heart failure) with a

margin of 2.0. Based on the estimated event rates listed above the following events and resulting power would be expected for each endpoint:

	MI	Stroke	Heart failure
Adjudicated events	98	108	168
Power %	90	93.9	99.9

The cumulative power to demonstrate NI with a margin of 2.0 for all three individual endpoints (assuming independent events) will be 84.4%.

Note that the events are not completely independent and therefore there will be some correlation between them. This would result in an increase in power and therefore the estimates above are conservative. The overall cumulative power would be expected to be above 85%.

All subjects will be followed up for at least 2 years. Recruitment is planned to continue until the required number of events has been recorded for the rarest of the individual endpoints. However, recruitment may stop before the last event is recorded if it is predicted that the required number of events will be observed by continuing to follow-up patients already recruited into the study. All the subjects will be followed up for at least 2 years. so once the planned number of events is reached, subjects may continue to be followed-up in the study, until study withdrawal, death, or conclusion of study follow-up.

Data analysis:

A detailed statistical analysis plan (SAP) will be prepared and finalised prior to the conduct of any study analysis or reporting. Full details on data transformations/derivations, categorical definitions, analyses, handling of missing data, and presentation of results will be described separately in the SAP.

Descriptive analyses

Details of patient enrolment and disposition will be provided in tables and/or figures.

The demographic and clinical profile of the study population will be described using data collected from the medical history during the pre-enrolment period and at the time of the enrolment visit. This profile will be inclusive of, but not limited to, details of COPD disease status, history of exacerbations and prior therapies, history of CV and cerebrovascular events and other medical history, overall and stratified according to treatment cohort (UMEC/VI, UMEC, and tiotropium). Summaries of the characteristics of each treatment cohort at the time of enrolment will be provided. Additionally, the balance in measured covariates between cohorts based on propensity scores (PS) will be assessed using the average standardized absolute mean (ASAM) difference approach. (McCaffrey, 2004)

Statistical analysis

Propensity scores (PS) will be used to adjust for differences in covariate balance between treatment groups (Rosenbaum, 1983; Stürmer et al, 2000). PS will be estimated separately for each treatment comparison (UMEC/VI versus tiotropium and UMEC versus tiotropium) using logistic regression to compute a predicted probability of initiating UMEC/VI or UMEC versus tiotropium. The estimated PS will then be used to ensure treatment cohorts are balanced on PS using stabilized IPTW (Robins et al 2000) or other weighting approach prior to analysis. Sensitivity analyses will be defined in the SAP and may include PS matching or stratification as well as traditional multivariate regression methods to adjust for baseline covariates.

Analyses corresponding to the primary objectives

- 1. To demonstrate non-inferiority of UMEC/VI combination and UMEC to tiotropium for risk of MI, stroke and heart failure individually based on an analysis of time to first event.*

Cox regression analyses will be used to compare the time to first event (MI, stroke, and new onset or acute worsening/decompensation heart failure) from start of initiated treatment between PS balanced cohorts of UMEC/VI and tiotropium initiators, and between PS balanced cohorts of UMEC and tiotropium initiators. The hazard ratio along with 95% confidence interval will be calculated for each treatment comparison for each endpoint. If the upper bound of the 95% confidence interval for the hazard ratio exceeds 2.0, the non-inferiority assumption will be rejected. If the lower bound of the 95% CI is above 1.0, non-inferiority will not be assumed. Kaplan-Meier curves comparing the time to each endpoint for each treatment cohort will also be presented.

For the primary analysis, only events which were confirmed upon adjudication during the follow-up period will be included. The follow-up period for survival models will be

defined as the period between the prescription index dates until the earliest of: date when the planned number of events has been reached. At an individual patient level this is 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death. Sensitivity analyses will include stratified analyses by age, gender, concomitant use of inhaled corticosteroids as well an application of alternative methods like matching by propensity scores and multivariate adjustment of un-balanced cohorts, in addition to the analysis of events observed and recorded during follow-up time until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

- 2. To quantify the incidence rate and frequency of MI, stroke, and heart failure for new users of UMEC/VI combination, UMEC, and tiotropium.*

Incidence rates (number of first events per person-year) of each of MI, stroke and new onset or acute worsening/decompensation heart failure will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with 95% confidence intervals. The number and percentage of patients with each event (MI, stroke, or new onset or acute worsening/decompensation heart failure), the total number of each event and the event rate (total number of events per person-year) will also be summarised. Further, incidence rate ratios accompanied by 95% confidence intervals will be derived.

For the primary analysis, only events which were confirmed upon adjudication during the follow-up period will be included. The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

Analyses corresponding to the secondary objectives

- 1. To compare UMEC/VI combination and UMEC to tiotropium for risk of the composite endpoint of MI, stroke, heart failure or sudden cardiac death based on an analysis of time to first event.*

Cox regression analyses will be used to compare the time from start of initiated treatment to first composite event (MI, stroke, new onset or acute worsening/decompensation heart failure or sudden cardiac death) between PS balanced cohorts of UMEC/VI and tiotropium initiators, and between PS balanced cohorts of UMEC and tiotropium initiators. The hazard ratio along with 95% confidence interval will be calculated for each treatment comparison. Kaplan-Meier curves comparing the time to first endpoint for each treatment cohort will also be presented.

For this analysis, only events which were confirmed upon adjudication during the follow-up period will be included. The follow-up period will be defined as the period between the prescription index dates until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

2. *To quantify the incidence rate and frequency of the composite endpoint of MI, stroke, heart failure or sudden cardiac death for new users of UMEC/VI combination, UMEC, and tiotropium.*

Incidence rates (number of first event per person-year) of the composite of MI, stroke and new onset or acute worsening/decompensation heart failure or sudden cardiac death will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with the 95% confidence intervals. The number and percentage of patients with a composite event and the total number of composite events will also be summarised.

For this analysis, only events which were confirmed upon adjudication during the follow-up period will be included. The follow-up period will be defined as the period between the prescription index dates until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

3. *To quantify the incidence rate and frequency of serious pneumonia/ serious LRTI (composite endpoint) for new users of UMEC/VI combination, UMEC, and tiotropium.*

Incidence rates (number of first events per person-year) of serious pneumonia/ serious LRTI as a composite endpoint will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with 95% confidence intervals. The number and percentage of patients with serious pneumonia/serious LRTI, the total number of serious pneumonia/serious LRTI events and the event rate (total number of events per person-year) will also be summarised. Cox regression analyses will be used to compare the time to first event (serious pneumonia/serious LRTI) from start of initiated treatment between PS balanced cohorts of UMEC/VI and tiotropium initiators, and between PS balanced cohorts of UMEC and tiotropium initiators. The hazard ratio along with 95% confidence interval will be calculated for each of the treatment comparisons. Kaplan-Meier curves comparing the time to each endpoint for each treatment cohort will also be presented.

The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

4. *To quantify the overall mortality rate, cardiovascular and non cardiovascular mortality rates for new users of UMEC/VI combination, UMEC, and tiotropium*

Mortality rates (number of deaths per person-year) for all-cause mortality, CV mortality, and non-CV mortality will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with 95% confidence intervals. The number and percentage of patients who died and the total number of deaths (all-cause, adjudicated CV, adjudicated non- CV and undefined) will be reported.

The follow-up period will be defined as the period between the prescription index date

until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

Analyses corresponding to other safety objectives

1. *To quantify the incidence rate and frequency of haemorrhagic stroke, ischaemic stroke and undefined stroke for new users of UMEC/VI combination, UMEC, and tiotropium.*

Incidence rates (number of first events per person-year) for each of haemorrhagic stroke, ischaemic stroke and undefined stroke will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with 95% confidence intervals. The number and percentage of patients with each event and the total number of each event will also be summarised.

The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

2. *To quantify the incidence rate and frequency of hospitalisation for heart failure for new users of UMEC/VI combination, UMEC, and tiotropium*

Incidence rates (number of first events per person-year) of hospitalisation for heart failure will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with the 95% confidence intervals. The number and percentage of patients with the event, the total number of events and the event rate (total events per person-year) will also be summarised.

The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

3. *To quantify the incidence rate and frequency of reported SAEs and drug-related AEs for new users of UMEC/VI combination, UMEC, and tiotropium.*

Incidence rates (number of first events per person-year) will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with 95% confidence intervals. The number and percentage of patients with each event and the total number of each event will also be summarised. AEs will be summarised according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT).

The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

Characteristics of patients with SAEs will be summarised in a listing of individual SAE events in study reports. These characteristics may include medical history including recent use of UMEC/VI, UMEC, or tiotropium, use of other COPD medications,

exacerbations, underlying medical conditions, respiratory and other concomitant medication use, and dosing/timing of administration of study medications and other clinically relevant events and procedures.

Characteristics of patients with drug-related AEs will be reported similarly.

Case narratives will be provided for each SAE and drug related AE.

- 4 To quantify the incidence rate and frequency of serious CV AESIs, including transient ischaemic attacks and angina pectoris, cardiac arrhythmias (including Torsades de pointes), acquired long QT, heart failure, cardiac ischaemia, and hypertension for new users of UMEC/VI combination, UMEC, and tiotropium.*

Incidence rates (number of first events per person-year) of the specified serious CV AESIs computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with 95% confidence intervals. The number and percentage of patients with each event and the total number of each event will also be summarised.

The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

Characteristics of patients with CV AESIs will be presented as tables in the study reports. Specified characteristics include prior medical history, including recent use of UMEC/VI, UMEC, or tiotropium; use of other COPD medications; exacerbations; underlying medical conditions; respiratory and other concomitant medication use; and dosing/timing of administration of study medication. Case narratives will also be provided for each event.

Analyses corresponding to effectiveness objectives

- 1. To quantify persistence with study medication for new users of UMEC/VI combination, UMEC, and tiotropium.*

Persistence (adherence) will be assessed by describing treatment patterns including time to discontinuation of initiated COPD medication or switch in therapy; the proportion of days covered (PDC) during follow-up; and medication possession ratio (MPR).

Medication possession ratio (MPR) will be calculated by summing the number of days supplied for all but the last prescription before the patient switched or discontinued the index medication and divided by the number of days between the first and last prescription (Note: each patient will have a unique denominator). Additions to the original medication are allowed as long as the patient is still exposed to the index medication. The MPR will be expressed as a percentage, with non-adherence primarily defined as $MPR < 80\%$ and adherence defined as $MPR \geq 80\%$.

PDC will be calculated as the number of days for which the patient had possession of the initially prescribed medication divided by the number of days in the specified time period of 364.25 days for a given 0-12 month time period among patients who complete at least

12 months of follow-up.

Cox regression analysis will be used to compare the time to (earliest of) discontinuation of initiated COPD medication (including death or withdrawal from the study), or switch in COPD maintenance medication from start of initiated treatment within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators. The hazard ratio along with 95% confidence interval will be calculated for each treatment comparison. Kaplan-Meier curves comparing the time to endpoint for each treatment cohort will also be presented. The MPR and the proportion of days covered (PDC) during follow-up based on prescription dates will also be reported.

- 2. To quantify the incidence rate and frequency of moderate/severe COPD exacerbation (requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalisation) for new users of UMEC/VI combination, UMEC, and tiotropium.*

Cox regression analyses will be used to compare the time to first moderate/severe COPD exacerbations (requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalisation) from start of initiated treatment within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators. The hazard ratios along with 95% confidence intervals will be calculated for each treatment comparison. Kaplan-Meier curves comparing the time to first moderate/severe exacerbation for each treatment cohort will also be presented.

Incidence rates (number of first events per person-year) of moderate/severe exacerbation will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with the 95% confidence intervals. The number and percentage of patients with moderate/severe COPD exacerbations and the event rate (total number of events per person-year) will also be summarised.

The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

- 3. To quantify all cause and COPD related health-care utilisation for new users of UMEC/VI combination, UMEC, and tiotropium.*

The incidence rate, the number and percentage of patients with an event, the total number of events and the event rate will be calculated for hospital admission (COPD-related and all-cause), and emergency department visits (COPD-related and all-cause) and contacts with primary and secondary care within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with 95% confidence intervals.

Follow-up time will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

4. AMENDMENTS AND UPDATES

There are no amendments or updates.

5. EXPECTED MILESTONES

Milestone	Planned date
Start of data collection	2015
End of data collection	2023
Interim report 1	2019
Interim report 2	2021
Registration in the EU PAS register	To be registered after PRAC protocol approval
Final report of study results	2024

6. RATIONALE AND BACKGROUND

6.1. Background

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterised by obstruction of airflow in the airways and/or parenchyma that leads to difficulty breathing and lung airflow limitation that is not fully reversible (Qaseem, 2011). The resulting clinical manifestations include dyspnoea, chronic cough with or without sputum production, wheezing and poor exercise tolerance (Monsó, 1999; Sethi, 2008; Sint, 2008; Peacock, 2011; Qaseem, 2011). In 2011, COPD was the fourth leading cause of death globally, claiming the lives of 3.2 million people (WHO, 2013). With recent projections indicating that the disease will become the third leading cause of death by 2030, demand for effective treatments will rise.

Umeclidinium bromide/vilanterol trifenate (UMEC/VI) (ANORO™/Laventair™) and umeclidinium bromide (UMEC) (INCRUSE™) are two new inhaled medications developed by GlaxoSmithKline (GSK) that are maintenance bronchodilator treatments indicated to relieve symptoms in adult patients with COPD. These were approved by the European Commission in 2014. UMEC/VI is a fixed dose-combination long-acting muscarinic antagonist (LAMA)/ long-acting beta2-agonist (LABA) for the treatment of COPD. UMEC is a newly developed LAMA for the maintenance treatment of COPD. Vilanterol (VI) is a LABA that is also part of a combination inhaled corticosteroid (ICS)/LABA with fluticasone furoate (RELVAR™) approved for the treatment of COPD.

Current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend use of inhaled LAMAs and LABAs for maintenance treatment of COPD (GOLD, 2014). The combination of two classes of COPD therapies– each with a distinct mode of action has been shown to be more effective at improving lung function and reducing symptoms (Donohue, 2013; Celli, 2014; Decramer, 2014) than either therapy alone. Currently, there is another fixed-dose LAMA/LABA combination medication (glycopyrronium/indacaterol- trade names Ultibro/Ulunar/Xoterna) that is approved for COPD prior to UMEC/VI by the European Commission. Additionally, several

medications containing a LAMA only and a LABA only are available for treatment of COPD.

The safety and efficacy of monocomponent LABA and LAMA containing medications in COPD have been studied extensively. LAMA containing medications are considered a gold standard of bronchodilation of COPD patients demonstrating benefits of improved lung function and dyspnoea reduction. Both the LABA and LAMA class of drugs have been associated with some increased risk of CV and cerebrovascular events in meta-analyses of randomised clinical trials (Salpeter, 2004; Singh, 2011; Singh, 2013).

In a meta-analysis conducted by Singh et al., comprised of 17 trials enrolling 14,783 patients, the rate of CV and cerebrovascular events was increased by 58% among patients who used inhaled muscarinic antagonists for more than 30 days (Singh, 2008). In particular, increased risks of cardiovascular (CV) death, myocardial infarction (MI), and stroke were predominantly apparent in long-term trials. However, given that none of the included trials were designed a priori to monitor for CV risk, and that the trials were generally of short duration, failed to adjudicate outcome events, and were unable to control for strong confounders (e.g. smoking, hypertension and diabetes), the results of this meta-analysis are inconclusive.

Tiotropium is a LAMA which is well established as a treatment for stable COPD. In a four-year randomised controlled trial published after the Singh et al. meta-analysis, (titled “Understanding Potential Long-Term Impacts on Function with Tiotropium [UPLIFT]”) investigators noted a decreased risk for fatal CV events in patients randomised to Tiotropium (rate ratio = 0.57) (Tashkin, 2008). In light of the new contradictory evidence, Celli and colleagues conducted a meta-analysis that re-analysed CV risk among COPD patients taking muscarinic antagonists compared to placebo (Celli, 2010). Their findings (rate ratio = 0.83) were in agreement with results from the UPLIFT study, supporting the hypothesis that LAMAs are not an independent risk factor for CV death, MI or stroke. Another study reported no difference in the risk of CV events in tiotropium (Handihaler) users versus users of other respiratory medications (Louis, 2007). Three studies explored the risk of CV and cerebrovascular events in tiotropium (Handihaler) users versus LABA users (Gershon, 2013; Jara, 2007; Jara, 2012). Only the risk of stroke was significantly increased and only in one study among tiotropium users (Gershon, 2013). This was not identified in two other studies.

Initially, specific concerns were identified for users of tiotropium administered in a nebulised formulation via Respimat. Tiotropium Respimat administration was repeatedly associated with an increased risk of CV events as compared to tiotropium dry powdered formulation administered via Handihaler in clinical and observational studies (Jenkins, 2013; Verhamme, 2013). However, in a 17,000 patient randomized controlled trial designed to determine any difference in CV cerebrovascular risks associated with tiotropium Respimat compared to Handihaler, no difference in risk was observed between the two treatments (Wise, 2013).

Pooled analysis of eight phase III randomised controlled trials (RCT) shows no clinically relevant increase in CV events with UMEC/VI or UMEC compared with placebo. The number of cardiac ischaemic events was low and inconsistent with small imbalances

between treatments observed in some individual studies. No increased risk of Major Cardiovascular Events (Adjudicated Cardiovascular Death, Stroke or Cardiac Ischemia/MI) was observed with UMEC/VI or UMEC compared to placebo. A small increase in atrial arrhythmias was observed with UMEC compared to placebo which has been observed previously with other LAMAs (Naccarelli, 2014, Anthonisen, 2002, FDA Briefing Document, 2009, CDER Medical Review, acclidinium bromide, 2012).

Given the high prevalence of CV co-morbidities among COPD patients, observational research that aims to elucidate causal relationships between LAMAs and CV events will be an important approach to monitor patient safety (Fabbri, 2008; Müllerova, 2013). In order to generate systematically collected data to better understand the potential relationship between exposure to UMEC/VI or UMEC and CV endpoints of MI, stroke, and new onset, or acute worsening/decompensation heart failure, the MAH is planning to conduct a post-authorisation safety (PAS) study to examine the long-term safety risk profile of UMEC/VI and UMEC. The proposed study is a post-marketing commitment to examine the safety profile among new users of UMEC/VI or UMEC each compared with new users of tiotropium when used in real world settings. The study will determine if UMEC/VI and UMEC can be considered non-inferior to tiotropium in terms of the risk of MI, stroke or new onset, or acute worsening/decompensation heart failure among newly-prescribed COPD patients. Incidence rates of a composite endpoint of MI, stroke, acute worsening/decompensation heart failure or sudden cardiac death will be explored as well. Mortality rates and incidence rates of a composite endpoint of serious pneumonia and lower respiratory tract infection (LRTI) in new users of UMEC/VI, UMEC and tiotropium will also be assessed as requested by the Pharmacovigilance Risk Assessment Committee (PRAC).

6.2. Rationale

GSK has proposed an observational study which aims to collect data reflecting the ‘real-world’ experience with UMEC/VI combination and UMEC in the post approval setting to expand the understanding of potential CV risks (MI, stroke and heart failure) of UMEC/VI and UMEC in COPD patients as compared to tiotropium. The PRAC accepted the proposed study summary and the European Commission confirmed the obligation to perform the study as a condition of the European licences for UMEC/VI and UMEC.

The overall study design is an observational cohort study designed to demonstrate non-inferiority for each of the three individual potential CV and cerebrovascular outcomes: MI, stroke and new onset, or acute worsening/decompensation heart failure, comparing COPD patients initiating treatment with UMEC/VI with COPD patients initiating treatment with tiotropium and COPD patients initiating treatment with UMEC with COPD patients initiating treatment with tiotropium. Analyses will be based on the time to the first event of MI, stroke, and new onset, or acute worsening/decompensation heart failure and non-inferiority will be considered to be demonstrated if the upper bound of the 95% confidence interval around the hazard ratio is 2.0 or less. If the lower bound is greater than 1.0, non-inferiority will not be assumed.

7. RESEARCH QUESTION AND OBJECTIVE(S)

The study will address the research question of whether the incidence rates of CV and cerebrovascular events differ among new users of UMEC/VI combination or UMEC compared with tiotropium in patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD).

Primary objectives:

1. To demonstrate non-inferiority of UMEC/VI combination and UMEC to tiotropium for risk of MI, stroke or heart failure individually based on an analysis of time to first event.
2. To quantify the incidence rate and frequency of MI, stroke, and heart failure for new users of UMEC/VI combination, UMEC, and tiotropium.

Secondary objectives:

1. To compare UMEC/VI combination and UMEC to tiotropium for risk of the composite endpoint of MI, stroke, heart failure or sudden cardiac death based on an analysis of time to first event.
2. To quantify the incidence rate and frequency of the composite endpoint of MI, stroke, heart failure or sudden cardiac death for new users of UMEC/VI combination, UMEC, and tiotropium.
3. To quantify the incidence rate and frequency of serious pneumonia/ serious LRTI (composite endpoint) for new users of UMEC/VI combination, UMEC, and tiotropium.
4. To quantify the overall mortality rate, cardiovascular and non cardiovascular mortality rates for new users of UMEC/VI combination, UMEC, and tiotropium.

Other objectives:

I Safety

1. To quantify the incidence rate and frequency of haemorrhagic stroke, ischaemic stroke and undefined stroke for new users of UMEC/VI combination, UMEC, and tiotropium.
2. To quantify the incidence rate and frequency of hospitalisation for heart failure for new users of UMEC/VI combination, UMEC, and tiotropium
3. To quantify the incidence rate and frequency of reported serious adverse events (SAEs) and drug-related adverse events (AEs) for new users of UMEC/VI combination, UMEC, and tiotropium.
4. To quantify the incidence rate and frequency of serious CV events of special interest (CV AESIs), including transient ischaemic attacks and angina pectoris, cardiac arrhythmias (including Torsades de pointes), acquired long

QT, heart failure, cardiac ischaemia, and hypertension for new users of UMEC/VI combination, UMEC, and tiotropium.

II Effectiveness

1. To quantify persistence with study medication for new users of UMEC/VI combination, UMEC, and tiotropium.
2. To quantify the incidence rate and frequency of moderate/severe COPD exacerbation (requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalisation) for new users of UMEC/VI combination, UMEC, and tiotropium.
3. To quantify all-cause and COPD-related health-care utilisation for new users of UMEC/VI combination, UMEC, and tiotropium.

8. RESEARCH METHODS

8.1. Study design

This will be a multinational, prospective, observational, non-randomised study, which will be carried out in several European Union (EU) and non EU countries which will have UMEC/VI and UMEC and tiotropium available on prescription.

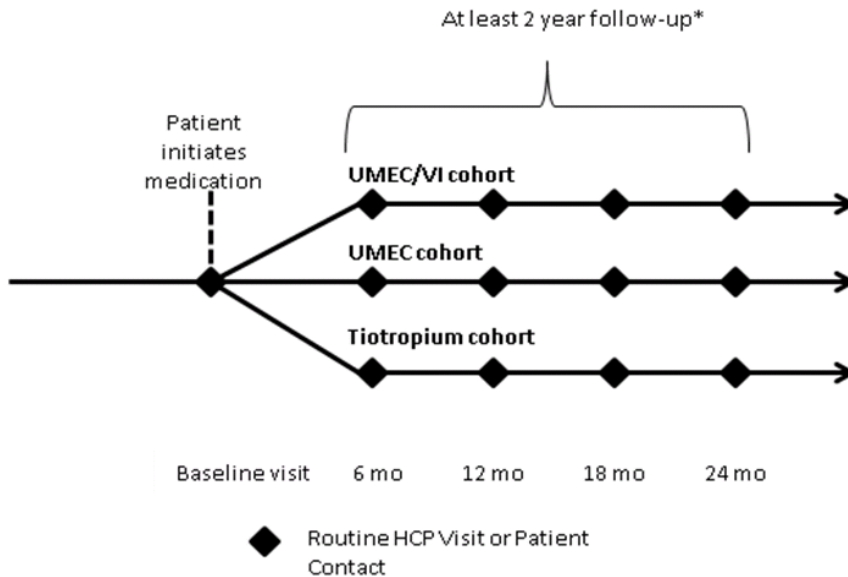
Patients will be enrolled in the study at the time of a new UMEC/VI, UMEC or tiotropium prescription. This is consistent with a new user design recommended for observational studies of medication effects to avoid bias associated with inclusion of prevalent users of a medication who have “survived” and continued taking the drug beyond the period of early use (Ray, 2003). These new therapies may be added on to existing treatments. All patients will have a diagnosis of COPD, confirmed with current or historical spirometry and will be required to have no maintenance treatment with medications containing LAMA exceeding 60 days in the prior 12 months. Eligible patients will be enrolled by primary care physicians and pulmonologists. All patients will be assessed from the initiation of UMEC/VI, UMEC or tiotropium until the required number of events has been observed in the study population whilst on initially assigned treatment, and confirmed upon adjudication. Individual patients will be observed over at least a 24 month time frame, or until withdrawal of consent, loss to follow-up, or death. During this period, data will be collected at routine and unscheduled visits to the treating physician as they occur. Routine visits are expected to be at least twice yearly as part of normal care. Patients who are not seen for a period of 6 months will be contacted directly by their health care practice to collect minimal patient safety information, provided that this contact is considered by the treating physician to be within the standard of care for this patient. Hospital discharge summaries will also be collected. When the subject is enrolled into the study, the patients’ prior and concurrent CV or cerebrovascular disease history and history of pneumonia and LRTIs as well as CV risk will be recorded. In addition, the patient will complete the modified Medical Research Council and COPD Assessment Test. As it is important to ascertain that patients who are enrolled in the study have a clinically valid diagnosis of COPD made in accordance with GOLD 2014 guidelines, patients will only be enrolled when a spirometric diagnosis of COPD is available (GOLD 2014). At no point will any patient be requested to undergo spirometry procedure solely for the purposes of participating in this study. The primary analyses will

be censored at time of 14 days after discontinuation of the initiated medication (UMEC/VI, UMEC, or tiotropium). The estimated duration of study participation from enrolment to final follow up is between 2 and 5 years. Patients will be encouraged and expected to remain in the study until the conclusion of study follow-up regardless of discontinuation of the initiated study medication (UMEC/VI, UMEC, or tiotropium). The decision to initiate use of UMEC/VI, UMEC, or tiotropium is to be made independently by the participant and their treating physician and is not mandated by the study design or protocol.

Figure 1 provides a schematic of the design and follow-up schedule for the study. Table 1 provides details of expected contacts with the treating physician.

CV and cerebrovascular endpoints will include: MI, new onset, or acute worsening/decompensation heart failure, sudden cardiac death and stroke (haemorrhagic, ischaemic or other). These events will be adjudicated. Other CV AESIs including transient ischaemia, angina, acquired long QT interval, cardiac arrhythmias, cardiac ischaemia, and hypertension will be recorded. Further, information on cause of death will also be collected and where feasible, death certificates will be requested by the investigators for the Event Adjudication Committee (EAC) to adjudicate CV or non-CV death. A complete listing of study outcomes is provided in Section 8.3.1

Figure 1 Design and Follow-up Schedule for COPD PASS



Footnote: The follow-up period will be defined as the period between the prescription index date until the earliest of: date when the planned number of events has been reached, 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

8.2. Setting

The study will enrol an estimated 7,800 patients from a total of approximately 700 centres throughout selected EU and non-EU countries over a four year time period. This is an event driven study, required to observe at least 98 events for each of MI, stroke and heart failure in each pair of treatments. The number of patients required will be monitored and updated throughout the study based on observed data. Enrolment in non-EU countries will be capped at approximately 50%. Site selection criteria will include experience in treating patients with COPD, ability to prescribe the three treatments (UMEC/VI, UMEC, and tiotropium), access to the eligible patient population, ability to comply with study protocol procedures, and adequate site resources to meet study requirements. Selection criteria and basic site information (e.g. site size, site type) will be collected via a site qualification survey. While the majority of sites will be primary care physicians, some pulmonologists (expected to represent up to approximately 30% of total sites), will be selected.

Sites will be required to maintain a patient enrolment log of eligible patients at their treatment centres. This log will document how patients were included or excluded from the study in order to assess the representativeness of the study population.

The study will not provide or recommend any treatment; all decisions regarding treatment are made at the sole discretion of the treating physician in accordance with their usual practices. The decision to enrol a patient in this study must not be made until after the treating physician has prescribed one of the three study treatments. All patients presenting at a given site during the enrolment period will be assessed for eligibility according to the defined selection criteria, and all eligible patients at a site should be consecutively enrolled in the study to the extent feasible.

The overall number and location of sites may be adjusted during the study to meet enrolment goals, if needed. Frequent interim monitoring of patient recruitment into each of the three treatment cohorts at a site and country level will be conducted on a regular basis (such as monthly) so that recruitment may be adapted in response to insufficient enrolment in one or more treatment cohorts. Actions may include implementation of temporary or permanent caps on enrolment of one or more treatment cohorts to ensure adequate numbers of patients are enrolled in each cohort, with patients enrolled in at least two treatment cohorts in any given country. Enrolment caps on one or more specific treatment cohorts would be implemented at the country level or study level, not at the site level so as to minimize the likelihood of any impact on prescribing. As sites will be trained and clearly instructed that the treatment decision should be independent of enrolment into the study, the potential for use of enrolment caps on a given treatment cohort(s) to influence the treatment decision should be no different than in an observational study of a single treatment where other treatments for the indication of interest exist.

Additional monitoring of number of confirmed and unconfirmed MI, stroke, and heart failure events will be conducted throughout the study follow-up period to ensure that the required number of events to address the primary objectives is attained. Additional

discussion of sample size considerations and the number of required events is provided in Section 8.5.

8.2.1. Inclusion criteria

The following criteria must be met in order for a patient to be enrolled in the study:

A clinical diagnosis of COPD verified by spirometry (defined as a post bronchodilator forced expiratory volume in one second/forced vital capacity [FEV1/FVC] ratio of <0.7). It is to be noted that at no point will any patients be requested to have spirometry solely for the purposes of participating in this study.

- Initiation of treatment with one of the three study treatments, UMEC/VI, UMEC, or tiotropium according to the decision of the treating physician (an index prescription may precede enrolment visit by up to seven days)
- Adult over 18 years of age who are willing and able to provide written informed consent
- Patient with medical records available for at least the 12 month period prior to enrolment.
- Patient able to read and write.

8.2.2. Exclusion criteria

Patients meeting the following criterion are not eligible for participation:

- Current participation in any interventional clinical trials in which treatment regimen and/or monitoring is dictated by a protocol
- Patients with hypersensitivity to UMEC, VI, tiotropium or excipients
- Maintenance treatment with a LAMA-containing medication during the 12 months prior to enrolment. Maintenance treatment is defined as 60 or more days of continuous use.

8.2.3. Patient withdrawal

Patients may withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment. If a patient is withdrawn prior to completing study follow-up period, any known reason for withdrawal must be documented in the database. In cases where contact cannot be made with the patient, the patient may be considered lost to follow-up after the site has attempted actions for contact, as detailed in the Study Procedures Manual (SPM). All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient.

Patients will be encouraged and expected to remain in the study until the conclusion of study follow-up regardless of discontinuation of the initiated study medication (UMEC/VI, UMEC, or tiotropium).

8.3. Variables

8.3.1. Outcome definitions

The primary safety outcomes of this study are:

- Time to first MI
- Time to first stroke
- Time to first heart failure event (new onset, or acute worsening/decompensation)
- Incidence rate of MI (number of first events per person-year)
- Incidence rate of stroke (number of first events per person-year)
- Incidence rate of new onset, or acute worsening/decompensation_heart failure (number of first events per person-year)
- Total number of events (including recurrent events) of each of MI, stroke, and new onset, or acute worsening/decompensation heart failure

Definitions for the primary safety outcomes to be used as guidelines for event adjudication by the EAC are provided in [APPENDIX 1](#).

The secondary safety outcomes of this study are:

- Time to first composite endpoint of MI or stroke, or new onset, or acute worsening/decompensation, heart failure or sudden cardiac death (composite endpoint)
- Incidence rate of composite endpoint of MI, stroke, or new onset, or acute worsening/decompensation_heart failure or sudden cardiac death (number of first event per person-year)
- Incidence rate of serious pneumonia/ serious LRTI events (number of first event per person-year)
- Total number of events (including recurrent events) and event rate (total number of events per person-year) of all pneumonia/LRTI AEs.
- Mortality rates (number of events per person-year) for all-cause mortality, CV mortality, and non-CV mortality
- Number and percentage of patients who died and the total number of deaths (all-cause, CV and non-CV)
- Incidence rate of haemorrhagic stroke, ischaemic stroke and undefined stroke (number of first event per person-year)
- Total number of events (including recurrent events) for both haemorrhagic stroke, ischaemic stroke and undefined stroke
- Incidence rate (number of first event per person-year) of hospitalisation for heart failure
- Total number of events (including recurrent events) for hospitalisation for heart failure

- Incidence rate (number of first events per person-year) of all reported SAEs, summarised according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT)
- Total number of events (including recurrent events) of all reported SAEs, summarised according to MedDRA SOC and PT
- Incidence rate (number of first events per person-year) of all reported drug-related AEs, summarised according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT)
- Total number of events (including recurrent events) of all reported drug-related AEs, summarised according to MedDRA SOC and PT
- Incidence rate (number of first events per person-year) of all reported serious CV AESIs, including, but not limited to:
 - transient ischaemic attacks
 - angina
 - cardiac arrhythmias
 - acquired long QT interval (including Torsades de Pointes)
 - cardiac ischaemia
 - hypertension

Treatment effectiveness outcomes will include:

- Persistence with initiated medication (including time from start date to date of discontinuation or switch in therapy, allowing for a defined “permissible gap” of ≤ 30 days in use; Medication Possession Ratio [MPR] and Percent Days Covered [PDC])
- Time to (earliest of) discontinuation of initiated COPD medication (including death or withdrawal from the study), or change in COPD maintenance medication from start of initiated treatment.
- Time to first moderate/severe COPD exacerbation (*i.e.*, requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalisation)
- Rate of moderate/severe COPD exacerbation per year (total number of events per person-year)
- Rate of hospitalisations per year from all causes (total number of events per person-year)
- Rate of COPD-related hospitalisations per year (total number of events per person-year)
- Rate of emergency department visits per year from all causes (total number of events per person-year)
- Rate of COPD-related emergency department (ED) visits (total number of events per person-year)
- Rate of health care utilisation including visits to the treating physician, hospitalisations and ED visits from all causes (total number of events per person-year)
- Rate of COPD-related health care utilisation including visits to the treating physician, hospitalisations and ED visits (total number of events per person-year)

Detailed documentation of all CV and cerebrovascular events of interest, serious pneumonia and serious LRTI events, other SAEs, and deaths will be sought from the

treating physicians, medical records, death certificates, post mortems and other sources as available and relevant to the event of interest. Biochemical and imaging test results, including ECGs measures taken in association with CV and cerebrovascular events of interest, for diagnosis and at time of hospital discharge will be obtained.

This documentation will be used by the EAC to classify the primary safety outcomes including MI, stroke, and new onset, or acute worsening/decompensation_heart failure as “confirmed” or “unconfirmed” using predefined algorithms based on the endpoint definitions referenced in [APPENDIX 1](#). The EAC will be blinded to exposure status with regard to treatment with UMEC/VI, UMEC, or tiotropium. In the context of an observational study, no medical follow-up or specific diagnostic procedures are mandated outside of usual care, and thus available evidence for clinical confirmation of events is limited to that available from subject medical records, death certificates, post mortems and discussion during visits with the treating physician. Serious pneumonia and serious LRTI outcomes will be considered confirmed on the basis of diagnosis by the treating physician, and will not be adjudicated by the EAC. Deaths will be considered confirmed on the basis of the diagnosis by the treating physician and/or death certificate. The EAC will also determine CV versus non-CV death based on death certificate information and other documentation as available.

8.3.2. Exposure definitions

This is an observational study of real-world treatment practices of new users of UMEC/VI, UMEC or tiotropium for COPD. This protocol does not recommend the use of any specific treatments. No study medication is provided as part of participation.

As a long-term observational study to evaluate treatment patterns and outcomes in patients treated in the post-marketing setting, no restrictions on concomitant treatments are associated with the study. All concomitant treatments including concomitant use of ICS-containing medications will be carefully recorded in order to evaluate their potential influence on the outcomes of interest.

Classification of exposure to UMEC/VI, UMEC or tiotropium will be based on the data obtained from the treating physician, patient medical charts, and patient self-report. The exposure information will, in most instances, be recorded before the occurrence of outcomes in this prospective study and confirmation of CV and cerebrovascular endpoints by the EAC will be conducted blinded to exposure status.

Three new user cohorts will be defined as follows:

1. New users of UMEC/VI
2. New users of UMEC
3. New users of tiotropium

For these three cohorts of new users all the following conditions will apply:

- New user is defined by the first prescription for this medication
- The date of the first prescription is the study start date. This is also described as prescription index date.

- No maintenance treatment with LAMA-containing medication in the 12 months prior to enrolment. Maintenance treatment is defined as 60 or more days of continuous use.
- NB: Reason for the choice of LAMA-containing medication prior to initial prescription index date will be rigorously recorded.

If any of the exposures are predominantly prescribed as a second line maintenance treatment for COPD, recruiting a representative cohort of new users would be compromised and study delivery timelines delayed. If during either (a) feasibility analysis or (b) the initial 12 months of recruitment, it becomes apparent that any of the exposures are preferentially prescribed to patients already exposed to long-term maintenance LAMA medication, modifications to the new user and/or the comparator definitions will be considered and discussed with the PRAC.

Patients will be classified as exposed to UMEC/VI, UMEC, or tiotropium beginning on the date of prescription (index date) at enrolment visit and including a maximum of 7 days prior to the enrolment until the date of medication stop defined as the date of discontinuation of initiated medication plus 14 days. The exposure period occurs while the subject is on the originally prescribed treatment (add-on treatments are permitted).

8.3.3. Confounders and effect modifiers

Propensity scores (PS) will be estimated for each pairwise treatment comparison using multivariate logistic regression models to compute a predicted probability of initiating either UMEC/VI or UMEC each compared with tiotropium. The set of covariates considered for inclusion in the stepwise logistic regression models for the PS model will include the list of measures as below, assessed at the time of study enrolment; variable selection will be performed separately for each treatment comparison and will be based on a priori clinical relevance and/or statistical significance within the multivariate model. The same set of covariates will also be considered for inclusion in multivariate regression models without use of PS based on a priori clinical relevance and/or change-in-estimate criterion (Grayson, 1987). The potential confounders and effect modifiers of primary interest will include but are not limited to

- Site characteristics
 - Primary care or specialist (pulmonologist or other)
 - Care setting
- Patient Demographics
 - Country of enrolment
 - Date of enrolment
 - Age
 - Gender
 - Race and ethnicity
 - Highest educational level reached
 - Predominant occupation during working age, e.g. manual/clerical/management/homemaker
 - Alcohol intake history (units/ week)

- Clinical Assessments
 - Body Mass Index (BMI)
 - Systolic and diastolic blood pressure
 - New York Heart Association (NYHA) Heart Failure Class
- COPD Severity:
 - Spirometric measures: FEV₁/FVC and FEV₁ % predicted
 - Age at COPD diagnosis
 - GOLD 2014 classification
 - Number and severity of COPD exacerbations in past 12 months (requiring treatment with antibiotics, systemic steroids or hospitalisation)
 - Medications used to treat COPD in past 12 months (including dates of use, route of administration and dosage)
- Smoking history, status (current, ex-smoker, non-smoker)
- History of CV and cerebrovascular diagnoses: Diabetes mellitus, Hypertension, MI/Unstable angina, Stroke, transient ischaemic attack (TIA), Heart failure, Tachycardia, atrial or ventricular, Bradyarrhythmias, Cardiac arrest, Left bundle branch block, Revascularization. For MI/Unstable angina, Stroke, TIA, and Cardiac arrest, the number of prior events will also be collected.
- Other co-morbidities: Prior history of Asthma, LRTI, Pneumonia, Glaucoma, Psychiatric disorders, Dyslipidemia, Chronic kidney disease (CKD), and Cancer (Malignant/Benign) including lung cancer. Dyslipidemia will be also assessed by collecting the most recent information on Total cholesterol, HDL cholesterol, LDL-cholesterol, and Triglycerides each as recorded in past 12 months. Psychiatric disorders and glaucoma as well as other diagnoses of interest will be also assessed indirectly through the list of concomitant medications used to treat such conditions.
- Family History of CV and cerebrovascular diagnoses
- Concomitant medications/therapies of interest including respiratory medications: Information on all medications taken at study enrolment and during the prior 12 months will be collected via eCRF and a binary indicator flag (Use: Yes/Non-use) derived. Based on this concomitant medications database, all therapeutic agents, through pharmacotherapeutic groups, that are potentially associated with the risk of primary outcomes and exposure or primary outcomes only will be considered for inclusion in propensity scores and as covariates in multivariable models. The following pharmacotherapeutic groups will be primarily ascertained; other groups may be added as deemed necessary: Lipid lowering agents, angiotensin-converting-enzyme inhibitor inhibitors, Angiotensin II receptor antagonists (ARBs), Anti-anginals, Anti-arrhythmics, Anti-coagulants, Anti-platelets, Beta-blockers, Calcium channel blockers, Digitalis, Diuretics, Insulin, Oral antidiabetics, Systemic exposure to Glucocorticosteroids, Antidepressants, Glaucoma medications, and Cytostatics with cardiovascular damage potential.

Detailed information on prior exposure to COPD medications, in the 12 months prior to enrolment, will also be collected and accounted for in the analysis in a similar fashion.

- Patient reported outcome (PRO) measures: Modified Medical Research Council dyspnoea scale (mMRC) and COPD Assessment Test (CAT).

8.4. Data sources

Scheduled assessments for the study are presented in [Table 1](#) below. All data elements will be collected from information routinely recorded in the medical record, prospectively recorded by the investigator for the purposes of the study, or through patient self-report. Hospital discharge summaries will be requested by the investigator or site staff for all hospitalisations among enrolled patients.

Information regarding the use of study medication and concomitant medication will be captured at routine and unscheduled visits. Event information, including MI, stroke and new onset, or acute worsening/decompensation heart failure, sudden cardiac death, aCV all serious pneumonia/serious LRTI, CV mortality and non-CV mortality, haemorrhagic stroke, ischaemic stroke and undefined stroke, hospitalisation for heart failure all SAEs, all CV AESI and all drug related AEs will be collected at routine and unscheduled visits and/or through minimal direct contact with patients by their health care practice.

Non-serious CV AESI and non-serious pneumonia/LRTI will also be captured by the investigator in the electronic case report form (eCRF). All other non-serious events will be reported by the site investigator to GSK via national reporting systems

Detailed documentation of all CV and cerebrovascular events of interest, serious pneumonia and serious LRTI events, other SAEs, and deaths will be sought from the treating physicians, medical records, death certificates, post mortems and other sources as available and relevant to the event of interest. Biochemical and imaging test results, including ECGs measures taken in association with CV and cerebrovascular events of interest, for diagnosis and at time of hospital discharge will be obtained.

This documentation will be used by the EAC to classify the primary safety outcomes including MI, stroke, and new onset, or acute worsening/decompensation_heart failure as “confirmed” or “unconfirmed” using predefined algorithms based on the endpoint definitions referenced in [APPENDIX 1](#)

Table 1 Data Collection Schedule

Data Elements	Pre-Enrolment Medical History ^a	Enrolment Visit	Routine Care Visits ^b	Additional 6 Month Patient Contact ^c	Event related patient contact	Final Patient Contact (Study Completion) ^d
Informed consent		X				
Demographics (e.g., age, gender, ethnic origin)		X				
Clinical Assessments (e.g., height, weight, blood pressure)		X				
COPD disease severity	X	X				
Spirometry – (e.g., FEV ₁ , FVC) ^e	X	X	X		X	
History of CV and cerebrovascular diagnoses and treatments, other CV risk factors	X	X				
Comorbidities (e.g., diabetes, hypertension, heart disease)	X	X	X	X		X
Smoking history and status	X	X	X			X
Treatment with UMEC/VI, UMEC, or tiotropium including prescription dates, records, & report from patient interview		X	X	X	X	X
Moderate /severe COPD Exacerbations	X		X	X	X	X
Concomitant medication/ treatments	X	X	X	X	X	X
CV and cerebrovascular	X		X	X	X	X

Data Elements	Pre-Enrolment Medical History ^a	Enrolment Visit	Routine Care Visits ^b	Additional 6 Month Patient Contact ^c	Event related patient contact	Final Patient Contact (Study Completion) ^d
outcomes						
Pneumonia/ LRTI outcomes	X		X	X	X	X
All cause mortality					X	X
Cause of death ^f					X	X
SAEs			X	X	X	X
Cardiovascular adverse events			X	X	X	X
Pregnancy		X	X	X	X	X
Dyspnoea assessment – mMRC		X				
COPD Assessment Test (CAT)		X				

- a. Will be obtained from available from medical records, once informed consent is obtained.
- b. Data collection will occur during routine visits with treating physician once within each time window of ± 90 days of each 6 month time point following study enrolment.
- c. Only patients who have no recorded health care contact for a period of 6 months for whom a lack of contact is outside of normal health care practice will be contacted directly by their health care practice to collect minimal information regarding safety.
- d. Prior to the end of study follow-up, the patient will be contacted for endpoint and safety events of interest.
- e. Spirometry results, to include FEV₁ and FVC will be noted when the information is available as part of normal care
- f. As available e.g. from death certificates, hospital records.

Patient reported outcome (PRO) assessments will be the modified Medical Research Council (mMRC) dyspnoea scale and the COPD Assessment Test (CAT). The questionnaires will be completed at the enrolment visit and the responses given by the patient should not be influenced by friends, family or medical staff. The mode of collection of the PROs will be consistent across all patients and sites.

Table 2 summarizes the instrument descriptions.

Table 2 Patient-Reported Outcome Instruments

Instrument	Description
mMRC	The modified Medical Research Council (mMRC) scale is a single item assessment in which patients indicate their degree of exercise-related breathlessness. Patients pick one of five statements that best describes their experience covering the range of dyspnoea from none (Grade 0) to near complete incapacity (Grade 4) (Mahler, 1988; Hajiro, 1998).

Instrument	Description
CAT	The COPD Assessment Test (CAT) 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 development of the CAT has involved well accepted methodologies used to develop psychometric tools (Jones, 2009a; Jones, 2009b; Jones, 2012). The CAT is an eight-item questionnaire suitable for completion by all patients diagnosed with COPD. When completing the questionnaire, patients rate their experience on a six-point scale, ranging from zero to five with a maximum score of 40. Higher scores indicate greater disease impact.

8.4.1. Baseline/Enrolment

The following data elements will be collected during the enrolment visit for all enrolled patients after written informed consent has been obtained; (additional measures may be added during eCRF development):

- Details of initiated COPD treatment with UMEC/VI, UMEC, or tiotropium including duration of prescription and dose
- Patient Demographics (where feasible and permitted by country regulations)
 - Date of enrolment
 - Age
 - Gender
 - Race and ethnicity
 - Highest educational level reached
 - Predominant occupation during working age, e.g. manual/clerical/management/homemaker
 - Alcohol intake history (units/ week)
- Clinical Assessments
 - Weight and height for BMI calculation
 - Systolic and diastolic blood pressure
 - NYHA Heart Failure Class
 - Most recent serum lipid values as recorded in past 12 months, including: total cholesterol, HDL-cholesterol, LDL-cholesterol, Triglycerides
- COPD Status:
 - Spirometric measures: FEV₁/FVC and FEV₁ % predicted where available from medical records
 - Age at COPD diagnosis
 - Number and severity of COPD exacerbations in past 12 months (requiring treatment with antibiotics or systemic steroids, hospitalisation)
 - Treating physician assessment of disease severity i.e. stable/ unstable COPD

- Medication used to treat COPD in past 12 months (including dates of use, form and dosage).
- Smoking history, status (current, ex-smoker, non-smoker)
- History of CV and cerebrovascular diagnoses: Diabetes mellitus, Hypertension, MI/Unstable angina, Stroke, TIA, Heart failure, Tachycardia, atrial or ventricular, Bradyarrhythmias, Cardiac arrest, Left bundle branch block, Revascularization. For MI/Unstable angina, Stroke, TIA, and Cardiac arrest, the number of prior events will also be collected.
- Other co-morbidities: Prior history of Asthma, LRTI, Pneumonia, Glaucoma, Psychiatric disorders, Dyslipidemia, Chronic kidney disease (CKD), and Cancer (Malignant/Benign) including lung cancer. Dyslipidemia will be also assessed by collecting the most recent information on Total cholesterol, HDL cholesterol, LDL-cholesterol, and Triglycerides each as recorded in past 12 months.
- Family History of CV and cerebrovascular diagnoses.
- Concomitant medications/therapies of interest including respiratory medications:
- The following questionnaires will be completed by the patient at the enrolment visit:
 - mMRC
 - CAT

Detailed medical history will be collected at study enrolment using the eCRF. It is expected that medical history information will be provided by the treating physician and based on a combination of self-reported information from the enrolled patient and, where available, supplemented by patient's electronic medical record. History of physician diagnosed comorbidities will be collected using indicator flags (Current/Past/No medical history/Not assessed).

8.4.2. Follow-up

The following data as far as available from routine medical practice and/or physician report from patient interview will be collected for all enrolled patients at each follow-up contact:

- Change in concomitant medications including respiratory and CV medication
- Study medication exposure status from physician/medical records, including prescription records, and patient self-report
- Smoking status
- Indicators of possible safety events of interest, e.g., hospitalisations not collected elsewhere
- Outcomes of interest and additional data for each event of interest – additional data to be obtained from physician/medical records for reported primary CV and cerebrovascular events of interest, pneumonia and LRTI outcomes, moderate/severe COPD exacerbation, health resource utilisation outcomes, SAEs, CV SAEs, including the results of laboratory and imaging reports which were performed as standard of care for CV and cerebrovascular events.

8.4.3. Discontinuation

The following data will be collected for all enrolled patients at the time of discontinuation from the study:

- Date of discontinuation from the study
- Reason for discontinuation (e.g., withdrawal of consent, death, lost to follow-up) from the study
- Reason for discontinuation of initiated study medication

All events of interest will be followed until resolution or until the end of the follow-up period, whichever comes first. Discontinuation of the initiated COPD medication (UMEC/VI, UMEC, or tiotropium) will not affect the patient's continued participation in the study, and patients will be encouraged and expected to remain in the study until the conclusion of follow-up regardless of such discontinuation.

8.5. Study size

The estimated required number of events is intended to provide adequate power to demonstrate non-inferiority of UMEC/VI or UMEC, relative to tiotropium, for the risk of each primary endpoint based on an analysis of time to first event. The non-inferiority criterion will be the upper bound of the 95% CI around the hazard ratio not exceeding 2.0. If the lower bound of the 95% CI is above 1.0, non-inferiority will not be assumed. The primary endpoints will be the three individual CV and cerebrovascular endpoints of interest, namely MI, stroke, and new onset, or acute worsening/decompensation heart failure.

Assumptions are as follows:

- One-sided alpha 2.5%
- 90% power
- Non-inferiority margin of 2.0
- 1:1 ratio of treatment groups to be compared
- Events must be confirmed on adjudication and occur while the subject is on the originally prescribed treatment (add-on treatments are permitted)

The sample size calculation is applied separately to each comparison (UMEC/VI vs. tiotropium or UMEC vs. tiotropium) and to each endpoint of MI, stroke and new onset, or acute worsening/decompensation heart failure. Based on these assumptions, it is estimated that for each comparison made for each endpoint 98 patients with an adjudicated event occurring on originally prescribed treatment are required to be observed. Patients will be recruited and continue to be followed until the required number of patients with adjudicated events for each of the primary endpoints (each of MI, stroke, and new onset, or acute worsening/decompensation heart failure) has been observed. In order to convert this to an approximate number of patients, the following assumptions have been used:

- Event rate per 100 person-years of 1.3 for MI, 3.4 for heart failure and 1.6 for stroke (Jara, 2012).
- Mean follow-up time (person-time) of 1.5 years.

Based on these assumptions, an estimated sample size of approximately 2,600 patients per treatment cohort is required for the primary endpoint analysis yielding a total required sample size of approximately 7,800 total patients. The actual number of subjects recruited will depend on the observed event rate, the proportion of events confirmed by adjudication, the average length of exposure to the indexed treatment, recruitment patterns and the similarity of subject characteristics between the treatment arms. This information will be monitored throughout the study and the number of patients required will be updated accordingly.

Multiplicity will be addressed by ensuring that there is sufficient power to demonstrate non-inferiority on all three primary endpoints (MI, stroke, and heart failure) with a margin of 2.0. Based on the estimated event rates listed above the following events and resulting power would be expected for each endpoint:

	MI	Stroke	Heart failure
Adjudicated events	98	108	168
Power %	90	93.9	99.9

The cumulative power to demonstrate NI with a margin of 2.0 for all three individual endpoints (assuming independent events) will be 84.4%.

Note that the events are not completely independent and therefore there will be some correlation between them. This would result in an increase in power and therefore the estimates above are conservative. The overall cumulative power would be expected to be above 85%.

All subjects will be followed up for at least 2 years. Recruitment is planned to continue until the required number of events has been recorded for the rarest of the individual endpoints. However, recruitment may stop before the last event is recorded if it is predicted that the required number of events will be observed by continuing to follow-up patients already recruited into the study. All subjects will be followed for at least 2 years, so once the planned number of events is reached, subjects may continue to be followed up in the study until the last subject has withdrawn, died or the study follow-up concluded.

Interim analyses estimating the PS models comparing UMEC/VI to tiotropium and UMEC to tiotropium will be conducted at planned intervals of at least every six months to generate estimates of the degree of overlap of the PS distributions between treatment cohorts and of any adjustments that might be needed to the planned sample size or recruitment to reach the required number of events per treatment cohort and ensure adequate power. Analytic loss following implementation of PS methods is not anticipated, however, may impact the effective sample size available for analysis if

methods including “trimming” of the patients with extreme values of the PS or matching on PS are employed.

8.6. Data management

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the electronic data capture (EDC) system and followed up for resolution.

High data quality standards will be maintained and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data.

8.6.1. Data handling conventions

All data will be collected and entered directly into the EDC system. Sites will be responsible for entering extracted patient data into a secure internet-based EDC database via the eCRF. All participating sites will have access to the data entered regarding the individual site’s own enrolled patients. All sites will be fully trained on using the on-line data capture system, including eCRF completion guidelines and help files. Investigators and site personnel will be able to access their account with a unique username and password. All eCRFs must be completed by designated, trained personnel or the study coordinator, as appropriate. In most cases, the eCRF must be reviewed, electronically signed, and dated by the investigator. All changes or corrections to eCRFs will be documented in an audit trail and an adequate explanation is required. All participating sites will have access to the data entered by the individual site on their own enrolled patients through the EDC system.

8.6.2. Timings of interim analysis and safety update reports

There are two interim analyses planned for this study: reports for incidence rates of MI, stroke, and heart failure will be prepared in Q3 2019 and Q3 2021.

The current timeline for provision of the first interim report is based on the anticipation that recruitment will be complete by 1Q2019. The first interim report will include baseline patient characteristics and adjusted event rates of outcomes based on the available follow-up.

In addition to the currently planned first interim analysis, to be completed by 1Q2019, GSK will provide descriptive updates, including patient recruitment update, number of events observed for primary outcomes per number of patients exposed, and any emerging important safety information as a part of the regular PSURs (PBRERs) for UMEC/VI and UMEC, which are provided in accordance with the European Union reference list. These updates are currently submitted every 6 months for the first 2 years (2014 and 2015) and

then annually after marketing in the EU for a further 2 years, and thereafter at 3 yearly intervals. It is expected that these PSUR updates will provide pertinent information to allow regular safety monitoring during the early phase of the study.

8.7. Data analysis

8.7.1. Essential analysis

A detailed Statistical Analysis Plan (SAP) will be prepared and finalised prior to the conduct of any study analysis or reporting. Full details on data transformations/derivations, categorical definitions, analyses, handling of missing data, and presentation of results will be described separately in the SAP.

Descriptive analyses

Details of patient enrolment and disposition will be provided in tables and/or figures.

The demographic and clinical profile of the study population will be described using data collected from the medical history during the pre-enrolment period and at the time of the enrolment visit. This profile will be inclusive of, but not limited to, details of COPD disease status, history of exacerbations and prior therapies, history of CV and cerebrovascular events and other medical history, overall and stratified according to treatment cohort (UMEC/VI, UMEC, and tiotropium). Summaries of the characteristics of each treatment cohort at the time of enrolment will be provided. Additionally, the balance in measured covariates between cohorts based on PS will be assessed using the average standardized absolute mean (ASAM) difference approach. ([McCaffrey, 2004](#))

Statistical analysis- General Considerations

Information will be collected for COPD medications taken in the 12 months prior to enrolment. Further information will be collected throughout the follow-up. A prescription which either overlaps with, or is recorded after, the prescription index date of study exposure will be accounted for in the analysis. Prior exposure will be used for propensity scores derivation; the use during follow-up will be accounted for in the analysis. Concomitant use of inhaled corticosteroids (ICS) is of particular interest as a potential indicator of a level of COPD severity, its worsening or lack of control. In addition to adding the ICS use in the multivariable models, the primary results will be stratified by concomitant ICS use (yes/no) as a sensitivity analysis. New users of tiotropium will be compared with new users of UMEC/VI and UMEC Mono, respectively, independent of whether these new users of tiotropium were exposed prior to or after index prescription date to LABA. The concomitant use of LABA will also be flagged and accounted for in the propensity scores and multivariable analysis as appropriate. If a high proportion of concomitant use of tiotropium and LABA is observed, which is not expected based on published literature, then a sensitivity analysis will be planned, possibly using a stratification approach.

Propensity scores (PS) will be used to adjust for differences in covariate balance between treatment groups (Rosenbaum, 1983; Stürmer, 2000). PS will be estimated separately for each treatment comparison (UMEC/VI versus tiotropium and UMEC versus tiotropium) using logistic regression to compute a predicted probability of initiating UMEC/VI or UMEC versus tiotropium. The estimated PS will then be used to ensure treatment cohorts are balanced on PS using stabilized inverse probability of treatment weighting (IPTW) (Robins, 2000) or other weighting approach prior to analysis. Sensitivity analyses will be defined in the SAP and may include PS matching or stratification as well as traditional multivariate regression methods to adjust for baseline covariates. Proportional hazards assumptions will be tested and, where not satisfied, techniques including testing model covariates for their impact on non-proportionality and using an interaction of a particular covariate with a function of time or stratification model applied as a solution. Further, methods using survival models which relax the proportional hazard assumption and support time-dependent behaviour of the hazard ratio will be considered.

Analyses corresponding to the primary objectives

- 1. To demonstrate non-inferiority of UMEC/VI combination and UMEC to tiotropium for risk of MI, stroke and heart failure individually based on an analysis of time to first event.*

Cox regression analyses will be used to compare the time to first event (MI, stroke, and new onset or acute worsening/decompensation heart failure) from start of initiated treatment between PS balanced cohorts of UMEC/VI and tiotropium initiators, and between PS balanced cohorts of UMEC and tiotropium initiators. The hazard ratio along with 95% confidence interval will be calculated for each treatment comparison for each endpoint. If the upper bound of the 95% confidence interval for the hazard ratio exceeds 2.0, the non-inferiority assumption will be rejected. If the lower bound of the 95% CI is

above 1.0, non-inferiority will not be assumed. Kaplan-Meier curves comparing the time to each endpoint for each treatment cohort will also be presented.

For the primary analysis, only events which were confirmed upon adjudication during the follow-up period will be included. The follow-up period for survival models will be defined as the period between the prescription index dates until the earliest of: date when the planned number of events has been reached or at an individual patient level: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death. Sensitivity analyses will include stratified analyses by age, gender, concomitant use of inhaled corticosteroids as well an application of alternative methods like matching by propensity scores and multivariate adjustment of un-balanced cohorts, in addition to the analysis of events observed and recorded during follow-up time until the earliest of: withdrawal from the study, conclusion of study follow-up or death.

2. To quantify the incidence rate and frequency of each of MI, stroke, and heart failure for new users of UMEC/VI combination, UMEC, and tiotropium.

Incidence rates (number of first events per person-year) of each of MI, stroke and new onset or acute worsening/decompensation heart failure will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with 95% confidence intervals. The number and percentage of patients with each event (MI, stroke, or new onset or acute worsening/decompensation heart failure), the total number of each event and the event rate (total number of each event per person-year) will also be summarised. Further, incidence rate ratios accompanied by 95% confidence intervals will be derived.

For the primary analysis, only events which were confirmed upon adjudication during the follow-up period will be included. The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

During the follow-up, a COPD patient can experience one or more events considered as the study outcome.

For myocardial infarction, all events from the prescription index date until censoring will be flagged and their distribution summarized per exposure cohort. Further, to address the primary objective, the first adjudicated event of myocardial infarction from the prescription index will be considered and time from new use start date to this first event ascertained. The denominator will consist of all new users. The presence of past events of myocardial infarction, as collected from available patients' history, will be considered as a covariate.

Identical analysis will be conducted for the event of stroke. Prior history of stroke will be considered as a covariate.

For newly diagnosed or acute decompensating/worsening congestive heart failure both patients with new diagnosis of congestive heart failure and acute decompensating/worsening congestive heart failure will be counted. The denominator

will consist of all new users. Again, prior history of heart failure will be considered as a covariate.

Incidence rates (number of first events per person-year) and 95% confidence intervals of each of MI, stroke and new onset or acute worsening/decompensation heart failure will additionally be computed for the following subgroups of the total cohort of tiotropium initiators: tiotropium Handihaler initiators, tiotropium Respimat initiators, generic tiotropium initiators. The number and percentage of patients with each event (MI, stroke, or new onset or acute worsening/decompensation heart failure), the total number of each event and the event rate (total number of each event per person-year) will also be summarised for these subgroups.

Full definitions of myocardial infarction, stroke and heart failure events are given in the protocol [APPENDIX 1](#). All events of any of the outcomes will be collected and the first event (adjudicated first event for the primary analysis) of each of the outcomes flagged. In case of a patient being diagnosed with more than one outcome, the following rule will apply: For individual analysis of each of the three primary outcomes of stroke, myocardial infarction and heart failure, a patient can contribute with their outcome into any of the three analyses. The first event (first adjudicated event for the primary analysis) of the respective outcome will be counted and the possible other outcomes, if occurring prior to index event, considered as a covariate..

Analyses corresponding to the secondary objectives

- 1. To compare UMEC/VI combination and UMEC to tiotropium for risk of the composite endpoint of MI, stroke, heart failure or sudden cardiac death based on an analysis of time to first event.*

Cox regression analyses will be used to compare the time to first composite event (MI, stroke, new onset or acute worsening/decompensation heart failure or sudden cardiac death) from start of initiated treatment between PS balanced cohorts of UMEC/VI and tiotropium initiators, and between PS balanced cohorts of UMEC and tiotropium initiators. The hazard ratio along with 95% confidence interval will be calculated for each treatment comparison. Kaplan-Meier curves comparing the time to first endpoint for each treatment cohort will also be presented.

For this analysis, only events which were confirmed upon adjudication during the follow-up period will be included. The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death

- 2. To quantify the incidence rate and frequency of the composite endpoint of MI, stroke, heart failure or sudden cardiac death for new users of UMEC/VI combination, UMEC, and tiotropium.*

Incidence rates (number of first event per person-year) of the composite of MI, stroke and new onset or acute worsening/decompensation heart failure or sudden cardiac death will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with the 95%

confidence intervals. The number and percentage of patients with a composite event and the total number of composite events will also be summarised.

For this analysis, only events which were confirmed upon adjudication during the follow-up period will be included. The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death

3. *To quantify the incidence rate and frequency of serious pneumonia/ serious LRTI (composite endpoint) for new users of UMEC/VI combination, UMEC, and tiotropium.*

Incidence rates (number of first events per person-year) of serious pneumonia/ serious LRTI as a composite endpoint will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and between PS balanced cohorts of UMEC and tiotropium initiators, along with 95% confidence intervals. The number and percentage of patients with serious pneumonia/serious LRTI, the total number of serious pneumonia/serious LRTI events and the event rate (total number of events per person-year) will also be summarised. Cox regression analyses will be used to compare the time to first event (serious pneumonia or serious LRTI) from start of initiated treatment between PS balanced cohorts of UMEC/VI and tiotropium initiators, and between PS balanced cohorts of UMEC and tiotropium initiators. The hazard ratio along with 95% confidence interval will be calculated for each treatment comparison. Kaplan-Meier curves comparing the time to each endpoint for each treatment cohort will also be presented.

In principle, it is expected that a patient will be recruited into this observational study at stable state. Any acute LRTI/pneumonia event prior to new exposure start will be recorded based on available history and accounted for in the analysis.

The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

4. *To quantify the overall mortality rate, cardiovascular and non cardiovascular mortality rates for new users of UMEC/VI combination, UMEC, and tiotropium*

Mortality rates (number of deaths per person-year) for all-cause mortality, CV mortality, and non-CV mortality will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and between PS balanced cohorts of UMEC and tiotropium initiators, along with 95% confidence intervals. The number and percentage of patients who died and the total number of deaths (all-cause, adjudicated CV and adjudicated non-CV and undefined) will be reported.

For this analysis, only events which were confirmed upon adjudication during the follow-up period will be included. The follow-up period will be defined as the period between the prescription index dates until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

Analyses corresponding to other safety objectives

1. *To quantify the incidence rate and frequency of haemorrhagic stroke, ischaemic stroke and undefined stroke for new users of UMEC/VI combination, UMEC, and tiotropium.*

Incidence rates (number of first events per person-year) for type of stroke events (ischaemic stroke, haemorrhagic stroke and undefined stroke) will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with 95% confidence intervals. The number and percentage of patients with each event and the total number of each event will also be summarised.

The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

2. *To quantify the incidence rate and frequency of hospitalisation for heart failure for new users of UMEC/VI combination, UMEC, and tiotropium*

Incidence rates (number of first events per person-year) of hospitalisation for heart failure will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with the 95% confidence intervals. The number and percentage of patients with the event the total number of events and the event rate will also be summarised.

The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

3. *To quantify the incidence rate and frequency of reported SAEs and drug-related AEs for new users of UMEC/VI combination, UMEC, and tiotropium.*

Incidence rate (number of first events per person-year) will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with the 95% confidence intervals. The number and percentage of patients with the event and the total number of each event will also be summarised. AEs will be summarised according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT).

The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

Characteristics of patients with SAEs will be summarised in a listing of individual SAE events in study reports. These characteristics may include medical history including recent use of UMEC/VI, UMEC, or tiotropium, use of other COPD medications, exacerbations, underlying medical conditions, respiratory and other concomitant medication use, and dosing/timing of administration of study medications and other clinically relevant events and procedures.

Characteristics of patients with drug-related AEs will be reported similarly.

Case narratives will be provided for each SAE and drug related AE.

4. *To quantify the incidence rate and frequency of serious CV AESIs, including transient ischaemic attacks and angina pectoris cardiac arrhythmias (including Torsades de Pointes), acquired long QT, heart failure, cardiac ischaemia, and hypertension for new users of UMEC/VI combination, UMEC, and tiotropium.*

Incidence rates (number of first events per person-year) of the specified serious CV AESIs computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with 95% confidence intervals. The number and percentage of patients with each event) and the total number of each event will also be summarised.

The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

Analyses corresponding to effectiveness objectives

1. *To quantify persistence with study medication for new users of UMEC/VI combination, UMEC, and tiotropium.*

Persistence (adherence) will be assessed by describing treatment patterns including time to discontinuation of initiated COPD medication or switch in therapy; the proportion of days covered (PDC) during follow-up and MPR.

Medication possession ratio (MPR) will be calculated by summing the number of days supplied for all but the last prescription before the patient switched or discontinued the index medication and divided by the number of days between the first and last prescription (Note: each patient will have a unique denominator). Additions to the original medication are allowed as long as the patient is still exposed to the index medication. The MPR will be expressed as a percentage, with non-adherence primarily defined as MPR <80% and adherence defined as MPR ≥80%.

Proportion of days covered (PDC) will be calculated as the number of days for which the patient had possession of the initially prescribed medication divided by the number of days in the specified time period of 364.25 days for a given 0-12 month time period.

Cox regression analysis will be used to compare the time to (earliest of) discontinuation of initiated COPD medication (including death or withdrawal from the study), or change in COPD maintenance medication from start of initiated treatment within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators. The hazard ratio along with 95% confidence interval will be calculated for each treatment comparison. Kaplan-Meier curves comparing the time to endpoint for each treatment cohort will also be presented. The MPR and the proportion of days covered (PDC) during follow-up based on prescription dates will also be reported.

2. *To quantify the incidence rate and frequency of moderate/severe COPD exacerbation (requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalisation) for new users of UMEC/VI combination, UMEC, and tiotropium.*

Cox regression analyses will be used to compare the time to first moderate/severe COPD exacerbation (requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalisation) from start of initiated treatment within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators. The hazard ratios along with 95% confidence intervals will be calculated for each treatment comparison. Kaplan-Meier curves comparing the time to first moderate/severe exacerbation for each treatment cohort will also be presented.

Incidence rate (number of first events per person-year) of moderate/severe exacerbation will be computed within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with the 95% confidence intervals. The number and percentage of patients with moderate/severe COPD exacerbations and the event rate (total number of events per person-year) will also be summarised.

The follow-up period will be defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

3. *To quantify all cause and COPD related health-care utilisation for new users of UMEC/VI combination, UMEC, and tiotropium.*

The incidence rate, the number and percentage of patients with an event, the total number of events and the event rate will be calculated for hospital admission (COPD-related and all-cause), emergency department visits (COPD-related and all-cause) and contacts with primary and secondary care within PS balanced cohorts of UMEC/VI and tiotropium initiators, and within PS balanced cohorts of UMEC and tiotropium initiators, along with 95% confidence intervals.

Follow-up time will be defined as the period between the prescription index date until the earliest of: 14 days following discontinuation of COPD medication, withdrawal from the study, conclusion of study follow-up or death.

8.7.2. Exploratory analysis

Additional analyses will be outlined in the SAP prior to analysis.

8.7.3. General considerations for data analyses

All AE verbatim terms will be recorded and coded using the most recent version of MedDRA. Concomitant medication will be coded using a GSK validated medication dictionary, GSKDrug.

All computations and generation of tables, listings and data for figures will be performed using Statistical Analysis Software (SAS) version 9.2 or higher (SAS Institute, Cary, NC, USA).

Full details on handling of all missing data, which are common in observational studies, will be described separately in the SAP. The proportion of missing data will be reported for each measured variable in the study. In general, missing data will not be imputed and the data will be analysed as they are recorded in the study eCRFs.

8.8. Quality control

A study monitoring plan, including for-cause monitoring, that is appropriate for the study design will be developed and implemented.

During the site initiation visit, the monitor will provide training on the conduct of the study to the investigator, co-investigator(s), and all site staff involved in the study. In order to ensure the integrity of the data, sites will be monitored. Site monitoring will be conducted according to the approved study monitoring plan to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study. The monitor will perform source data verification by review of original patient records.

The monitor will close out each site after the last patient's final follow-up assessment is completed, all data have been entered and all outstanding monitoring issues have been resolved or addressed. All monitoring procedures and frequency of monitoring visits will be described in a Monitoring Plan. Monitor contact details for each participating site will be maintained in the Investigator Site File.

Representatives of the Sponsor's quality assurance unit/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs and the patients' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

8.9. Limitations of the research methods

Potential limitations of the study design and measures proposed to address them include the following:

Enrolment bias: sites will be expected to enrol all eligible patients that present at their site (subject to enrolment caps being imposed on a specific treatment group) and maintain screening logs of all patients meeting eligibility criteria, along with reasons for non-enrolment of otherwise eligible patients.

Channelling bias: factors associated with treatment choice (UMEC/VI, UMEC, or tiotropium) and also with any of the study outcomes of interest will be measured at enrolment and accounted for through PS methods or other multivariate analyses, as described further in Section 8.7. These factors include prescribing pattern differences across practices and countries and reimbursement differences

Healthy user bias/depletion of susceptibles: long-term users of a given medication have generally shown tolerance to the drug and may be at lower risk of CV events than new

users. Since patients will be enrolled at the time of initiation of a new medication regimen (new user study design), this will eliminate to a large extent bias associated with the study of prevalent medication users. It is acknowledged that patients may have used a previous LAMA medication as recently as 12 months prior to study enrolment; however, this liberal definition of “new user” is intended to be inclusive and representative of the population of patients who initiate use of UMEC/VI, UMEC, or tiotropium for COPD in order to characterize their comparative safety.

Inconsistent interpretation of eCRFs by participating centres: all centres/sites will undergo standardised training and utilise standardised documentation for completing of case report forms at enrolment and for each follow-up assessment.

Follow-up bias: a low lost to follow-up rate of less than 5% is expected, in part due to the ability to follow up directly with patients even if they do not return to the enrolling centre. Maintaining a low rate of lost to follow-up will lower the risk of bias that could result, for example, if patients with AEs were less likely to return to the study physician for follow up. Patients will be asked at the 6 and 18 month follow-ups if they have changed their health care provider and if so to provide the name and contact information for their new physician.

Representativeness of COPD population: The study’s new user design will recruit and enrol patients newly prescribed UMEC/VI, UMEC or tiotropium for COPD. While the selection of study sites and countries will be planned to be reflective of the subpopulation of COPD patients initiating new treatment with UMEC/VI, UMEC, or tiotropium, these patients may differ from the broader population of COPD patients, and are expected to comprise either younger and less severe patients recently diagnosed or previously managed with only short-acting medicines or patients adding LAMA to ICS/LABA who may be more severe patients with exacerbations or asthma-COPD overlap syndrome (ACOS). While this is not a limitation or challenge to the internal validity of the study in addressing its primary and secondary objectives among patients meeting the study inclusion and exclusion criteria, it should be noted as a potential limitation to the extrapolation of the results to the broader population of COPD patients.

Recruitment of patients treated with newly approved medications: uptake of new products such as UMEC/VI and UMEC is unpredictable and has the potential to impact the feasibility of meeting the recruitment targets, overall, and within each of the three treatment groups. However, continuous monitoring of subject recruitment at the site and country levels will allow strategies to be employed in response to any such challenges and to reduce or eliminate the potential impact of these factors. These include potentially imposing temporary or permanent caps on enrolment for a specific treatment group, initiation of additional sites within participating countries, and/or expansion of the study into additional countries. Temporary or permanent enrolment caps are one of the few tools available in an observational study to ensure that equal numbers of patients are enrolled in each treatment cohort when the frequency of prescribing differs across the treatments of interest in the eligible patient population. Enrolment caps on one or more specific treatment cohorts would be implemented at the country level or study level, not at the site level so as to minimize the likelihood of any impact on prescribing. As sites will be trained and clearly instructed that the treatment decision should be independent of

enrolment into the study, the potential for use of enrolment caps on a given treatment cohort(s) to influence the treatment decision should be no different than in an observational study of a single treatment where other treatments for the indication of interest exist.

8.9.1. Study closure/uninterpretability of results

The planned study closure is 3Q 2024, at the scheduled time of the final report of results. The end of study follow-up is projected to occur approximately 48 months following the inclusion of the last patient in the study.

The study can be terminated at any time for any reason by GSK in consultation with PRAC. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing institutional review board (IRB)/independent ethics committee (IEC) of the early termination of the study. The early termination of the study is considered a major amendment; therefore, the relevant competent authorities will be notified before a final decision is made and approval for termination is granted.

8.10. Other aspects

8.10.1. Changes to the protocol

Changes to the protocol will be documented in written protocol amendments. Major (i.e. substantial, significant) amendments will be approved by the relevant regulatory authorities and will usually require submission or notification to the relevant IRB/IEC for approval or favourable opinion, if applicable. In such cases, the amendment will be implemented at the site only after approval or favourable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed at each participating site and will be submitted to the relevant IRB/IEC or regulatory authorities where required by pertinent regulations. Any amendment that could have an impact on the patient's agreement to participate in the study requires the patient's informed consent prior to continued participation in the study.

8.10.2. Study governance and committees

The study will be conducted in close collaboration with two independent committees, comprised of qualified individuals with relevant experience and expertise. Each independent committee will be governed by a Charter, detailing responsibilities and processes.

The approximate composition of the Scientific Steering Committee (SSC) is seven external members with relevant clinical and epidemiologic experience, as well as four GSK employees, and one representative from Quintiles. The SSC will provide expert medical and epidemiological input and advice, review the interim and final reports of safety data, and monitor the overall study progress through regular teleconferences and meetings. The SSC will meet during the protocol development and thereafter

approximately every six months to review all interim study data and to make recommendations regarding the ongoing conduct and analysis of the study.

An EAC will be implemented to adjudicate CV and cerebrovascular events of interest (specifically, MI, stroke, and heart failure and CV death) in a blinded fashion continuously throughout the study. The EAC will include four independent medical specialists in cardiology and one neurologist who will conduct a blinded review of relevant data and documentation and validate events as confirmed or unconfirmed based on a predefined algorithm. The EAC charter will describe a process for reconciliation of multiple independent reviews from the committee members.

9. PROTECTION OF HUMAN SUBJECTS

To ensure the quality and integrity of research, this study will be conducted under the Guidelines for Good Pharmacovigilance Practices (GVPs) and Good Pharmacoepidemiology Practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE) (ISPE, 2008), the Declaration of Helsinki ([Declaration of Helsinki](#), 2008) and its amendments, and any applicable national guidelines.

9.1. Ethical approval and subject consent

An informed consent form (ICF) must be signed by the patient (or the patient's legally authorised representative) before his or her participation in the study. The medical file for each patient must document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed ICF must be provided to the patient or the patient's legally authorised representative. If applicable, it will be provided in a certified translation of the local language. All signed and dated ICFs must remain in each patient's study file and must be available for verification by study monitors at any time.

The ICF must be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate. For any updated or revised ICFs, the medical file for each patient must document the informed consent process and that written informed consent was obtained for the updated/revised ICF for continued participation in the study.

The informed consent will ensure that patients agree to the collection of PROs at enrolment visits and to provide contact details to the CRO only for direct follow-up if needed to collect data from a missing visit. Patients will also be asked to provide a secondary contact for follow-up should the patient be unreachable. All patient facing documents, including the informed consent, will undergo local language translation and back translation with a qualified vendor. A translation certificate will be provided for all such translations.

9.2. Subject confidentiality

In order to maintain patient confidentiality, each patient will be assigned a unique patient identifier upon study enrolment. This patient identifier will be used in place of patient name for the purpose of data analysis and reporting. Medical record number or other

local reference identifiers are not collected as part of the study database. All parties will ensure protection of patient personal data and will not include patient names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the countries in which the study is implemented, patients will be informed about data handling procedures and asked for their consent. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Every effort will be made to protect participant confidentiality according to the [Directive 95/46EC](#) on the protection of individuals, and in compliance with Safe Harbour privacy principles.

The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system meets approved established standards for the security of health information and is validated. The system also meets the standards of the International Conference on Harmonisation (ICH) guideline E6R1 regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

If, during the study, an adverse event (serious or non serious) is identified as explicitly attributed to any GSK product (including products not covered in the specific study objective), this will be reported to Quintiles. Quintiles will then inform GSK Global Clinical Safety and Pharmacovigilance within 24 hours of receiving the information.

10.1. Adverse events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE explicitly attributed to study treatment or to any GSK products, adverse events of special interest and SAEs. All SAEs are to be reported in the study by the investigator in the eCRF.

Non-serious CV AESI and non-serious pneumonia/LRTI are to be reported in this study by the investigator into the eCRF. All other non-serious events are to be reported by the site investigator to GSK via national reporting systems.

Definition of an AE

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

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This must be reported regardless of sequelae.

“Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE of special interest or SAE.

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject’s condition.

10.1.1. Definition of an SAE

An SAE is any untoward medical occurrence that, at any dose:

- a. Results in death
- b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- c. Requires hospitalisation or prolongation of existing hospitalisation

NOTE: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency department for observation and/or treatment that would not have been appropriate in the physician’s office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalisation” occurred or was necessary, the AE must be considered serious.

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

d. Results in disability/incapacity, or is a congenital anomaly/birth defect

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These must also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

All events of possible drug-induced liver injury with hyperbilirubinaemia defined as alanine transaminase (ALT) $\geq 3x$ upper limit of normal (ULN) and bilirubin $\geq 2x$ ULN ($>35\%$ direct) (or ALT $\geq 3x$ ULN and International normalized ratio (INR) >1.5 , if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

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

10.1.2. Sentinel events

A Sentinel Event is a GSK-defined SAE that has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. Medical monitor review of all SAEs for possible Sentinel Events is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

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

10.2. Cardiovascular and Cerebrovascular Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting all CV and cerebrovascular AEs in the eCRF.

10.2.1. Cardiovascular and Cerebrovascular AEs of Special Interest

The following are considered to be CV and cerebrovascular AEs of special interest :

- MI/unstable angina
- Heart failure
- Arrhythmias (including Torsades de Pointes)
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and TIA
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation
- Escalation of treatment for or new diagnosis of hypertension

This information must be recorded within one week of when the AE/SAE(s) are first reported.

10.2.2. Death events

In addition, all deaths will be recorded in the eCRF which includes questions regarding CV (including sudden cardiac death and non-CV death). This must be recorded within one week of when the death is first reported.

10.2.3. Pneumonia/LRTI events

All pneumonia/LRTI AEs are to be reported by the investigator in the eCRF within one week of when the event is first reported.

10.3. Disease-related events and/or disease-related outcomes not qualifying as SAEs

The following disease related events (DREs) are common in subjects with COPD and can be serious/life threatening:

- COPD exacerbation

COPD exacerbations are associated with the disease to be studied and will not be reported as AEs unless the exacerbation meets the definition of a 'serious' AE as defined in Section 10.1.1. Exacerbations that meet the definition of 'serious' AEs will be recorded on the appropriate eCRF section and must be reported to GSK.

Additionally, all moderate/severe exacerbations, defined as an acute worsening of symptoms requiring treatment with one or more of the following: antibiotics, systemic

steroids, hospitalisation, should be recorded in the COPD exacerbation eCRF page regardless of whether they met the criteria of an SAE or not.

10.4. Pregnancy

Any pregnancy that occurs during study participation must be reported using a specific pregnancy form. To ensure subject safety, each pregnancy must be reported within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

10.5. Time period and frequency of detecting AEs and SAEs

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE explicitly attributed to study treatment or to any GSK products as well as AESI and SAEs.

These events will be collected from the start of study treatment until the end of the observation period.

10.6. Detecting method and evaluation of AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

“How are you feeling?”

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

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

10.6.1. Assessment of AEs and SAEs intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgement. The intensity of each AE and SAE will be recorded on the AE/SAE eCRF as per the instructions and will be assigned to one of the following categories:

Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities

An AE that is assessed as severe is not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as “serious” when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

The maximum intensity/grade that occurred over the duration of the event must be recorded. Intensity/grade is utilized to rate the severity of the event. It is not the same as seriousness.

10.6.2. Assessment of causality

The investigator is obligated to assess the relationship between the products in observation and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there is facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the nature of the relationship and must indicate any other products that the event may be due to.

Alternative causes, such as natural history of the underlying diseases, concomitant medication, other risk factors, and the temporal relationship of the event to the product will be considered and investigated. The investigator will also consult the Product Information for marketed products in the determination of his/her assessment.

There may be situations when 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 makes an assessment of causality for every event prior to the initial transmission of the SAE. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.6.3. Prompt reporting of adverse events to GSK

AEs explicitly attributed to study treatment or to any GSK product, AESI and SAEs will be reported promptly by the investigator to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

Type of Event	Initial Reports		Follow-up Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
All SAEs	Within 24 hours of becoming aware	“SAE” data collection tool	24 hours	Updated “SAE” data collection tool
CV and Pneumonia/LRTI Non-serious adverse events of special interest	Within five calendar days of becoming aware	“AE” data collection tool	two weeks	Updated “AE” data collection tool
Non-serious adverse events related to study treatment or to any GSK products	Within five calendar days of becoming aware	“AE” data collection tool	Two weeks	Updated “AE” data collection tool
Pregnancy	Within two weeks of becoming aware	“Pregnancy” data collection tool	Two weeks	“Pregnancy” data collection tool
Cardiovascular or death event or pneumonia	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	“CV events” and/or “death” and or “pneumonia” data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated “CV events” and/or “death” and or “pneumonia” data collection tool(s) if applicable

All other events must be reported to either the manufacturer of that product or to the competent authority as per local regulations.

Additional details regarding definitions and reporting procedures will be provided in the Safety. Management Plan.

10.6.3.1. Regulatory reporting requirements for AEs and SAEs

GSK will provide information on relevant AEs to the regulatory authorities, as needed, according to the European Medicines Agency (EMA, 2012) Guideline on Module VI and other applicable local regulations.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target audience

The information generated by this study will be transmitted to Regulatory Authorities as required, primarily the EMA, and will contribute to the published literature. The results may be disseminated externally via manuscripts or presentations (see Section 11.2).

11.2. Study reporting and publications

Progress reports

Progress reports will be submitted to relevant competent authorities, as required. From the date of the international birthday: 18 December 2013 for UMEC/VI and 17th April 2014 for UMEC. PSURs and PBRERs are provided either upon request or every six months for the first two years, and then on an annual basis for years three through five, then every 3 years.

Final analyses and reporting

A final study report will be generated after all data collection is complete and will be submitted to the competent authorities within 12 months of the end of data collection. The final report will encompass all planned analyses, including a description of the complete study population, as described above and in the SAP.

In accordance with the 2010 EU pharmacovigilance legislation, information about this Post-authorisation Safety Study will be entered into the publically available European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) E-Register of Studies. The study protocol will be entered into the register before the start of data collection and will also be entered into clinicaltrials.gov. Updates to the study protocol in case of substantial amendments, progress reports where applicable, and the final study report will also be entered in the register.

Any publication of the results from this study will be consistent with GSK's publication policy and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated April 2010 (ICMJE, 2010). The rights of the Investigator and of the Sponsor with regard to publication of the results of this study are described in the Investigator contract. To comply with the requirements of the EU Pharmacovigilance Regulation, final manuscript of the article will be submitted to the Agency and competent authorities, within two weeks of first acceptance for publication.

All reporting will be consistent with Strengthening the Reporting of Observational studies in Epidemiology (STROBE, 2008) initiative checklist for cohort studies.

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13. APPENDIX 1– CLINICAL EVENT DEFINITIONS FOR MYOCARDIAL INFARCTION, STROKE, AND HEART FAILURE EVENTS

MYOCARDIAL INFARCTION

General Considerations

The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

In general, the diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); *And*
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

Criteria for Myocardial Infarction

1. Clinical Presentation

The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, congestive heart failure, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process.

2. Biomarker Elevations

For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the URL from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision

limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. In general, troponins are preferred. CK-MB should be used if troponins are not available, and total CK may be used in the absence of CK-MB and troponin.

For MI subtypes, different biomarker elevations for CK, CK-MB, or troponin will be required. The specific criteria will be referenced to the URL.

3. Electrocardiogram (ECG) Changes

Electrocardiographic changes can be used to support or confirm a MI. Supporting evidence may be ischaemic changes and confirmatory information may be new Q waves.

- **ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):**
 - ST elevation: New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women.
 - ST depression and T-wave changes: New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or new T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio > 1 .

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognised that lesser ECG abnormalities may represent an ischaemic response and may be accepted under the category of abnormal ECG findings.

- **Criteria for pathological Q-wave**
 - Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
 - Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, and aVF)*

*The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

- **ECG changes associated with prior myocardial infarction**
 - Pathological Q-waves, as defined above
 - R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

- **Criteria for prior myocardial infarction**

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischaemic causes
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause

- Pathological findings of a prior myocardial infarction

Universal Classification of Myocardial Infarction

Type 1: Spontaneous myocardial infarction

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, Assuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2: Myocardial infarction secondary to an ischaemic imbalance

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)

Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values $>5 \times 99$ th percentile URL in patients with normal baseline values (<99 th percentile URL) or a rise of cTn values $>20\%$ if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischaemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Type 4b: Myocardial infarction related to stent thrombosis

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/ or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)

Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values $>10 \times 99$ th percentile URL in patients with normal baseline cTn values (<99 th percentile URL). In addition, either (i) new pathological Q waves or new LBBB,

or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

STROKE

The distinction between a transient ischaemic attack and an ischaemic stroke is the presence of infarction. Persistence of symptoms is an acceptable indicator of acute infarction. Thus, duration of symptom persistence that will be used to distinguish between transient ischemia and acute infarction should be defined for this endpoint.

Subdural and epidural hematomas are intracranial haemorrhagic events and not strokes.

All strokes will be classified into one of the categories below:

- Haemorrhagic
- Ischaemic
- Undefined

Transient Ischaemic Attack

Transient ischaemic attack (TIA) is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, *without* acute infarction.

Diagnosis of stroke is based on clinical presentation (signs), duration and confirmatory investigations.

Clinical Presentation (At least 1 new neurological sign):

- Hemiplegia
- Hemianesthesia
- Hemiparesis
- Dysphasia
- Vertigo
- Diplopia
- Dysphagia
- Loss of vision on one side
- Amaurosis fugax
- Global amnesia
- Bilateral or alternating weakness or sensory symptoms
- Sensory loss
- Dysathria
- Ataxia
- Drop attacks
- Other neurological sign

Duration (must be either ≥ 24 hours or ≤ 24 hours because of a pharmacologic or non-pharmacologic intervention).

Confirmatory Investigations (At least 1):

- Neurologist evaluation
- Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

- Brain image study or procedure
 - Computed tomography (CT) scan
 - Magnetic resonance imaging ± magnetic resonance angiography (MRI ±MRA)
 - Cerebral vessel angiography

All strokes will be classified into one of the categories below:

- Ischaemic Stroke

Ischaemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue. Hemorrhage may be a consequence of ischaemic stroke. In this situation, the stroke is an ischaemic stroke with haemorrhagic transformation and not a haemorrhagic stroke.

- Haemorrhagic Stroke

Haemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

- Undefined Stroke

Undefined stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction but with insufficient information to allow categorization as ischaemic or haemorrhagic stroke.

- For haemorrhagic or undefined

strokes, association with trauma is determined based on the event narrative and on the imaging studies.

HEART FAILURE EVENT AND HOSPITALISATION

Hospitalisation is defined as admission, overnight or longer, to a hospital setting (emergency room, observation or inpatient unit), or equivalent, including admission to a day care facility.

Diagnosis of heart failure by at least 1 of the following symptoms and signs PLUS at least 1 of the following : medication/supportive measures or objective evidence of ventricular dysfunction.

Symptoms:

- Newly developed or worsening increasing dyspnea at rest or with exertion
- Newly developed or worsening orthopnea
- Newly developed or worsening PND (paroxysmal nocturnal dyspnea)

AND

Signs:

- Newly developed or worsening increasing peripheral edema
- Newly developed or worsening pulmonary basilar crackles/post-tussive rales
- Newly developed or worsening jugular venous distension
- Newly developed or worsening third heart sound or gallop rhythm
- Chest x-ray evidence of pulmonary venous congestion
- Renal hypoperfusion (worsening renal function) with no other apparent cause
- Pleural effusion
- Signs of cardiogenic shock

AND EITHER

Medication/Supportive Measures:

- Medication (**specifically for the treatment of worsening heart failure**)
 - New or additional oral diuretic
 - Intravenous diuretic
 - Intravenous vasodilator
 - Intravenous inotrope
 - Intravenous digitalis glycosides
 - Other
- Supportive Measures
 - CPAP (continuous positive airway pressure)
 - Mechanical ventilation
 - Mechanical support (e.g. intra-aortic balloon pump, ventricular assist device)
 - Other

OR

Objective Evidence of Ventricular Dysfunction:

Elevated BNP. BNP ≥ 400 pg/mL OR the following NT-proBNP levels according to age: <50 years, ≥ 450 ng/L; 50-75 years, ≥ 900 ng/L; >75 years, ≥ 1800 ng/L (45, 46). BNP 100-400 pg/mL (or NT-proBNP levels below the thresholds according to age given above) is not sufficient alone, evidence of structural heart disease is also required, see bullet below.

Structural heart disease with documentation of systolic dysfunction (LVEF <40%)

Diastolic dysfunction defined as: LV mass >95 g/m² (linear method) or >88 g/m² (2D method) in women; >115 g/m² (linear method) or >102 g/m² (2D method) in men, or E/A >1, or mitral (E wave) deceleration time <200 ms

Heart failure will be further classified into one of the categories below:

Left ventricular failure

Radiological evidence of pulmonary congestion and/or echocardiographic evidence of LV structural heart disease as mentioned above.

Isolated right ventricular failure

RV function (e.g., TAPSE) is reduced (TAPSE <16 mm). Tricuspid regurgitation peak velocity is increased (>3.4 m/s), suggesting increased RV systolic pressures. Systolic pulmonary artery pressure may be increased (>50 mm Hg) with pulmonary hypertension. The inferior vena cava may be dilated, with no respiratory collapse, suggesting increased right atrial pressures, RV dysfunction, volume overload, or pulmonary hypertension.

No signs of radiological evidence of pulmonary congestion and/or echocardiographic evidence of LV structural heart disease as mentioned above.

Both left and right ventricular failure

Radiological evidence of pulmonary congestion and/or echocardiographic evidence of LV structural heart disease as mentioned above. Furthermore RV function (e.g., TAPSE) is reduced (TAPSE <16 mm). Tricuspid regurgitation peak velocity is increased (>3.4 m/s), suggesting increased RV systolic pressures. Systolic pulmonary artery pressure may be increased (>50 mm Hg) with pulmonary hypertension. The inferior vena cava may be dilated, with no respiratory collapse, suggesting increased right atrial pressures, RV dysfunction, volume overload, or pulmonary hypertension.

DEATH

All deaths will be reviewed by the adjudicators to determine the cause of death, which will be classified as, cardiovascular death or non-cardiovascular death.

Definition of Cardiovascular Death

Cardiovascular death includes death resulting from an acute MI, sudden cardiac death, death due to HF, death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.

1. Death due to Acute Myocardial Infarction refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease [PAD]) \leq 30 days after an MI related to the immediate consequences of the MI, such as progressive heart failure or recalcitrant arrhythmia. We note that there may be assessable mechanisms of cardiovascular death during this time period, but for simplicity, if the cardiovascular death occurs \leq 30 days of the myocardial infarction, it will be considered a death due to myocardial infarction.

Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by post mortem findings showing recent MI or recent coronary thrombosis.

Death resulting from a procedure to treat a MI (PCI, CABG), or to treat a complication resulting from MI, should also be considered death due to acute MI.

Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

2. Sudden Cardiac Death refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:

- Death witnessed and occurring without new or worsening symptoms
- Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
- Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
- Death after unsuccessful resuscitation from cardiac arrest
- Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology
- Unwitnessed death in a subject seen alive and clinically stable \leq 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

General Considerations

Unless additional information suggests an alternate specific cause of death (e.g., death due to other cardiovascular causes), if a patient is seen alive \leq 24 hours of being found dead, sudden cardiac death should be recorded. For patients who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (e.g., a subject found dead in bed, but who had not been seen by family for several days).

3. Death due to Heart Failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF aetiology. Deaths due to heart failure can have various aetiologies, including single or recurrent myocardial infarctions, ischaemic or non-ischaemic cardiomyopathy, hypertension, or valvular disease.

4. Death due to Stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

5. Death due to Cardiovascular Procedures refers to death caused by the complications within 30 days of a cardiac procedure.

6. Death due to Cardiovascular Hemorrhage refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

7. Death due to Other Cardiovascular Causes refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or PAD).

8. Death due to Undetermined Cause of Death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is “patient died”) or when there is insufficient supporting information or detail to assign the cause of death. This category of death should be avoided as much as possible and should only apply to a minimal number of patients.

Definition of Non-Cardiovascular Death

Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. The following is a suggested list of non-cardiovascular causes of death:

- Pulmonary
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome [SIRS])
- Hemorrhage that is neither cardiovascular bleeding or a stroke
- Non-CV procedure or surgery
- Trauma
- Suicide
- Non-prescription drug reaction or overdose
- Prescription drug reaction or overdose
- Neurological (non-cardiovascular)
- Malignancy
- Other non-CV, specify: _
- Renal

ANNEX 1. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

<u>Section 1: Research question</u>	Yes	No	N/A	Page Number(s)
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	28
1.1.2 The objectives of the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	31
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	32
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	31
1.2.3 if applicable, that there is no <i>a priori</i> hypothesis?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

The study is designed to evaluate a non-inferiority hypothesis regarding the cardiovascular and cerebrovascular safety of UMEC/VI and UMEC each compared with tiotropium. Consistent with an observational design this is stated in the primary objective rather than as formal statements of null and alternative hypotheses.

<u>Section 2: Source and study populations</u>	Yes	No	N/A	Page Number(s)
2.1 Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	32
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	35
2.2.2 Age and sex?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	35
2.2.3 Country of origin?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	34
2.2.4 Disease/indication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	32
2.2.5 Co-morbidity?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<u>Section 2: Source and study populations</u>	Yes	No	N/A	Page Number(s)
2.2.6 Seasonality?	<input type="checkbox"/> <input type="checkbox"/>		<input checked="" type="checkbox"/>	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	35

Comments:

The study population is not restricted with regard to age or gender.

<u>Section 3: Study design</u>	Yes	No	N/A	Page Number(s)
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	31
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	32
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	49
3.4 Is sample size considered?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	47
3.5 Is statistical power calculated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	48

Comments:

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<u>Section 4: Data sources</u>	Yes	No	N/A	Page Number(s)
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	35
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	41
4.1.3 Covariates?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	39
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	35
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	41
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	39
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	57
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	46
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

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<u>Section 5: Exposure definition and measurement</u>	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	38
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	38
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	38
5.4 Is exposure classified based on biological mechanism of action?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	38
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

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<u>Section 6: Endpoint definition and measurement</u>	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	36, 62
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	36 62

Comments:

The primary endpoints of MI, stroke, and heart failure will be adjudicated by the Endpoint Adjudication Committee.
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<u>Section 7: Biases and Effect modifiers</u>	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address: 7.1.1 Selection biases? 7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	39
	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	39
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	39
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	39
7.4 Does the protocol address other limitations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	59

Comments:

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<u>Section 8: Analysis plan</u>	Yes	No	N/A	Page Number(s)
8.1 Does the plan include measurement of absolute effects?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	49
8.2 Is the choice of statistical techniques described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	49
8.3 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	49
8.4 Are stratified analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	49
8.5 Does the plan describe the methods for identifying:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	39
8.5.1 Confounders?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		39
8.5.2 Effect modifiers?				
8.6 Does the plan describe how the analysis will address:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	49
8.6.1 Confounding?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	49
8.6.2 Effect modification?				

Comments:

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<u>Section 9: Quality assurance, feasibility and reporting</u>	Yes	No	N/A	Page Number(s)
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	49
9.2 Are methods of quality assurance described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	49
9.3 Does the protocol describe quality issues related to the data source(s)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	49
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	36
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	28
9.5.2 Any progress report?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	28
9.5.3 End of data collection?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	28
9.5.4 Reporting? (i.e. interim reports, final study report)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	28
9.6 Does the protocol include a section to document future amendments and deviations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	28
9.7 Are communication methods to disseminate results described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	61
9.8 Is there a system in place for independent review of study results?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	61

Comments:

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<u>Section 10: Ethical issues</u>	Yes	No	N/A	Page Number(s)
10.1 Have requirements of Ethics Committee/Institutional Review Board approval	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	61

<u>Section 10: Ethical issues</u>	Yes	No	N/A	Page Number(s)
been described?				
10.2 Has any outcome of an ethical review procedure been addressed?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.3 Have data protection requirements been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	62

Comments:

Name of main author of study protocol: ██████████

Date: / /

Signature: _____