TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Study Protocol

Title:	WWE117397: Post-authorization safety Electronic Medical Records database retrospective cohort study of new users of inhaled UMEC/VI or new users of inhaled UMEC in the primary care setting- Amendment 2

Compound Number: GSK573719, GW642444

Development Phase IV

Effective Date: 14 SEP 2018

Subject: Drug Utilization Study, Post-Authorization Safety Study, Chronic Obstructive Pulmonary Disease, Electronic Medical Records, Long-Acting Muscarinic Antagonists, Long-Acting Beta-2-Agonists

Author(s): PPD

PASS information

Title	Post-authorization safety Electronic Medical Records database retrospective cohort study of new users of inhaled UMEC/VI or new users of inhaled UMEC in the primary care setting
Protocol version identifier	1.2
Date of last version of protocol	24 June 2016
EU PAS register number	ENCEPP/SDPP/7761
Active substance	Umeclidinium bromide/Vilanterol trifenatate (UMEC/VI) ATC R03AL03: Adrenergics in combination with anticholinergics Umeclidinium bromide (UMEC) ATC R03BB07: Anticholinergics
Medicinal product	UMEC (Incruse Ellipta™Rolufta Ellipta™), UMEC/VI (Anoro Ellipta™ /Laventair Ellipta™) OTHER long-acting bronchodilators will be included in the study analysis, provided they will be available to prescribers, inclusive but not limited to medications containing: Tiotropium Glycopyrronium Glycopyrronium/Indacaterol Aclidinium Indacaterol Formoterol Salmeterol

Product reference	The EU Marketing Authorisation numbers are: Anoro Ellipta EU/1/14/898/001 EU/1/14/898/002 EU/1/14/898/003 Laventair Ellipta: EU/1/14/899/001 EU/1/14/899/002 EU/1/14/899/003 Incruse Ellipta: EU/1/14/922/001 EU/1/14/922/002 EU/1/14/922/003 Rolufta Ellipta: EU/1/17/1174/001 EU/1/17/1174/002 EU/1/17/1174/003
Procedure number	Incruse Ellipta: EMEA/H/C/002809/0000 Rolufta Ellipta: EMEA/H/C/004654/0000 Anoro Ellipta: EMEA/H/C/002751/0000/ Laventair Ellipta: EMEA/H/C/003754
Marketing authorisation holder(s)	GlaxoSmithKline Research & Development Limited 980 Great West Road, Brentford Middlesex, TW8 9GS UK
Joint PASS	No

Research question and objectives	In the initial period of up to 24-months from the start of UMEC/VI and UMEC availability in the UK, we will identify patients newly prescribed long-acting bronchodilators (LABD) from a set of the UK primary care Electronic Medical Records (EMR) databases and conduct drug utilization review focusing on the following aims: Objective 1: In new users of UMEC/VI, UMEC, or other LABD report the proportion of patients with possible off-label prescribing and characterize them, using information available prior to and at the time of index prescription initiation, in respect to patient demographics, disease burden, co-morbidity, and COPD or asthma medication use. Objective 2: In new users of UMEC/VI or UMEC, quantify incidence of major cardiovascular and cerebrovascular events, mortality, pneumonia, and rate of exacerbations of COPD during follow-up. Objective 3: In new users of UMEC/VI or UMEC describe treatment patterns and adherence including Medication Possession Ratio and Proportion of Days Covered during follow-up.
Country(-ies) of study	United Kingdom
Author	PPD Director, Worldwide Epidemiology R&D Projects, Clinical Platforms & Sciences GlaxoSmithKline Building 9, Iron Bridge Road, Stockley Park West, Uxbridge, Middlesex, UB11 1BT Tel. PPD PPD

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	GlaxoSmithKline Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS UK
MAH contact person	PPD Manager, Respiratory Therapeutic Group Global Regulatory Affairs GlaxoSmithKline Research & Development Ltd

TABLE OF CONTENTS

PAGE

1. LIST OF ABBREVIATIONS

AE	Adverse Event
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
CAG	Confidentiality Advisory Group
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
PPD	PPD
CPRD-GOLD	CPRD database derived from Vision GP software
CV	Cardiovascular
CVD	Cardiovascular Disease
EMR	Electronic Medical Records
EHR	Electronic Healthcare Records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU-RMP	European Union – Risk Management Plan
FEV1	Forced Expiratory Volume (in one second)
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
GSK	GlaxoSmithKline
HES	Hospital Episodes Statistics
HRA	Health Research Authority
ICS	Inhaled Corticosteroids
ISAC	Independent Scientific Advisory Committee
LABA	Long-Acting Beta2-Agonists
LABD	Long-Acting Bronchodilator
LAMA	Long-Acting Muscarinics Antagonist
LRTI	Lower Respiratory Tract Infections
LTRA	Leukotriene Receptor Antagonists
MAH	Marketing Authorization Holder
MINAP	Myocardial Ischaemia National Audit Project
MPR	Medication Possession Ratio
MRC	Medical Research Council
OCS	Oral Corticosteroids
ONS	Office for National Statistics
PASS	Post Authorisation Safety Study
PDC	Proportion of Days Covered
SABA	Short-Acting Beta2-Agonists
SABD	Short-Acting Bronchodilators
SAE	Serious Adverse Event
SAMA	Short-Acting Muscarinic Antagonists
SD	Standard Deviation
THIN	The Health Information Network

UK	United Kingdom
UMEC	Umeclidinium bromide
VI	Vilanterol trifenatate

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
Anoro Ellipta
Incruse Ellipta
Laventair Ellipta
Rolufta Ellipta

Trademarks not owned by the GlaxoSmithKline group of companies
Handihaler
Respimat

2. RESPONSIBLE PARTIES

Sponsor

The Marketing Authorization 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: Manager, Respiratory Therapeutic Group, Global Regulatory Affairs

Name: PPD

Address: GlaxoSmithKline Research & Development Ltd.

Study Coordination

The MAH has contracted with PPD a research organisation specialising in observational studies and a managing body of the CPRD database, as a partner to provide scientific leadership and to conduct the study. The PPD will conduct the study with review and input from the MAH. A Scientific Committee (SC) will provide expert medical and epidemiological input and advice, review the interim and final reports and monitor the overall study progress through regular teleconferences and meetings. The responsibilities of the SC are further described below.

PPD

Study Scientific Committee

The SC consists of epidemiologists and clinicians with expertise in designing observational studies in EMR databases. It consists of three external members with relevant clinical and epidemiologic experience, as well as three GSK employees, and two representatives from the PPD This group is assisting with protocol development, and will develop and review the statistical analysis plan, provide technical input during study development, and assist with interpretation and dissemination of study results. Further clinical and methodological advice can be sought with other members of academia on an ad-hoc basis.

The SC will convene on a regular basis in association with important study milestones: protocol development, statistical plan approval, annual interim analysis and final study report.

External Members

PPD (Professor, Head of the Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine).

PPD (Professor, Department of Epidemiology, Erasmus MC University Medical Center Rotterdam, The Netherlands)

Dr PPD (Consultant in Chest Medicine and Clinical Senior Lecturer in Respiratory Epidemiology, Imperial College)

PPD **Members**

PPD (Senior Researcher, PPD

PPD (Senior Researcher, PPD

GSK Members

PPD (Manager, Real World Evidence & Epidemiology)

PPD (Director, Real World Evidence & Epidemiology)

SPONSOR SIGNATORY:

Andrew Roddam VP, Real World Evidence and Epidemiology	**Date**

SPONSOR INFORMATION PAGE

WWEpi Project Identifier:

WWE117397 (GSK Epidemiology: WEUSKOP6679)

GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: PPD

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate 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.

Sponsor Medical Monitor Contact Information: Not Applicable

Sponsor Serious Adverse Events (SAE) Contact Information:

Case Management Group,
GCSP –Stockley Park, UK
Email: PPD
Fax: PPD

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.

Daniel Dedman

Investigator Signature	Date

3. ABSTRACT

Title

Post-authorization safety Electronic Medical Records database retrospective cohort study of new users of inhaled UMEC/VI or new users of inhaled UMEC in the primary care setting

Short title: Retrospective EMR distributed network LABD drug utilization study

Rationale and background

This study primarily aims to collect data reflecting the 'real-world' experience with umeclidinium/vilanterol (UMEC/VI) and umeclidinium (UMEC) in the post-approval setting. UMEC/VI and UMEC as well as other medications containing only long-acting bronchodilators (LABD) are indicated for the treatment of Chronic Obstructive Pulmonary Disease (COPD). They are not indicated for the treatment of asthma without a concomitant treatment with inhaled steroids (ICS); such use is considered off-label. In addition, both LABD classes of drugs, the long-acting beta2-agonists (LABA) and long-acting antimuscarinics (LAMA) have been associated with some increased risk of cardiovascular events that warrants further investigation. This study will describe the patient population newly prescribed with 1) UMEC/VI, 2) UMEC and 3) other LABD and determine the frequency of possible off label prescribing as well as evaluate feasibility of undertaking potential future risk-benefit studies.

This study fulfils a voluntary commitment made in the European Union – Risk Management Plans (EU-RMP) for UMEC/VI and UMEC to examine the utilisation (including possible off-label prescribing) of these medications in a real-world, post-approval setting.

Research question and objectives

In the initial post-approval period of up to 24 months from the start of UMEC/VI and UMEC availability in the UK, we will identify patients newly prescribed long-acting bronchodilators (LABD) from a set of the UK primary care Electronic Medical Records (EMR) databases and conduct drug utilization review focusing on the following aims:

Objective 1: In new users of UMEC/VI, UMEC, or other LABD report the proportion of patients with possible off-label prescribing and characterize them, using information available prior to and at the time of index prescription initiation, in respect to patient demographics, co-morbidity, disease burden, and COPD or asthma medication use.

Objective 2: In new users of UMEC/VI or UMEC quantify incidence of major cardiovascular and cerebrovascular events, mortality, pneumonia, and rate of exacerbations of COPD during follow-up.

Objective 3: In new users of UMEC/VI or UMEC with 12 or more months of follow-up following initiation, describe treatment patterns and adherence including Medication Possession Ratio and Proportion of Days Covered during follow-up.

Study design

Retrospective longitudinal non-interventional observational study of new users of UMEC/VI, UMEC, or other LABD and followed-up from their index prescription date until censoring at death, leaving GP practice, the practice's last collection date or end of follow-up on June 30, 2017.

Population

To address Objective 1, new users of UMEC/VI, UMEC or other LABD will be included, while Objectives 2 and 3 will be limited to new users of UMEC/VI or UMEC only.

Variables

Exposures

We will identify all new users of UMEC/VI, UMEC or other LABD during the identification period of July 1, 2014 to June 30, 2016, corresponding with a period up to 24 months of UMEC/VI or UMEC availability to prescribers in the UK (See Section 8.3.1 for exposure definition). New use is defined as never having had a prescription for the same medication (UMEC/VI, UMEC or specific active substance of other LABD) ever recorded in the past. The first day of the first qualifying new use prescriptions will be the index date. Prior or concomitant use of respiratory medications containing a *different active substance to the one being initiated* will be allowed. A single patient is able to contribute more than one qualifying new use medication (UMEC/VI, UMEC or other LABD) during the exposure identification period of July 1, 2014 to June 30, 2016 if they meet the definition of new use for multiple medications.

The other LABD group will be analysed as a single combined group, and where appropriate and sample size allows, stratified as LAMA, LABA, and LAMA/LABA. No other LABD drugs will be analysed individually.

Outcomes

To address Objective 1, we will flag possible cases of off-label prescribing by reporting a proportion of new UMEC/VI, UMEC, or other LABD users who were diagnosed with (a) COPD (b) asthma or (c) neither COPD nor asthma. For Objective 2 we will quantify incident events of myocardial infarction, heart failure, or stroke in patients at risk during the follow-up period based on their available history. Further, events of death, pneumonia, and exacerbations of COPD will be counted. For Objective 3 we will describe treatment patterns and adherence to inhalation therapy.

Data sources

Data will be derived from the Clinical Practice Research Datalink (CPRD)-GOLD database and the Health Information Network (THIN) database.

Study size

This is a descriptive study. A sample size of 1,000 new users in each group produces a 95% confidence interval equal to the sample proportion plus or minus 1.3% when the estimated proportion of possible off-label prescribing is 5%. As this study is non-interventional, we cannot influence how many patients will initiate UMEC/VI, UMEC, or other LABD.

Data Analysis

Objective 1: Patients in the new user UMEC/VI, UMEC, or other LABD cohorts will be split according to presence or absence of a respiratory diagnosis record for (a) COPD (b) asthma or (c) neither COPD nor asthma, and described by their demographics, co-morbidity, disease burden, and other COPD or asthma medication use in the period prior to (and including) the initiation of their treatment with UMEC/VI, UMEC, or other LABD.

Objective 2: In new users of UMEC/VI or UMEC, we will enumerate count and incidence (new events/person-time) of myocardial infarction, heart failure, or stroke as well as events of death, pneumonia, and rate of exacerbations of COPD during follow-up. All analyses will be descriptive.

Objective 3: Among new users of UMEC/VI or UMEC with 12 or more months of follow-up following initiation, we will describe treatment patterns and adherence to treatment using medication possession ratio during total follow-up and proportion of days covered during the 0-12 months of follow-up.

Milestones

Start of periodic data evaluation: March 2015

Statistical and Operational analysis plan finalised: July 2016

Interim report: February 2018 (Drug utilization, possible off-label prescribing (up to relevant time period achieved)

Final report completed: By Q4 2019 (All objectives)

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	05 August 2016	3; 7; 8.1; 8.2.1.2; 8.3.2.2; 8.3.2.3; 8.7.1.3; 8.7.1.4	Objectives 2 and 3 to be conducted in all new users (not specifically in those with COPD).	There may be differences in the patient characteristics and safety endpoints between patients who are potentially prescribed ANORO off-label and on label users and thus it is valuable to include both populations and stratify results by off label/on label use.
2	05 August 2016	3; 7; 8.1; 8.2.1.2; 8.3.2.2; 8.7.1.3	Objective 2 to be conducted in only UMEC/VI and UMEC cohorts; removing other LABD cohort from this objective.	Objective 2 is a secondary aim of this study, intended to evaluate feasibility of undertaking potential future risk-benefit studies of events that have been associated with the LABA and LAMA class of drugs, such as cardio- and cerebrovascular events and pneumonia. In order to accomplish this, it is planned to descriptively quantify the frequency of these events in our sample of 1,000 UMEC and UMEC/VI users, thus generating inputs for power/sample size calculations for future comparative study protocols, if required. It is not the intention of Objective 2 to serve as a comparative analysis of the risk of these events against users of “other LABD”, as this study is neither powered for such comparison nor designed to ensure patient or disease characteristics, which may

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
				influence the risk of these outcomes, is balanced between the "other LABD" group and the UMEC and UMEC/VI groups, respectively. As such, the SSC felt that it was out of scope and scientifically inappropriate for the WWE117397 study to report outputs associated with Objective 2 in the "other LABD" group. GSK is conducting a second post-approval safety study (Study #201038), which is a longitudinal prospective observational non-interventional study specifically designed to address the comparative risk of cardiovascular events of interest versus Tiotropium. This study is prospective in nature and employs appropriate propensity score balanced analysis and adequate study size to detect differences in the study primary endpoints.
3	05 August 2016	3; 8.3.2.1; 8.7.1.2; 8.7.2	Definitions of COPD and asthma edited to reflect diagnosis of these conditions in an EMR database scenario, so as to identify more precisely the primary endpoint	Due to potential delays in the recording of COPD in an EMR database, the definition of COPD was edited to allow capture of cases diagnosed before and after the index medication. Further, the definition of asthma was simplified to better reflect how asthma

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			(possible off-label prescribing).	is captured in an EMR database. Lastly, the group of patients that meet neither the COPD nor asthma definitions will be characterised in an "other category" but will not be further defined as specific respiratory diseases as we expect small patient numbers for specific other respiratory diseases.
4	05 August 2016	3; 8.1; 8.3.1.1	Definition of new user refined to allow patients to qualify for more than one active treatment.	The original protocol allowed patients to enter into the study for only the first qualifying drug (UMEC/VI, UMEC or other LABD). This requirement had the potential to create an immortal time bias within the study population and thus was edited to allow for patients to contribute data for all medications which meet the "new use" definition during the identification period.
5	05 August 2016	3; 8.1; 8.3.1.3; 8.3.2.3; 8.7.1.3; 8.7.1.4 8.7.2	Patient follow-up period and drug exposed period during follow-up redefined; discontinuation incorporated into this definition and removed as part of treatment patterns objective.	The definitions of the total follow-up period until censoring and the drug exposed periods during follow-up have been further refined. This includes simplification of the potential reasons for censoring a patient during follow-up and provides greater detail around exposed person-time for the purposes of calculation of (incidence) rates of study endpoints.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
6	05 August 2016	3; 7; 8.3.2.2; 8.3.3; 8.7.1.2; 8.7.1.3; 8.7.1.4;	Removed descriptive endpoint “health care resources utilization”.	There are limitations to using the number of GP visits as a proxy for health status as each time a record is opened to add information about that visit (i.e. to add lab values, etc), it appears as a consultation and thus there is a potential for misclassification of the true number of GP visits. Further, capturing hospitalizations for causes other than COPD will add limited value since most hospitalization in this population will be for COPD and will therefore be adequately captured in the severe COPD exacerbation endpoint.
7	05 August 2016	3; 6.2; 7; 8.3.2.2; 8.3.3; 8.7.1.3; 8.9	Removed descriptive endpoint lower respiratory tract infections (LRTI) from pneumonia/LRTI category, so that this category represents pneumonia only.	Clinically and technically, using LRTI medical diagnosis codes in the CPRD primary care, electronic health record (EHR) database (used in this study) is likely to a result in a classification of acute exacerbations of COPD (AECOPD) events as LRTI. 1) Clinically, it is estimated that 50-70% of AECOPD are due to LRTI [Millet 2013; Sapey 2006]. Hence, AECOPD represent a substantial proportion of LRTI events among COPD patients and a combined endpoint of LRTI/pneumonia would in fact mostly represent

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
				AECOPD/pneumonia events. This was not seen as desirable, because AECOPD are reported as a separate outcome associated with Objective 2. Moreover, the exposure with respiratory medications may lead to a reduction of AECOPD, whereas incidence of pneumonia is not impacted or increased, depending on the respiratory medications class. Therefore, a composite endpoint of LRTI/pneumonia does not allow for reporting of a specific estimate of physician-recorded pneumonia, which is most of interest as a safety concern. 2) Technically, GPs are recording AECOPD as LRTI without further specification in EHRs. A recently completed validation study conducted in the PPD compared recorded codes with the original GP records and detected that about 75% of LRTI recordings in COPD patients are actually confirmed as AECOPD (PPV~75%) [Rothnie, 2016]. Thus, in EHR type studies, LRTI is part of the definition used to identify AECOPD and therefore it is not appropriate to have

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
				these as separate endpoints.
8	05 August 2016	8.3.2.2; 8.7.1.3	Remove acute worsening of heart failure descriptive endpoint.	There is a high potential to misclassify acute worsening of heart failure with an acute exacerbation of COPD in an EMR database. [Valk, 2015] As such, only newly diagnosed heart failure will be described in this study.
9	05 August 2016	8.2; 8.3.2.2; 8.4	Potential linkage to MINAP registry for CVD outcomes removed.	Linkage to the MINAP registry is not necessary in order to adequately capture the CVD events of interest in this study [Herrett, 2013] and requiring this linkage will decrease the number of datasets to potentially include in the distributed network design as not all databases link to MINAP.
10	05 August 2016	8.2; 8.3.2.2; 8.4	Linkage to ONS death registry will be used in Objective 2 in an analysis of cardiovascular death among patients eligible for linkage.	Cardiovascular death is an informative endpoint. However, cardiovascular death cannot be explored in the full study population as not all patients are eligible for linked data. Analysis of this endpoint will therefore be confined to those patients for are eligible for linkage.
11	05 August 2016	8.3.3	Charlson score comorbidity variable removed. Instead, the following comorbidities will be examined at baseline: peripheral vascular disease,	Charlson score is redundant as it does not provide additional information above the key specific COPD-related morbidities that will individually studied.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			gastroesophageal reflux disease, renal disease (acute and chronic), pneumonia, and cancer.	
12	05 August 2016	8.3.3 (Table 4)	Oxygen use removed as a covariate to describe prior COPD medication use at baseline.	Oxygen is poorly recorded in UK EMR and any estimate of oxygen use is likely to be underestimated when using EMR alone.
	05 August 2016	8.3.3 (Table 4)	Leukotriene receptor antagonists (LTRA) and anti-IgE medications removed from medication list in Table 4 (medication use at baseline).	These drugs were removed as they are typically used to treat asthma and the revised definition of asthma does not require medication use.
13	05 August 2016	8.3.3; 8.7.1.3	Including past history of beta-blocker prescribing as a covariate. Stratification of analyses for cardiovascular endpoints in objective 2 by concomitant beta-blocker prescribing.	Patients prescribed beta-blockers are likely to have fewer adverse cardiovascular events. It is therefore important to understand the effects of cardiovascular endpoints conditional on beta-blocker prescribing for patients in the UMEC and UMEC/VI groups for objective 2.
14	05 August 2016	8.3.2; 8.3.2.3; 8.7.1.4	In objective 3, treatment patterns will be explored for inhalation therapies only and only among patients who are not censored 31 to 90 days after their last prescription within	It is not possible to determine whether a patient discontinues if they are censored 31-90 days after their last prescription (see section 8.3.1.3). Inhalation therapies are of greatest interest.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			the initial 12 months follow-up.	
15	05 August 2016	8.3.2; 8.3.2.3; 8.7.1.4	Treatment patterns for objective 3 have been refined (see Figures 3 and 4 in section 8.3.2.3) and will be examined in first 12 months following index date among patients with a full 12 months of follow-up. Adherence for objective 3 also examined in first 12 months following index date among patients with a full 12 months of follow-up.	Treatment patterns needed to be mutually exclusive and cover all potential treatment changes. Time limit means patients who initiate early in the study period, and are therefore followed up for longer, did not have spuriously high rates of switching, augmentation and discontinuation relative to patients who initiate late and are followed up for less time. Adherence patterns have been changed so that all analyses for objective 3 conducted amongst same group of eligible patients.
16	05 August 2016	8.3.3;	COPD exacerbations at baseline will be identified in two ways (a) using primary-care data for all patients and (b) using primary- and secondary-care data for patients eligible for linkage.	During the recent development of an updated algorithm for identification of COPD exacerbations [Rothnie, 2016], it was established that the CPRD (and thus other primary-care databases) is an insufficient source to identify all instances of hospitalized exacerbations of COPD. Therefore, the most reliable way of capturing COPD exacerbation events is to supplement primary care data with information from secondary care (HES).
17	05 August 2016	8.3.2.2; 8.7.1.3	For objective 2, the primary analysis will identify events	The most reliable way of capturing cardiovascular, pneumonia, death and

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			using information recorded in primary care, secondary care (HES) and mortality data (ONS). This analysis will be conducted using the subset of patients who are eligible for linkage with HES and ONS data. A secondary analysis will be conducted among all (eligible) patients using information from primary care only.	COPD exacerbation events is to supplement primary care data with information from secondary care (HES) and mortality data (ONS). The secondary analysis conducted among all patients will provide information on the extent of under-recording of these events in primary care data. Additionally, as death events are well recorded in primary care data, the secondary analysis of death (where all patients are included) will provide greater confidence in estimates of survival rate.
18	05 August 2016	8.3.3	Removed region covariate used to describe new users of UMEC, UMEC/VI and other LABD.	Region variable not available in all partner databases.
19	05 August 2016	8.3.3	Removed derived variable for COPD severity which classifies patients into GOLD groups A, B, C and D.	Previous studies of COPD using CPRD data suggest a very high proportion of patients will have missing information for this variable.
20	05 August 2016	10	Explanation added in line with SOP 52214 as to why adverse events cannot be reported from this study.	Because this study uses anonymised electronic medical records, the minimum criteria for reporting adverse events is not met. A statement to this effect was added.
21	14 Sept 2018	n/a	'off-label use' has been changed throughout the document to 'possible off-label prescribing'	As we only have information about prescriptions it is more appropriate employ 'possible prescribing' than 'use'.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
22	14 Sept 2018	PASS information	The new trade names have been added: Anoro Ellipta Incruse Ellipta Laventair Ellipta Rolufta Ellipta EU authorisation numbers and procedure number have been added for Rolufta Ellipta	The EMA approve the new tradenames in EU on 10th August 2018. Update information for Rolufta Ellipta
23	14 Sept 2018	5	Milestones- Interim report date modified	Interim report was submitted to the EMA as part of the PBRER (Periodic Benefit Risk Evaluation Report of Anoro/Laventair, number 2017N342954) on 23rd February 2018, so the date has been changed accordingly.
24	14 Sept 2018	6.1	We have added: "Only one LAMA, tiotropium, is currently approved as an add on-treatment for asthma for patients who are currently treated with the maintenance combination of ICS/LABA and who experienced one or more severe exacerbations in the previous year."	To reflect the authorisation of tiotropium in September 2014 to be used as an add on therapy to ICS/LABA for the treatment of asthma in patients with asthma exacerbations
25	14 Sept 2018	6.1	E.g. GOLD 2014, has been changed to GOLD 2018	References have been updated to more recent ones
26	14 Sept 2018	6.2	We have added: "This study fulfils a voluntary	To clarify the intention of a voluntary commitment made in the European

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			commitment made in the European Union – Risk Management Plans (EU-RMP) for UMEC/VI and UMEC to examine the utilisation (including possible off-label prescribing) of these medications in a real-world, post-approval setting."	Union – Risk Management Plans (EU-RMP)
27	14 Sept 2018	7	Change from "*a set*" of UK databases to just "*two"* UK databases	Initially a set of EMR databases was proposed however adequate sample size was reached with just two databases (CPRD and THIN)
28	14 Sept 2018	8.1	Figure 1 -we have added: 'only for new users of UMEC or UMEC/VI'	To clarify in the Figure 1 that the follow-up period to examine medication patterns and counts of events (objective 2 and 3), will be only done in new users of UMEC or UMEC/VI
29	14 Sept 2018	8.2	Information about potential data sources has been deleted and just left the two databases employed in the study	Initially a set of EMR databases was proposed however adequate sample size was reached with just two databases and therefore details of only those two databases have been included (CPRD and THIN)
30	14 Sept 2018	8.3.1.1	We have added: "For the LAMA/LABA sub group of other	Clarification about considering the inclusion of fixed and open combinations.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			LABD, fixed dose combinations will be included as well as open combinations of a LABA and a LAMA in two devices only if they are prescribed on the same exact date."	
31	14 Sept 2018	8.3.1.1	"A single patient is able to contribute more than one qualifying index medication during the ~~study~~ identification period"	Clarification about the contribution of a patient to more than one qualifying index medication, if they meet the definition of new use, will be only during the identification period, not during the whole study period.
32	14 Sept 2018	8.3.1.2	We have added: "Only single device or fixed dose combination maintenance therapies will be considered when defining concomitant maintenance medications."	Clarification about definition of concomitant maintenance medications
33	14 Sept 2018	8.3.1.3	Paragraphs explaining the exposure categories for the person-time exposed to UMEC or UMEC/VI during follow-up have been changed	Additional detail provided to ensure correct classification of UMEC or UMEC/VI patients into current and previous exposure time, taking into account all follow up time until censoring.
34	14 Sept 2018	8.3.2.1	"Patients will be considered to have asthma if their most recent asthma	Clarification of Asthma definition

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			medical code is a maximum of two years prior to their index date".	
35	14 Sept 2018	8.3.2.1	New paragraphs have been added to clarify this	Clarification of 'possible off-label prescribing' for the 3 exposure groups
36	14 Sept 2018	8.3.2.2	We have added: "in those currently or previously exposed to…"	To specify that the objective 2 will be performed in those currently or previously exposed to UMEC or UMEC/VI
37	14 Sept 2018	8.3.2.2	We have added: "HES/ONS"	Data linked with ONS data will be used as well as linked with HES
38	14 Sept 2018	8.3.2.3	We have added: "in new users of UMEC/VI or UMEC defined during the identification period"	Clarification that only new users of UMEC/VI or UMEC defined during the identification period will be considered.
39	14 Sept 2018	8.3.2.3; 8.7.1.4	We have changed the paragraph to one similar to the objective 2: "It will not be possible to determine whether a patient discontinues UMEC or UMEC/VI if they are censored between 31 and 90 days after their last prescription. These patients will be flagged, and the primary analysis will take a conservative approach for these	Objective 3, will follow the same approach that objective 2.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			patients and assume they were only exposed for the 30 days period following their last prescription."	
40	14 Sept 2018	8.3.2.3	Table with possible treatment switches or augmentations has been modified removing ICS/LAMA	Among the possible treatments ICS/LAMA have been removed as it is not a common treatment option
41	14 Sept 2018	8.3.2.3	Paragraph has changed to this: "treatment patterns that will be considered include continuous use of both drugs, discontinuation of the index medication (continue to use the concomitant medication), discontinuation of the concomitant medication (continue to use the index medication), discontinuation of both medications at the same time.	Options for switches or augmentations to calculate treatment patterns have been clarified
42	14 Sept 2018	8.3.2.3	More detailed explanation and formulae of the calculation for MPR and PRC have been added.	To ensure transparency in the calculation and which populations are included in each measure of adherence
43	14 Sept 2018	8.3.3.3	As part of the demographics baseline variables, we have added	For those with an indication of neither asthma nor COPD we want to explore which

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			"Respiratory conditions"	respiratory conditions they have
44	14 Sept 2018	8.3.3.3	COPD severity will be characterised by lung function test and FEV_1/FVC ratio in the 24 months prior to index date	COPD severity will be explored in the 24 months prior to index date, instead of in the 12 months prior, using much information available to better characterise patient's severity.
45	14 Sept 2018	8.3.3.3	COPD or asthma medication have been changed for 'Respiratory' medication	Respiratory medication is more adequate as general term
46	14 Sept 2018	8.3.3.3	Table 4 has been changed accordingly	For the purposes of this analysis, only fixed dose combinations will be considered.
47	14 Sept 2018	8.4	Some updated references and figures about CPRD have been added. As well a new paragraph about THIN database.	Information about CPRD has been updated. And, information about THIN database has been added
48	14 Sept 2018	8.7.1.2	We will select the first ever diagnosis code in their medical history	In case a patient has more than one diagnoses codes, clarify which code will be selected to calculate the proportion of patients with a diagnosis before or after their index medication
49	14 Sept 2018	8.7.1.2	We have added: "Further, the descriptive statistics will be repeated in the groups of patients who are identified as on label and potentially	To add the possibility to repeat some tables by exposure groups.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			prescribed off label UMEC or UMEC/VI."	
50	14 Sept 2018	8.7.1.3	Objective 2- We have changed the paragraph to: "First, using the full cohort of patients with identification of events in primary care data only (both CPRD and THIN data sources). And secondly, using information from primary care, secondary care (HES) and mortality data (ONS) in patients eligible for linkage with both HES and ONS data. Two secondary analyses will be carried out in both primary care data only and in those with linked to HES and ONS."	To make this more complete and straightforward, we edited this paragraph to essentially do these 3 analyses in both datasets.
51	14 Sept 2018	8.9	We have added: "By this design, new users of Other LABD who may have switched to either UMEC or UMEC/VI after the identification period during the *one-year follow-up*	To acknowledge the limitation that the design of the study only assigns current and previously exposed follow-up time to users identified within the period of July 1, 2014 to June 30, 2016. Patients initially taken 'other LABD' will not be taken

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
			window will not have that UMEC or UMEC/VI exposure time counted in this study'	into account for the analyses if they switch to UMEC or UMEC/VI after the identification period.
52	14 Sept 2018	8.9	The paragraph about the expected complexity of data analysis has been changed to "The final sets of databases, CPRD GOLD and THIN, are both based on the same GP software (Vision) and have comparable data structures and coding schemes. This reduces complexity in the analyses"	Initially a distributed network design was proposed, but finally only two final sets of databases have been used, therefore the complexity in the analyses have been reduced.

5. MILESTONES

Milestone	Planned date
Start of data collection	March 2015
End of data collection	June 30, 2017
Registration in the EU PAS register	October 2014
Interim report 1 (Drug Utilization, possible off-label prescribing) (up to relevant time period achieved)	February 23rd, 2018
Final report of study results (All objectives)	By Q4 2019

Interim and final analysis timings: due to dependence on the natural uptake of a medication by medical doctors, the actual interim and final analysis timings may differ. The study progress reports will provide regular information about physician prescribing and numbers of new users on a 6-monthly basis.

6. RATIONAL AND BACKGROUND

6.1. Background

Umeclidinium bromide/vilanterol trifenatate (UMEC/VI) fixed dose-combination LAMA/LABA and umeclidinium bromide (UMEC) LAMA monotherapy were recently approved by the European Commission for the treatment of COPD on May 2014 and April 2014, respectively. LAMA/LABA fixed-dose combinations are identified in the treatment guidance document for COPD, when severity warrants the use of both medications [GOLD, 2018]. Currently, other fixed-dose LAMA/LABA combination medication (glycopyrronium/indacaterol) was approved for COPD by the European Commission (approved prior to UMEC/VI). Additionally, several medications containing LAMA only and LABA only are available for treatment of COPD patients experiencing breathlessness, including medications containing salmeterol, formoterol, indacaterol, glycopyrronium, tiotropium, and aclidinium.

The safety and efficacy of mono component LABA and LAMA containing medication in COPD have been studied extensively. LAMA containing medications are considered a gold standard of bronchodilation in COPD patients demonstrating benefits of improved lung function and reduced dyspnoea [GOLD, 2018]. As there are fewer approved fixed dose LAMA/LABAs less is known about their risk/benefit profile.

There is a potential for off-label prescribing of UMEC/VI as a controller medication in asthma. However, the use of UMEC/VI for asthma would not be consistent with established guidance by the Global Initiative for Asthma [GINA, 2018]. Long-acting beta2-agonists are not recommended as monotherapy in asthma, as they do not influence airway inflammation and are potentially associated with a risk of asthma-related deaths [Bateman, 2008; Nelson, 2006; Sears, 2009; Morales, 2013]. LABAs are most effective when combined with glucocorticosteroids, and this combination is the preferred treatment when

glucocorticosteroid monotherapy fails to control asthma. Additionally, the benefits of LAMAs in asthma management have not yet been established. Only one LAMA, tiotropium, is currently approved as an add on-treatment for asthma for patients who are currently treated with the maintenance combination of ICS/LABA and who experienced one or more severe exacerbations in the previous year. There is a wide range of licensed and established controller treatment options available to physicians for the management of asthma including glucocorticosteroids, leukotriene modifiers, LABAs in combination with glucocorticosteroids, sustained-release theophylline, cromones and anti-IgE therapy [GINA, 2018].

We conducted a systematic review of observational studies describing the incidence or relative risk of major cardio- and cerebrovascular events in users of LAMA in COPD. Two out of the identified studies, using a single database source, reported incidence rates of events specified in Table 1 below in users of Tiotropium and LABA [Jara, 2012; Jara, 2007].

Table 1 Incidence rates (per 1,000 person-years) of Cardiovascular events among users of Tiotropium or LABA in the THIN database [Jara, 2012; Jara; 2007]

Outcome	Tiotropium (rate per 1,000 person-years)	LABA (rate per 1,000 person-years)
Atrial fibrillation & flutter	17.0 to 31.9	24.1 to 33.4
Heart failure	34.0 to 42.6	46.4 to 59.0
Myocardial Infarction	12.7 to 14.9	10.0 to 12.1
Tachycardia	5.40 to 19.1	4.80 to 24.1
Ventricular tachycardia	0.70	0.40

One study reported no difference in relative risk of cardiovascular events in users of tiotropium administered via Handihaler device vs. users of other respiratory medications [de Luise , 2007]. Three studies evaluated a relative risk of cardio- and cerebrovascular events in tiotropium (Handihaler) users vs. LABA users [Jara, 2012; Jara, 2007; Gershon, 2013], specified in Table 2. Only the risk of stroke was significantly increased in only one study among tiotropium users [Gershon, 2013].

Table 2 Risk of Cardio- and Cerebrovascular events among Tiotropium vs. LABA users [Jara, 2012; Jara, 2007; Gershon, 2013]

Outcome	Jara, 2012 HR (95% CI)	Jara, 2007 HR (95% CI)	Gershon, 2013 OR (95% CI)
Heart failure	0.85 (0.63 - 1.14)	0.65 (0.37 - 1.12)	1.08 (0.79 - 1.47)
Myocardial Infarction	1.26 (0.72 - 2.21)	1.29 (0.45 - 3.66)	1.10 (0.78 - 1.56)
Atrial fibrillation & flutter	0.99 (0.71 - 1.38)	0.60 (0.25 - 1.42)	
Stroke	1.49 (0.91 - 2.45)		1.73† (1.06 - 2.83)

†Statistically significant (p value of 0.03); All other estimates were Not statistically significant

Specific concerns were identified for users of tiotropium administrated via Respimat device. Tiotropium Respimat administration was repeatedly associated with an increased risk of cardiovascular events as compared to tiotropium administered via Handihaler in clinical and observational studies [Jenkins, 2013; Verhamme, 2013]. A large randomised clinical trial, TIOSPIR, designed to answer a question of the cardio- and cerebrovascular risks associated with tiotropium Respimat vs. Handihaler, reported noninferiority for the primary outcome of all-cause mortality; however, an imbalance of counts of some cardiovascular events was observed with Respimat administration [Wise, 2013].

Any risk of medication treatment related cardio- and cerebrovascular events in COPD needs to be interpreted taking into account an increased background prevalence of such events in COPD patients and their risk factors when compared with patients without COPD [Mullerova, 2012].

Respiratory infections, including pneumonia and lower respiratory tract infections (LRTI) [Mannino, 2009] often occur in patients with COPD. The incidence and prevalence of pneumonia in COPD patients can be difficult to estimate because of the application of different definitions of pneumonia (e.g. radiographic confirmation of pneumonia). In a COPD cohort of 40,414 patients in the UK, the incidence of pneumonia was 22.4 per 1,000 person-years and increased with disease severity [Mullerova, 2012]. Incidence rates of pneumonia were 18.2, 19.2, and 35.9 per 10,000 person-years for mild, moderate, and severe COPD patients respectively, where severity was estimated based on respiratory medication use [Mullerova, 2012].

Data from two large United States cardiovascular health studies observed that the rates of pneumonia requiring hospitalisation among patients with COPD ranged from 0.9 per 1000 person years for ages 45-49 and increased markedly with age (2.5, 5.4, 6.7, 12.2, and 19.5 per 1000 person years for patients 60-64, 65-71, 72-75, 76-79, ≥80) and GOLD stage (GOLD II: 6.9 per 1000 person years, GOLD III/IV: 22.7 per 1000 person years, normal lung function: 1.5 per 1000 person years) [Mannino, 2009].

6.2. Rationale

In the early post-approval period for UMEC/VI and UMEC, this study aims to collect data reflecting the 'real-world' experience of new users of LABD. We will focus on cohorts of new users of UMEC/VI and UMEC aiming to place the analysis output into context of experience of new users of other LABD. There is no a priori hypothesis to be tested. This study fulfils a voluntary commitment made in the European Union – Risk Management Plans (EU-RMP) for UMEC/VI and UMEC to examine the utilisation (including possible off-label prescribing) of these medications in a real-world, post-approval setting.

We will focus our investigation on characteristics (clinical, demographic) of new users of UMEC/VI, UMEC, or other LABD including whether pre-existing conditions like cardio- and cerebrovascular disease or pneumonia are impacting on physician's choice of maintenance therapy for COPD patients by informally comparing the distribution of comorbidities in the three cohorts at the time of index prescription.

Another specific focus is on quantifying and characterizing possible off-label prescribing in patients diagnosed with asthma alone (without COPD diagnosis) as LABD alone, including UMEC/VI and UMEC, without concomitant ICS use, are not indicated for the treatment of asthma.

In addition, as both the LABA and LAMA class of drugs have been associated with some increased risk of cardio- and cerebrovascular events, it is of interest to pursue evaluation of cardio- and cerebrovascular safety of UMEC/VI and UMEC during the post-approval stage. To enable rapid development of any possible future risk-benefit studies, as a feasibility evaluation, we will descriptively quantify incidence during follow-up of cardio- and cerebrovascular events of interest in patients using UMEC/VI and UMEC as well as report on the incidence of events of pneumonia.

We will also describe treatment patterns and adherence to medication among new users UMEC/VI and UMEC.

7. RESEARCH QUESTION AND OBJECTIVE(S)

In the initial post-approval period of up to 24 months from the start of UMEC/VI and UMEC availability in the UK, we will identify patients newly prescribed long-acting bronchodilators (LABD) from two UK primary care Electronic Medical Records (EMR) databases and conduct drug utilization review focusing on the following aims:

Objective 1: In new users of UMEC/VI, UMEC, or other LABD report the proportion of patients with a possible off-label prescribing and characterize them, using information available prior to and at the time of index prescription initiation, in respect to patient demographics, co-morbidity, disease burden, and COPD or asthma medication use.

Objective 2: In new users of UMEC/VI or UMEC, quantify incidence of major cardiovascular and cerebrovascular events, mortality and pneumonia, and rates of exacerbations of COPD during follow-up.

Objective 3: In new users of UMEC/VI or UMEC with 12 or more months of follow-up following initiation, describe treatment patterns and adherence including Medication Possession Ratio and Proportion of Days Covered during follow-up.

8. RESEARCH METHODS

8.1. Study Design

This study will take a naturalistic approach, capturing routine medical care using a retrospective longitudinal non-interventional observational design. The study will identify patients based on a new prescription (index prescription date) for UMEC/VI, UMEC, or other LABD who will be followed-up from their index prescription date until their censoring date which is the earliest of the following events:

1. Death
2. Leaving GP practice
3. the practice's last collection date or
4. End of follow-up on June 30, 2017.

We will identify all new users of UMEC/VI, UMEC or other LABD during the exposure identification period of July 1, 2014 to June 30, 2016, corresponding with a period up to 24 months of UMEC/VI or UMEC availability to prescribers in the UK (See Section 8.3.1, Figure 1, Figure 2).

A minimum period of at least 12 months prior to index prescription date, defined as being registered with the practice for at least one year, is required for all new users to allow for a standardised period of history to describe selected patient demographics, disease burden, and previous respiratory medication use (Figure 1, Figure 2).

To evaluate Objective 1, all patients newly prescribed UMEC/VI, UMEC, or other LABD will be included; Objectives 2 and 3 will be limited to new users of UMEC/VI or UMEC only.

Figure 1 Study Schematic: Individual patient history assessment

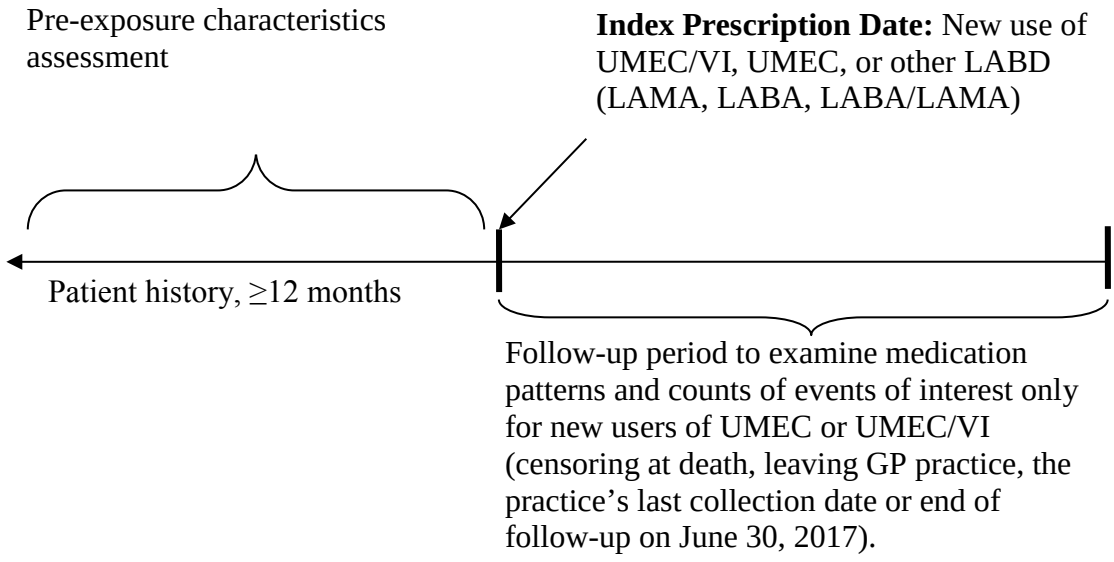
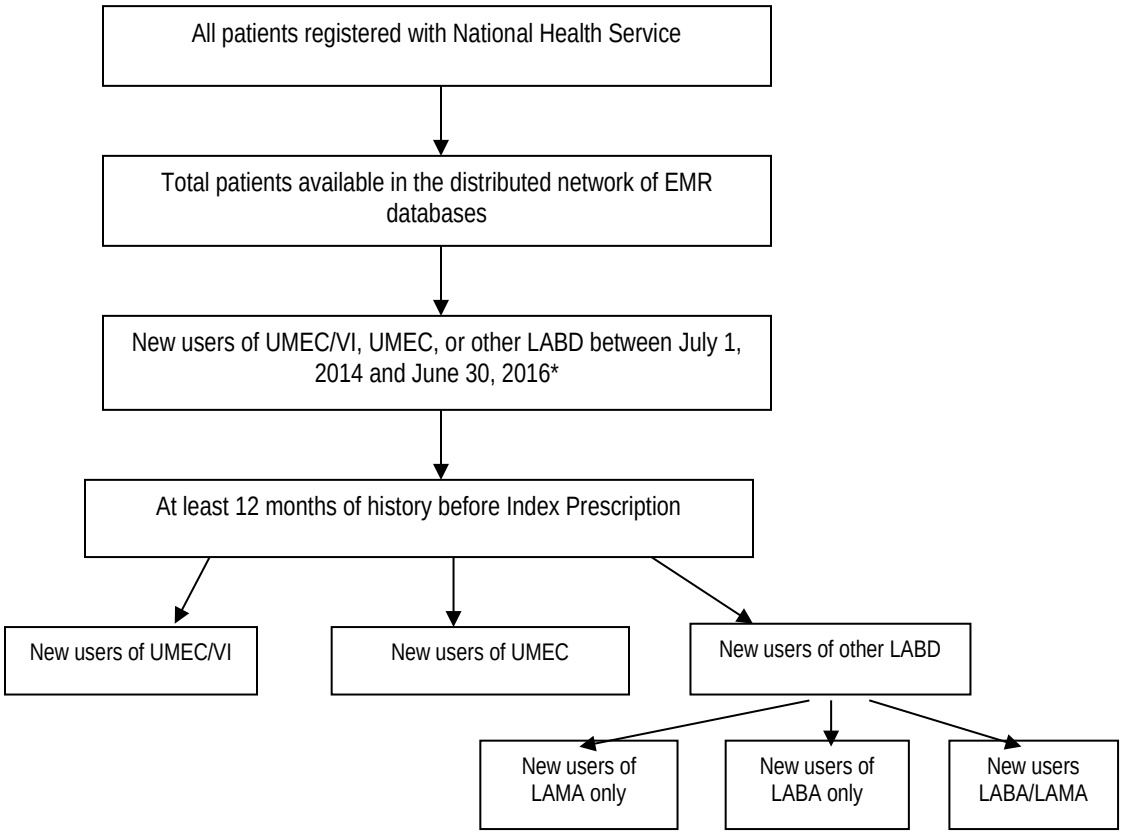


Figure 2 Consort Diagram Schematic: Cohort Selection



* A patient may qualify for more than one exposure category if they meet the "new user" definition for more than one drug during the exposure identification period.

8.2. Setting

The study population will be identified from two UK data sources, the Clinical Practice Research Datalink GOLD database (referred to hereafter as CPRD-GOLD) and The Health Improvement Network (referred to hereafter as THIN). The required sample size will be achieved using these two data sources. Each database currently comprises EMR data from a single vendor system, and the ones we will consider for inclusion were those databases which contain data from one of the three main systems which currently cover over 85% of UK general practices: Vision from In Practice Systems (InPS)As the co-coordinating centre for the study, PPD will obtain and evaluate data from the THIN database, using criteria agreed in advance with GSK.

Patients in each database are unique at two levels. First, at the patient level we consider only so-called permanently registered patients; such patients can register with one GP practice at a time only. The movement across practices is considered to be low. Secondly, at the database level, we will use practice identifiers to ascertain if any practice is contributing to more than one system in the distributed network.

Primary care records of eligible patients only from the CPRD-GOLD will be linked where possible, to additional datasets such as the Hospital Episode Statistics (HES) and the Office for National Statistics (ONS) mortality statistics database to potentially improve capture of study outcome events and obtain richer information about study outcome events.

These linked datasets, covering population of England only, will be used primarily for outcome ascertainment and validation. Further details on datasets are provided in Table 3 and Section 8.4.

Table 3 Summary of the characteristics for the EMR databases to be included in the study

	CPRD-GOLD	THIN
EMR System	Vision (InPS)	Vision (InPS)
Database size: a) total patients b) current (or active) patients c) total practices d) current (or active) practices	 a) 14.2M b) 3.5M d) 406	 a) 11.1M b) 3.7M c) 578 d) n/k
Patient geographical coverage	UK	UK
Linked data available	For a subset of English practices: HES, ONS, NICOR (MINAP)	A small subset of practices has been linked to HES
Regularity of data uploads	Monthly	Monthly
Allows obtaining further evidence from GP practice medical records	Yes (subset of practices)	Yes
Further specifications		~50% of flagged practices overlap with the CPRD.

8.2.1. Study Populations

The study population will consist of new users of UMEC/VI, UMEC or other LABD treatment (See Section 8.3.1 for exposure definition).

8.2.1.1. Inclusion Criteria

Patients are required to:

1. Have a record for a new prescription of UMEC/VI, UMEC, or other LABD between July 1, 2014 and June 30, 2016 (inclusive).
2. Have at least 12 months of recorded data prior to index prescription date to allow characterization of patient's status, demographics and clinical characteristics.

8.2.1.2. Exclusion Criteria

Having a prescription for the same exact substance (or combination) of LABD ever recorded in the past.

To evaluate Objective 1, all patients newly prescribed UMEC/VI, UMEC, or other LABD will be included; Objectives 2 and 3 will be limited to new users of UMEC/VI or UMEC only.

8.3. Variables

8.3.1. Exposure definition

8.3.1.1. New users (UMEC/VI, UMEC or other LABD)

We will identify all new users of UMEC/VI, UMEC or other LABD during the exposure identification period of July 1, 2014 to June 30, 2016, corresponding with a period up to 24 months of UMEC/VI or UMEC availability to prescribers in the UK. New use is defined as never having had a prescription for the same medication (UMEC/VI, UMEC or specific active substance (or combination) of other LABD) ever recorded in the past. The first day of the first qualifying new use prescriptions will be in the index date. Prior or concomitant use of respiratory medications containing a different specific active substance (or combination) then the new substance (or combination) being initiated will be allowed.

Other LABD includes but is not limited to medications containing: tiotropium, glycopyrronium, glycopyrronium/indacaterol, aclidinium, indacaterol, salmeterol, olodaterol, and formoterol, according to the availability. This list may need to be further modified depending on newly authorised medications in the class. For the LAMA/LABA sub group of other LABD, fixed dose combinations will be included as well as open combinations of a LABA and a LAMA in two devices only if they are prescribed on the same exact date. The other LABD group will be analysed as a single combined group, and where appropriate and sample size allows, stratified as LAMA, LABA, and LAMA/LABA. No other LABD drugs will be analysed individually. The new use of ICS/LABA combinations in a single device is not considered as new other LABD unless it is accompanied with a new prescription for LAMA.

All individual prescriptions will be given a *default length of 30 days per container prescribed* irrespective of whether they have a recorded value for script length (less than 1% had a value recorded).

A single patient is able to contribute more than one qualifying index medication during the identification period if they meet the definition of new use for multiple medications. A patient may qualify for new uses of both UMEC and UMEC/VI if that patient switches between the two during the identification period. A patient may also qualify for more than one ‘other LABD’ containing the same active substance (e.g. glycopyrronium and glycopyrronium/indacaterol) or an ‘other LABD’ (such as tiotropium) and UMEC or UMEC/VI.

Note: prescriptions are used as proxy for pharmacy dispensing, as it is known that a percentage of patients never take a prescription to the pharmacy or fail to collect a filled prescription.

8.3.1.2. Concomitant use of other medications at index date (UMEC/VI, UMEC)

Given the naturalistic nature of the study design, it is possible that some patients will initiate UMEC or UMEC/VI while on other maintenance medications. In some instances, these patients will be transitioning from the old medication to the new one and there is a small overlap. In other cases, they may continue to take both medications for a period of

time. Of particular interest is concomitant use of an ICS-containing medication along with the index medication, as this will be used as a stratification variable for several of the study objectives.

We will search the patient record and flag instances when patients are receiving concomitant COPD maintenance therapy at the time of the index prescription. Concomitant therapy will be defined as at least two continuous prescriptions for the other COPD maintenance therapy which start either before, or up to 30 days after the index date, and overlap for at least 30 days with the index treatment. Only single device or fixed dose combination maintenance therapies will be considered when defining concomitant maintenance medications.

8.3.1.3. Follow up period and person time (UMEC/VI, UMEC)

For Objective 2, new users of UMEC/VI and UMEC, defined in the identification period, will be followed from their index date until their censoring date (death, leaving the GP practice, the practice's last collection date or 30th June 2017) for disease outcomes. Person-time exposed to UMEC or UMEC/VI during follow-up will be classified in several exposure categories:

Currently exposed to UMEC/VI or UMEC: current exposure is person-time starting from the index date and continuing until the earliest of:

1. The censoring date (ie. patient continuously used the index medication during the whole study period)

   OR

2. Discontinuation of prescribing the index medication (UMEC or UMEC/VI) considered to have occurred if there is either:

   - A break of at least 91 days between prescriptions for the index medication. The discontinuation date is set at 30 days after the prescription prior to the break. (Note: After this break, the patient may resume the same index medication (drug hiatus) or switch to a different inhaled COPD medication (See Section 8.3.2.3).

     or

   - Complete discontinuation in prescribing of the index medication and no further inhaled COPD medication of any kind until the censoring date (See Section 8.3.2.3). The discontinuation date is set at 30 days after the final prescription.

   It will not be possible to determine whether a patient discontinues UMEC or UMEC/VI if they are censored between 31 and 90 days after their last prescription. These patients will be flagged, and the primary analysis will

take a conservative approach for these patients and assume they were only exposed for the 30 days period following their last prescription.

If a patient discontinues the index medication but resumes taking that index medication at a later date, the second exposure period will also be considered as part of "currently exposed" time.

OR

3. An immediate switch to another inhaled COPD medication (See Section 8.3.2.3)
    - Patient starts taking another inhaled COPD medication during an interval that is between ≤30 days before the discontinuation date for the index treatment and ≤60 days after the discontinuation date for the index treatment. The immediate switching date will be defined as the date of first prescription for the new therapy.

Previously exposed to UMEC/VI or UMEC: for patients with a defined discontinuation date or a switch date (see above), previous exposure to an index medication is all person-time starting from the discontinuation or switch date and continuing until either the censoring date (in instances of complete discontinuation or latent switch), or, the date the patient resumes taking the same index medication (in instances of a drug hiatus).

Note: Patients who continuously use their index medication through to censoring will have no "previously exposed time" defined.

Concurrent exposure to other COPD maintenance therapies: As it is possible that some patients will be taking another COPD maintenance therapy concomitantly at index date or will start up another COPD maintenance therapy at some time during follow up while still taking their index medication, we will also flag patients who have had periods of time where they are exposed to more than just the index medication. Concurrent exposure is person-time starting from the date of the first prescription for another COPD maintenance therapy (or the index date in the case of therapies started concomitant with the index medication), and continuing until the earliest of the censoring date, the discontinuation date for the other COPD maintenance therapy (if observed, i.e. complete cessation or a break of at least 91 days between prescriptions) or the discontinuation date for the index medication (if observed). After treatment patterns have been assessed, the most common concurrent medications observed will be considered for this analysis.

8.3.2. Outcome definitions

All codes and detailed algorithms will be reviewed by a clinician, agreed with the study Scientific Committee and summarised in the detailed statistical analysis plan.

8.3.2.1. Objective 1

For *Objective 1* to estimate possible off-label prescribing, new users of UMEC/VI, UMEC, or other LABD will be further split by a diagnosis of: (a) COPD, (b) asthma, or (c) neither COPD nor asthma, as described below. These definitions will be applied in a stepwise manner, whereby the definition of COPD will be applied first. For those who do not meet the COPD definition, we will then look to see if they fulfil the case definition of asthma. Lastly, patients who meet neither the COPD nor asthma definition will be captured in the third category.

1. **COPD:** Patients will be considered to have COPD if they have a COPD diagnosis recorded any time in their PPD history up to and including the index UMEC/VI, UMEC, or other LABD prescription date through their censoring date and were age 35 years or older at the time of their first ever COPD medical code.
2. **Asthma:** Patients who did not fulfil the case definition of COPD as described above will be considered to have asthma if their most recent asthma medical code is a maximum of two years prior to their index date (up to and including the index UMEC/VI, UMEC, or other LABD prescription date through to their censoring date). The asthma code list is derived from a recently published asthma diagnosis validation study in CPRD (Nissen, 2018).
3. **Neither COPD nor asthma:** Patients will be classified into this category if they did not meet either the definition of COPD or asthma above.

Different time periods for identification of the COPD or asthma diagnosis will be explored (See Section 8.7.2 for sensitivity analysis description).

For the purposes of this study, possible off-label prescribing is defined as use in a patient not classified as having COPD.

Possible off label prescribing of UMEC:

- **Proportion of all UMEC users in the asthma group or the neither asthma nor COPD group**

$$\frac{\text{\# patients in “Asthma group” or “Neither asthma nor COPD group” with an index prescription for UMEC}}{\text{\# patients with an index prescription for UMEC}}$$

Possible off label prescribing of UMEC/VI:

- **Proportion of all UMEC/VI users in the asthma or the neither asthma nor COPD group**

$$\frac{\text{\# patients in “Asthma group” or “Neither asthma nor COPD group” with an index prescription for UMEC/VI}}{\text{\# patients with an index prescription for UMEC/VI}}$$

Possible off label prescribing for the other LABD group will be calculated as described above separately for other LAMA, other LABA and other LAMA/LABA. Denominators in both cases will be all patients with an index prescription in that particular LABD group.

For the other LAMA subgroup only, a secondary definition will also be used to account for the September, 2014 authorisation of tiotropium to be used as an add on therapy to ICS/LABA for the treatment of asthma in patients with asthma exacerbations. Other LAMA sub-group off-label prescribing definition 2 will therefore be defined as prescribing of other LAMA in patients in the asthma or other diagnosis group *unless they had an asthma diagnosis and a prescription for 2.5mcg tiotropium along with a concomitant prescription of an ICS/LABA* on or after 13/09/2014.

For the other LABA subgroup only, a secondary definition will also be used to account for the fact that LABA plus an ICS in two devices might be an option utilized to treat asthma. Other LABA sub-group off-label prescribing definition 3 will therefore be defined as prescribing of an 'Other LABA' in the asthma or other diagnosis group *unless they had an asthma diagnosis and a concomitant ICS at index date along with their index Other LABA.*

8.3.2.2. Objective 2

For *Objective 2*, in those currently or previously exposed to UMEC/VI or UMEC we will enumerate all events that occur from index prescription date until censoring of the following incident events:

1. Myocardial infarction, Heart failure, Stroke

We will derive diagnoses for these events using Read Code or ICD-9 or ICD-10 code lists. Validated code lists have been published from multiple UK EMR databases, including CPRD, for myocardial infarction event [Hammad, 2008; Coloma, 2013; Herrett, 2013] and ischaemic stroke [Ruigomez, 2010]. In the primary analysis these outcomes will be defined using information recorded in primary care (i.e. the GP record) and supplemented with information from secondary care (HES/ONS). For heart failure, we will focus on recorded instances of newly diagnosed heart failure, i.e. first ever congestive heart failure diagnosis in the available history after the index date.

2. Pneumonia

We will derive diagnoses for these events using Read Code or ICD-9 or ICD-10 code lists based on a code list from a recently published study on pneumonia in COPD patients using the CPRD GOLD data [DiSantostefano, 2014].

In the primary analysis, pneumonia will be defined based on a recorded diagnosis in the GP record, and further supplemented with the HES record. A secondary analysis will consider pneumonia recorded only in the GP record.

3. Death

The event of death will be primarily derived from EMR databases using Read Code lists or specifics flags, depending on the database. The primary analysis will also consider cardiovascular death using data from ONS mortality statistics, where available.

4. Episodes of COPD exacerbations

The count and exacerbation rate per person year will be calculated. COPD exacerbations will be identified using a validated algorithm based on medical and treatment codes that have been shown to result in PPV of 86% and sensitivity of 63%: (1) a medical diagnosis of LRTI or acute exacerbations of COPD, or (2) a prescription of COPD-specific antibiotic combined with OCS for 5-14 days, or (3) a record of two or more respiratory symptoms of acute exacerbations of COPD along with a prescription of COPD-specific antibiotics and/or OCS on the same day [Rothnie, 2016]. These combined strategies will be used only after removing any acute exacerbation of COPD events occurring on the same date as codes suggestive of a visit for annual COPD review or provision of rescue packs for COPD-specific antibiotics or OCS.

In the primary analysis, exacerbations will be defined in the GP record and further supplemented with HES data. A secondary analysis will define exacerbations using only information in the GP record.

8.3.2.3. Objective 3

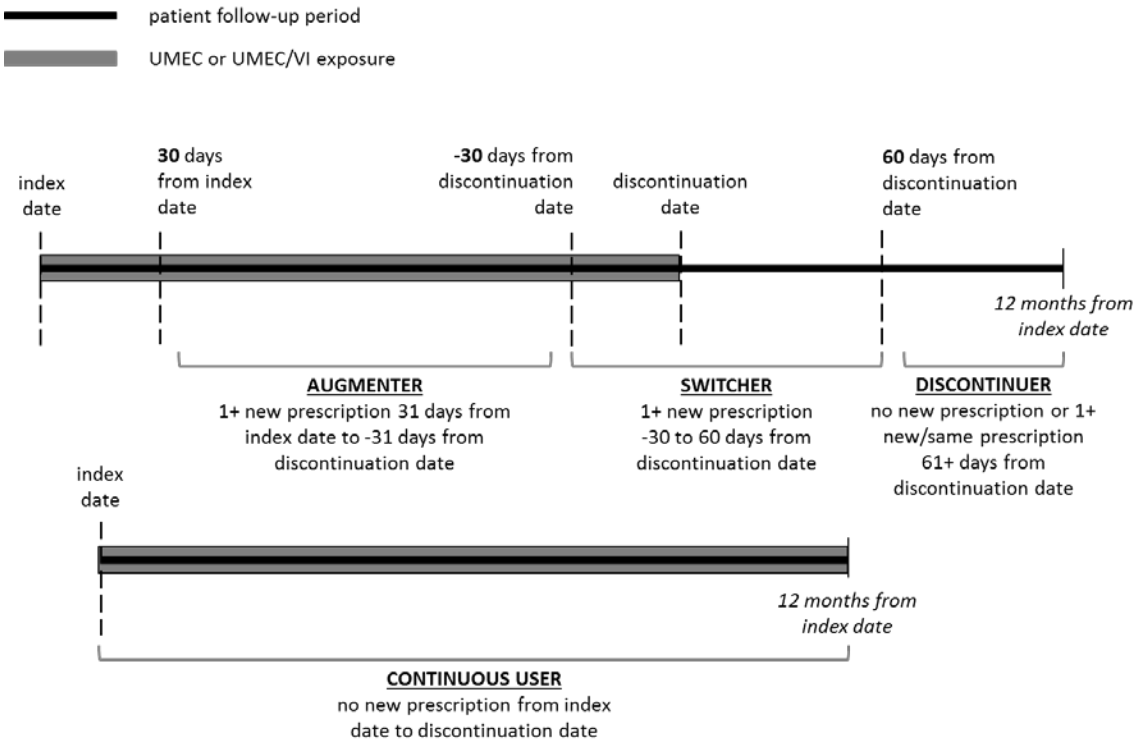
For *Objective 3*, in new users of UMEC/VI or UMEC defined during the identification period, with at least 12 months of recorded data following initiation, we will separately describe treatment patterns and adherence of inhalation therapies.

Treatment patterns

Treatment patterns will be considered only in patients with at least 12 months of follow-up after their index treatment. It will not be possible to determine whether a patient discontinues UMEC or UMEC/VI if they are censored between 31 and 90 days after their last prescription. These patients will be flagged, and the primary analysis will take a conservative approach for these patients and assume they were only exposed for the 30 days period following their last prescription.

For patients who are not taking a concomitant COPD (inhalation) maintenance therapy at the time of the index prescription, a number of mutually exclusive treatment patterns will be defined (as shown in Figure 3). We will describe the first change within the 12 months period following initiation.

Figure 3 Treatment patterns for patients who are not taking a concomitant COPD maintenance therapy



a. *Continuous Use:* Patient DOES NOT start taking another inhaled COPD maintenance therapy, and continues to use index treatment through the 12 months after the index date.

b. *Augmentation:* Patient starts taking another inhaled COPD maintenance therapy (1 or more prescriptions) and the new treatment starts ≥31 days after the index date and ≥31 days before the discontinuation date for the index treatment or the end of 12 months following the index date. The augmentation date will be defined as the date of first prescription for the new COPD maintenance therapy. Note: for patients who qualify for more than one index medication (i.e. both UMEC and UMEC/VI), the change from the first qualifying medication to the second qualifying medication will be considered a switch and not an augmentation. This is in line with the decision to allow patients to enter the study separately for UMEC and UMEC/VI (i.e. they are considered as separate products).

c. *Immediate Switching:* Patient starts taking another inhaled COPD maintenance therapy (1 or more prescriptions) within 12 months of the index date, and the new treatment starts during an interval that is between ≤30 days before the discontinuation date for the index treatment and ≤60 days after the discontinuation date for the index treatment. The switching date will be defined as the date of first prescription for the new COPD maintenance therapy. Note: for patients who qualify for more than one index medication (i.e. both UMEC and UMEC/VI), the change from the first qualifying medication to the second qualifying medication will always be considered a switch as described.

d. *Discontinuation:* Patient meets the definition of discontinuation as defined in 8.3.1.3 within 12 months of the index date.

Discontinuers will be followed until 12 months after the index date and classified according to whether they:

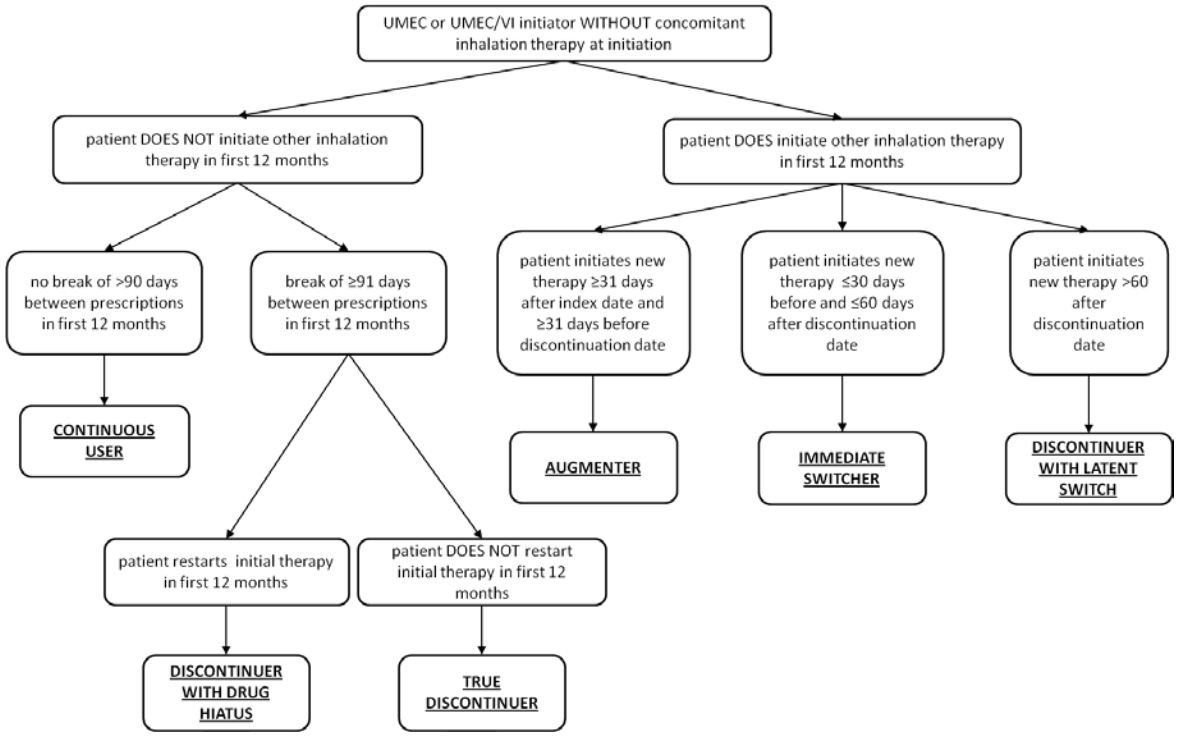
a) do not restart the index medication and do not start a new inhaled COPD maintenance treatment (i.e. true discontinuers)

b) restart the index medication (i.e. patients taking a drug hiatus)

c) start a new inhaled COPD maintenance treatment >60 days after discontinuation (i.e. latent switchers). Note: for patients who qualify for more than one index medication (i.e. both UMEC and UMEC/VI), the change from the first qualifying medication to the second qualifying medication will be considered a latent switch based on the rationale described earlier.

The six mutually exclusive treatment groups will be identified using the algorithm shown in Figure 4.

Figure 4 Algorithm for identifying mutually exclusive groups of treatment patterns for patients who are not taking a concomitant COPD maintenance therapy at index date



The following treatment switches or augmentations may possibly occur:

Initial treatment	Treatment switch	Treatment augmentation
UMEC	LAMA[1]	LABA
	LABA	ICS/LABA[2]
UMEC/VI	ICS/LABA[3]	
	LABA	ICS/LABA[2]
	LAMA	
	LAMA/LABA[1]	
	ICS/LABA[2]	

1. LAMA and LAMA/LABA different to the index medication
2. Fixed Combination of Inhaled Corticosteroid and Long-Acting Beta2-Agonist

For patients who are taking a concomitant COPD (inhalation) maintenance therapy at the time of the index prescription, treatment patterns that will be considered include continuous use of both drugs, discontinuation of the index medication (continue to use the concomitant medication), discontinuation of the concomitant medication (continue to use the index medication), discontinuation of both medications at the same time.

We will only describe the first change within the 12 months period following initiation and may consider only those mostly commonly occurring concomitant medications at index date.

Treatment adherence

Treatment adherence will be assessed from the index UMEC/VI or UMEC prescription until the end of the 12 months after the index date. Treatment adherence will be measured in the first 12 months of follow-up, for patients with at least 12 months of follow-up after initiation of the index drug.

Medication possession ratio (MPR) will be calculated only in those with 12 complete months of follow-up from the index date and at least one additional UMEC or UMEC/VI prescription after the index prescription.

Calculated as follows:

$$\frac{\text{Number of days in possession of UMEC (or UMEC/VI) between last prescription date and index date}}{\text{Total number of days between index date and last prescription date}}$$

Where number of days in possession is calculated by multiplying the number of prescriptions in the period (minus the last prescription) by the assumed duration of 30 days and where last prescription date is the last prescription date recorded before the end of the follow-up period or discontinuation date, whichever occurs first. (Note: each patient will have a unique denominator). Additions to the index medication are allowed as long as the patient is still exposed to the index medication.

The MPR will be expressed as a percentage, with nonadherence defined as MPR <80% and adherence defined as MPR ≥80%.

Proportion of days covered (PDC) will be calculated in patients with 12 complete months of follow-up from the index date.

Calculated as follows:

$$\frac{\text{Number of days in possession of UMEC (or UMEC/VI) over 12 months follow-up period}}{\text{365 days}}$$

where number of days in possession is calculated by multiplying the number of prescriptions (at any dose) in the period (minus the last prescription) by the assumed duration of 30 days and where last prescription date is the last prescription date recorded before the end of the follow-up period or discontinuation date, whichever occurs first.

All eligible patients are included in the PDC calculation as only a single prescription of the index mediation is required.

The PDC will be expressed as a percentage. For the 0-12 months period, PDC values will range from a minimum of 8% (only had one index prescription over 365 days) to a maximum of 100% (had medication available every day for the 365 days study period). The PDC will also be dichotomised, with nonadherence defined as PDC <80% and adherence defined as PDC ≥80%.

8.3.3. Confounders and effect modifiers

The following variables will be used in Objective 1 to describe new users of UMEC/VI, UMEC, or other LABD in respect to patient demographics, co-morbidity, disease burden, and COPD or asthma medication use.

Demographics at baseline

- **Age at index prescription date**: Mean (SD) and categories of: younger than 65, 65 years or older. For objective 1, we will also create two additional categories: younger than 18 years, 18 to 64 years.

- **Gender**: (female or male)

- **Smoking status**: categories of: current smoker, ex-smoker, no/never smoker, and missing. Smoking will be ascertained using records searched through all available history up to three months after the index date. Nearest record to index date will be used.

- **BMI:** Mean (SD) and categories of: Underweight <18.5, Normal 18.5 - 24.9, Overweight 25.0 - 29.9, and Obese ≥30.0. BMI is either taken as recorded in the database or calculated as weight in kilograms divided by height in meters squared. This value can occur any time before to three months after the index date; value taken nearest prior to index date will be used.

- **Area based deprivation measures:** the most recently available version of each national index of multiple deprivation (IMD) or Townsend deprivation data will be used to classify small areas according to quintiles or deciles of relative

deprivation. Patients will then be classified according to the deprivation level of their own area of residence.

- Region of practice at index date: The Strategic Health Authority for practice postcode within England, and the country i.e. Wales, Scotland, or Northern Ireland for the rest.

- Respiratory conditions: For the Neither Asthma nor COPD diagnosis group only, common Respiratory READ codes (Chapter H: Respiratory System Codes) occurring in the 12 months prior to index date will be analysed to describe other respiratory conditions.

Disease burden at baseline

- **COPD exacerbations** will be flagged in the 12 months prior to index date and the rate (per person-year) and 95% confidence interval will be calculated. Further, the total number of exacerbations will be described and also presented as 0, 1 and 2+ events This will be done in two groups, first using primary care data only for the full group of patients and second using both primary care and secondary care (HES) data for the subset of patients eligible for linkage. In this second group, we will further differentiate between those with moderate exacerbations (i.e. recorded only in primary care) and those with moderate and severe exacerbations (i.e. recorded in primary and/or secondary care). (See Section 8.3.2.2 for definition)
- **Dyspnoea** will be identified as having a code for Medical Research Council (MRC) dyspnoea in the 12 months prior to index date and will be characterised into MRC Grades 1-5 or MRC missing. The count and percent of patients in each group and the mean (SD) MRC will be reported. Value taken nearest prior to index date will be used.

- **COPD severity** will be characterised by airflow limitation as measured by lung function test (spirometry) in the 24 months prior to index date. Lung function parameter of forced expiratory volume in one second, FEV_1, percent predicted will be used and expressed as Mean (SD) and split in categories modified from the GOLD 2006 classification of airflow limitation [GOLD, 2009], using cut points of $FEV_1 \geq 80\%$ predicted for mild Grade 1, $\geq 50\%$ to $<80\%$ FEV_1 predicted for moderate Grade 2, $\geq 30\%$ to $<50\%$ FEV_1 predicted for severe Grade 3, and $<30\%$ FEV1 predicted for very severe Grade 4. Patients with missing values will be categorised as 'missing'. The count and percent of patients in each group will be reported. Value taken nearest prior to index date will be used.

  Further, the value for FEV_1/FVC ratio in the 24 months prior to index date will flagged and expressed as Mean (SD) and categorised as less than 70%, equal or more than 70%, and missing. Value taken nearest prior to index date will be used.

Comorbidity

- **Past history of cardio-and cerebrovascular diseases** will be flagged (Yes/No) in all available history prior to index date (See Section 8.3.2.2 for definition)

- **History of beta-blocker prescribing** will be identified in the one year period prior to index date (See Section 8.3.2.2 for definition). The proportion of patients with one or more prescriptions for a beta-blocker will be reported.

- **Past history of pneumonia, gastroesophageal reflux disease, diabetes, renal disease (acute and chronic) and cancer** (recorded only in primary care) will be flagged (Yes/No) in all available history prior to index date (See Section 8.3.2.2 for definition).

Prior use of respiratory medication at baseline

Utilization of other respiratory therapies in the 12 months prior to index date will be flagged and the count and percentage of patients with at least one prescription for that type of medication will be calculated. Further, the total number of prescriptions of each type of drug will be described. The types of COPD therapies to be ascertained are outlined in Table 4 below. For the purposes of this analysis, only fixed dose combinations will be considered.

Table 4 Categories of respiratory medications

Category	Description
SABD§	Short-Acting Beta2-Agonist (SABA), Short-Acting Anticholinergic (SAMA), Fixed Combinations of SABA/ Cromoglycate Fixed Combinations of SABA/SAMA
ICS and SABA/ICS*	Inhaled Corticosteroids OR Fixed Combination of Short-Acting Beta2-Agonist and Inhaled Corticosteroid
LABA	Long-Acting Beta2-Agonists
ICS/LABA*	Fixed Combination of Inhaled Corticosteroid and Long-Acting Beta2-Agonist
LAMA*	Long-Acting Anticholinergics
LAMA/LABA	Fixed Combination of Long-Acting Beta2-Agonist along with a Long-Acting Anticholinergic
Theophylline*	Theophylline and its derivates
Roflumilast	Roflumilast (Oral PDE4 inhibitor)
Oral corticosteroids*	

§ Asthma medications categorised as "reliever"
*Asthma medications categorised as "maintenance"

For SABD, we will also describe the count and percent of patients with more than four prescriptions.

For Oral Corticosteroids (OCS), we will describe only "chronic use" which is defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days.

8.4. Data sources

Primary care data

The study population will be identified in a distributed network of the UK Primary Care EMR databases, see Section 8.2 and Table 3.

CPRD-GOLD will serve as the main primary care database for development and benchmarking of analyses. It contains data extracted from Vision Primary Care EMR systems, and is described in more detail below. Other databases comprising data from the other main primary care EMR systems will vary to some extent. Nevertheless, a number of common factors constrain all systems such that there is a large degree of similarity in terms of both the information captured, and the data models:

- All systems capture information from the same underlying health system.
- All systems must comply with national NHS information standards and procedures. This includes implementing standard clinical and therapeutic terminologies, and communications with pathology laboratory systems.

- All systems are required to generate and report comparable information for national initiatives such as the Quality and Outcomes Framework, and National Diabetes Audits

- All systems are required to support some level of interoperability, exemplified by the GP2GP standard for electronic transfer of individual EMRs when a patient moves to a different practice.

CPRD-GOLD contains the anonymised, longitudinal medical records of patients registered with contributing primary care practices across the UK. The GOLD database covers approximately 3.6% of the current UK population, including practices in England, Northern Ireland, Scotland and Wales. As of July 2018 there were 738 GP practices and 15.5M acceptable (research quality) patients in GOLD, of which 2.3M are active (still alive and registered with the GP practice). Data has been collected from GP practices since 1987.The CPRD-GOLD database has been used previously for descriptive drug utilization studies for prescription medications in respiratory diseases [Ashworth, 2004;

van Staa, 2003; DiSantostefano, 2014]. Descriptive and pharmacoepidemiological studies of patients with COPD have been conducted in PPD including validation of physician-recorded COPD diagnosis [

Quint, 2014] and evaluation of COPD co-morbidities [Soriano, 2005].

The Health Improvement Network (THIN) was established in 2002 and facilitates the collection of non-identified patient data from UK General Practice (GP) clinical systems. IQVIA has a License Agreement to use the data collected by THIN for medical research and treatment analysis. As of January 2018, the THIN data available for research includes the Electronic Medical Records (EMRs) from over 17 million patients in the UK, 3.1 million of which are registered with an actively contributing THIN GP practice. All data are fully anonymised, processed and validated by CSD Medical Research UK [THIN 2017].

CPRD-GOLD and THIN contain patient registration information and all care events that general practice staff record in order to support the ongoing clinical care and management of their patients. This includes demographic information (age, sex, weight etc.), records of clinical events (medical diagnoses), referrals to specialists and secondary care settings, prescriptions issued in primary care, records of immunisations/vaccinations, diagnostic testing, lifestyle information (e.g. smoking and alcohol status), and all other types of care administered as part of routine GP practice. Furthermore, free text notes which are routinely entered in the comment field of the electronic patient record can also be accessed, once they have been anonymised. The NHS dictionary of medicines and devices (dm+d) is used as a dictionary containing unique identifiers (codes) and associated textual descriptions for representing medicines and medical devices in information systems and electronic communications (http://www.dmd.nhs.uk/). CPRD-GOLD and THIN contain data from the Vision EMR system which uses Read codes - specifically the Unified 5-byte Version 2 Read code set - as the basic means to record patient findings and procedures, and other relevant information.

Linked data

Linkage of CPRD-GOLD data to other patient level datasets including but not limited to HES, is possible for a subset of around 2 million patients. Patients in CPRD-GOLD are considered eligible for linkage if they are currently registered with the 224 consented English practices that continue to participate in the linkage scheme. Additionally, patients must have the necessary identifiers (e.g. NHS number) to enable linkage of the primary care data (CPRD-GOLD) with other patient level datasets.

- Hospital Episodes Statistics (HES): HES is a data warehouse containing details of all inpatient episodes of care (including day cases), outpatient appointments and A&E attendances at NHS hospitals in England. This data is collected during a patient's time primarily for administrative reasons, but is designed to enable secondary use. As well as patient demographic information and admission and discharge information, the inpatient data includes coded information about diagnoses (ICD-10) and procedures (OPCS 4 codes). Outpatient data contains information about appointment dates and times, and specialties, but much less coded clinical information. Further information is available at: http://www.hscic.gov.uk/hes.

- Office for National Statistics (ONS) Mortality statistics: Mortality data for England and Wales are based on the details collected when deaths are certified and registered. Details available in the linked data include underlying and contributory causes of death (ICD-10).

Monitoring uptake of study drugs

Regular data uploads will be used to evaluate LABD uptake by identifying patients taking UMEC/VI, UMEC or other LABD during the exposure identification period from July 1, 2014 until June 30, 2016. We will pilot various time intervals of data uploads depending on the upload frequency in each database participating in the distributed network. These data will also be useful in determining when the necessary sample size is expected to be reached.

Description of validated diagnoses

All code lists will be agreed with data partners across the distributed network of EMR databases and include review with at least one physician currently practicing in the UK. Where possible code lists already validated and published will be utilised. Further, a recently completed validation study in the PPD will provide validated definitions of COPD diagnosis and COPD exacerbations for this study [Rothnie, 2016] and of asthma diagnosis [Nissen, 2018]. Availability of some validated code lists is indicated in the Section 8.3.2 Study Outcomes.

8.5. Study size

The three objectives of this study are descriptive in nature. Hence, we do not propose a formal hypothesis-driven specification of sample size.

If we assume 5% of patients will use UMEC/VI off-label, then a sample size of 1,000 new users in each group produces a 95% confidence interval equal to the sample proportion plus or minus 1.3% (NCSS PASS: Confidence interval of a proportion)

A recently conducted study (GSK protocol: WEUSKOP6976) identified nearly 40,000 (N=39,639) new users of COPD maintenance therapy with a long acting bronchodilator in a prevalent COPD cohort over a 4-year period (2009-2012) extracted from the CPRD GOLD. Fifty-four percent (N=21,366) of these new users were newly prescribed with LAMA containing treatment regimen. Therefore, we can expect at least 10,000 new LABD users in the CPRD GOLD alone over the up to 24 month of the patients' identification period.

We will conduct regular checks of the UMEC/VI and UMEC uptake, on a 6-monthly basis.

8.6. Data management

Data will be collected retrospectively from the selected databases. All programming will be performed using Stata (StataCorp. College Station, TX) or SAS (Cary, NC). A trained epidemiologist and database analyst will perform all programming and analysis work.

Selection of the data integration model will be dependent on the final choice of partner databases. We will evaluate all options including:

- A minimally integrated model where all data extraction, processing and analysis is conducted entirely separately for each database, with a pooled analysis of aggregate data undertaken by the co-ordinating centre.

- A maximally integrated model where data from each database is combined at the earliest opportunity using a common data model. Whether the integrated dataset exists physically (in a single database), or virtually (with data stored in a number of structurally identical but physically separated databases), all subsequent processing analysis is carried out using a single suite of programs.

- In practice the level of data integration may fall between these two extremes, and may vary for different database partners.

For all data management and analysis tasks undertaken by database partners, we will encourage standardisation as far as possible through provision of detailed specifications including dataset specifications and variable naming conventions, algorithms and pseudo-code for derived variables, and sharing of Stata programs for complex analytical tasks.

8.6.1. Data handling conventions

Definitions and data handling conventions are described in other sections.

8.6.2. Resourcing needs

GSK will outsource this study to the PPD GSK will closely collaborate and monitor the deliverables including finalization of the study protocol, acquisition of data from data partners, development of the common data model, and development of programs and conducting the analysis, and finalizing the study report. Further, the Scientific Committee will provide an oversight of the study conduct including deliverables from the PPD

8.6.3. Timings of Assessment during follow-up

The proposed analysis design is descriptive using retrospective EMR cohort of patients newly prescribed with UMEC/VI, UMEC or other LABD. As this study is purely observational without any intervention, there are no specific assessments.

8.7. Data analysis

A detailed statistical analysis plan will be prepared and managed by the PPD and agreed with GSK and Scientific Committee.

8.7.1. Essential analysis

8.7.1.1. Describing the exposure cohorts

Descriptive statistics (mean (SD); median (range)) on the duration of time until censoring and the reasons for censoring for the full cohort as well as by index medication group (UMEC, UMEC/VI or other LABD) will be described. Descriptive statistics will also be provided for all cohorts (CPRD+THIN, CPRD-GOLD only, THIN and CPRD-GOLD patients eligible for linkage with both HES and ONS data).

For the UMEC and UMEC/VI cohort, descriptive statistics (mean (SD); median (range)) on the duration of time *currently exposed* will be also described.

The proportion of patients contributing more than one index drug will also be described. For these patients the mean (SD) time in days between the discontinuation date of the first index medication and the index date of the subsequent medication (in cases where the two index medications do not overlap) or the mean (SD) time during which the two index medications overlap (in cases where the medication do overlap) will also be calculated.

Further, the proportion of UMEC and UMEC/VI users that were flagged as taking concomitant maintenance therapy at the index date (See Section 8.3.1.2 for definition) will be calculated and the type of concomitant drug described. Lastly, descriptive analysis using traits specified in Section 8.3.3 for each of the three drug groups (UMEC, UMEC/VI and other LABD) will be performed with count and percentage for categorical variables and mean (SD) for continuous variables. The total count of exacerbations will be categorised as described in Section 8.3.3. As well, the exacerbation rate (expressed per person-year) and 95% confidence interval will be calculated. For the rate calculations, the numerator will be the total number of exacerbations and the denominator will be all person time from

12 months prior to the prescription initiation date up to and including the prescription initiation date.

8.7.1.2. Objective 1

In new users of UMEC/VI, UMEC, or other LABD, report the proportion of patients with possible off-label prescribing and characterize them, using information available prior to and at the time of index prescription initiation, in respect to patient demographics, disease burden, co-morbidity, and COPD or asthma medication use.

This objective will be explored among all new users combined and for each cohort, UMEC/VI, UMEC, or other LABD separately. If sample size allows, patients in the other LABD cohort will be further stratified by type of index LABD (LAMA, LABA, LAMA/LABA).

Patients in each defined exposure category (UMEC/VI, UMEC, or other LABD) will be split into the three pre-defined disease categories of 1) COPD, 2) asthma, and 3) neither COPD nor asthma (see Section 8.3.2.1 for definitions) and frequencies tabulated. The proportion of patients with potential off-label prescribing will also be calculated as defined in Section 8.3.2.1.

As well, for the COPD and asthma groups, we will describe what proportion had the diagnosis before and after their medication index date (as a binary variable (before/after) and by distinct time periods before and after such as 0-3 months, 3-6 months, etc).

Descriptive analysis using traits specified in Section 8.3.3 will be reported for each of the three main disease categories of COPD, asthma, and neither COPD nor asthma with count and percentage for categorical variables and mean (SD) for continuous variables. Further, the descriptive statistics will be repeated in the groups of patients who are identified as on label and potentially prescribed off label UMEC or UMEC/VI.

The total count of exacerbations will be categorised (for patients with COPD) as described in Section 8.3.3 and a summary per category tabulated. As well, the exacerbation rate (expressed per person-year) and 95% confidence interval will be calculated. For the rate calculations, the numerator will be the total number of exacerbations and the denominator will be all person time from 12 months prior to the prescription initiation date up to and including the prescription initiation date.

8.7.1.3. Objective 2

In new users of UMEC/VI and UMEC, quantify incidence of major cardiovascular and cerebrovascular events, mortality, pneumonia, and rate of exacerbations of COPD during follow-up.

We will enumerate counts and rates (new events/person-time) of pre-defined events (See Section 8.3.2.2 for definitions) within each of the new user cohorts of UMEC/VI and UMEC during follow-up. All analyses will be descriptive. Further, all analyses will be split by concomitant ICS-containing medication use at index date.

For the primary analysis, we will enumerate counts and rates for outcome events occurring during follow-up time classified as *currently exposed to UMEC or UMEC/VI* (see section 8.3.1 for exposure definitions). First, using the full cohort of patients with identification of events in primary care data only (both CPRD and THIN data sources). And secondly, using information from primary care, secondary care (HES) and mortality data (ONS) in patients eligible for linkage with both HES and ONS data.

Two secondary analyses will be carried out in both primary care data only and in those with linked to HES and ONS:

1. enumerate counts and rates for outcome events occurring during follow-up classified as *currently AND previously exposed to UMEC or UMEC/VI*.

2. enumerate counts and rates for outcome events occurring during follow-up classified as *currently exposed* to UMEC or UMEC/VI in patients who have had a concurrent treatment with other maintenance therapy at any time (see Section 8.3.1.3 for definition of concurrent treatment), and separately, enumerate counts and incidence (or rate for COPD exacerbations) for outcome events occurring during *currently exposed* follow-up to UMEC or UMEC/VI in patients who have NOT had a concurrent treatment at any time.

For counts of myocardial infarction, first *and* subsequent events occurring during the relevant follow up will be included. For calculation of incidence rates with 95% confidence intervals, we will consider only the first occurrence of myocardial infarction for each patient, and censor the person time for any patient at the time of occurrence of the first outcome event. The incidence rate will be stratified by presence of past events of myocardial infarction as collected from available patients' history and stratified as none, one, and two or more prior events. Further, we will take the first event of myocardial infarction and ascertain time from index date to the first event. The time to first event will be visualised using Kaplan-Meier plot.

Identical analysis will be conducted for the events of stroke and pneumonia.

For newly diagnosed congestive heart failure, only patients with new diagnosis of congestive heart failure will be placed in numerator. The denominator will only consist of patients at risk of incident congestive heart failure, i.e., excluding patients with ongoing management of heart failure at index date from the analysis.

Counts and incidence for cardiovascular outcomes will be stratified by concomitant beta-blocker prescribing at index date. Concomitant use will be defined as in Section 8.3.1.2 - at least two continuous prescriptions for a beta-blocker which start either before, or up to 30 days after the index date, and overlap for at least 30 days with the index treatment.

Death will be flagged and summarised as a proportion of patients who died. Further, we will calculate survival rate by dividing the total number of deaths by person-time from index date until date of death or other censoring. Survival time will be visualised using Kaplan-Meier plot. The primary analysis will additionally enumerate counts and incidence of cardiovascular death.

For exacerbations of COPD (as defined in Section 8.3.3) all events occurring during the relevant follow up will be included. For calculation of rates with 95% confidence intervals, the rate will be calculated as total count of exacerbation events divided by the relevant person-time and standardised per person year. To account for additional variability in exacerbation rates between individuals, negative binomial regression will be also considered to produce the rates as well as 95% confidence intervals [Glynn, 1993; Glynn, 1996].

8.7.1.4. Objective 3

In new users of UMEC/VI or UMEC with at least 12 months of follow-up, describe treatment patterns and adherence including Medication Possession Ratio and Proportion of Days Covered within the first 12 months of follow-up.

The following analyses will be undertaken separately for new users of UMEC and UMEC/VI. Only prescriptions for inhaler therapies will be considered.

1. Treatment patterns

Among patients that have at least 12 months of follow-up and that do not have concomitant use of another maintenance therapy at index date, describe the count and percentage of patients falling into the four main mutually exclusive categories defined in Section 8.3.2.3 (continuous users, augmenters, switchers and discontinuers). The count and percentage of discontinuers that (a) truly discontinue, (b) restart the index therapy after a break, and (c) start a new maintenance therapy after a break, will also be described. As well, the mean (SD) time (in days) from the index to the first change (among those with a change) will be reported and a Kaplan-Meier plot created.

For patients with at least 12 months of follow-up who are taking a concomitant COPD maintenance therapy at index date, the count and percentage of patients falling into the mutually exclusive categories defined in Section 8.3.2.3 will be described. Treatment patterns may be limited to only the commonly prescribed concomitant therapy groups may be described to ensure adequate sample size. As well, the mean (SD) time (in days) from the index date to the first change (among those with a change) will be calculated and a Kaplan-Meier plot will be created.

Note: As it is not possible to determine whether a patient discontinues UMEC or UMEC/VI if they are censored between 31 and 90 days after their last prescription, these patients will be flagged, and the primary analysis will take a conservative approach for these patients and assume they were only exposed for the 30 days period following their last prescription.

2. Treatment adherence

Calculate the count and percentage of patients who are adherent to the initially prescribed therapy during follow-up using the MPR and PDC as described in Section 8.3.2.3. As well as cut offs of >=80% for the MPR and PDC, the mean (SD) of these measures as continuous variables during follow-up will also be calculated.

The calculation of MPR requires that patients received at least two prescriptions during the required 12 months period of follow-up; the PDC can be calculated with only one prescription and also requires a fixed follow-up period of 12 months. Therefore, the denominator and the numbers of patients eligible for these two measures will differ.

Patients will first be stratified as adherent or non-adherent to initial therapy with UMEC or UMEC/VI based on (a) MPR >=80% and MPR <80% during follow-up, and (b) PDC >=80% and PDC <80% during the first 12 months of follow-up. Patient demographics, co-morbidity, disease burden, and other COPD and asthma medications (as defined in Section 8.3.3) will be described for adherent and non-adherent patient groups for each of MRC and PDC definitions with count and percentage for categorical variables and mean (SD) for continuous variables. Additional analyses and adjustments to the planned analysis may be performed as the data warrant.

8.7.2. Exploratory analysis

The following exploratory sensitivity analyses are planned:

1. For the definition of possible off-label prescribing in Objective 1, in addition to the definitions described in Section 8.3.2, an alternative time period to identify COPD or asthma diagnoses that spans the whole patient history until the prescription index date only, will be used.
2. For Objective 2, just the primary analysis will be further stratified by on-label and possible off-label prescribing.
3. For Objective 3 analyses will be further stratified by on-label and possible off-label prescribing.

8.7.3. General considerations for data analyses

Not Applicable

8.8. Quality control

CPRD-GOLD has been used previously for descriptive drug utilization studies for prescription medications in respiratory diseases [DiSantostefano, 2014; Ashworth, 2004;

van Staa, 2003]. Validated code lists have been published from multiple databases including CPRD for myocardial infarction event [Hammad, 2008; Coloma, 2013; Herrett, 2013] and ischaemic stroke [Ruigomez, 2010].

The standard operating procedures of PPD and of each research partner in the distributed network will guide the conduct of the study, and will include internal quality audits; following rules for secure storage and backup of confidential data and study documentation; quality control procedures for programming, and requirements for senior scientific review. All patients will be required to have data of acceptable research quality according to each database standards.

The QC of analysis will be performed in accordance with GSK Standard Operating Procedures (SOPs) and Guidance Documents, specifically the SOP_52213 (4.0) : Conducting Quality Control Review of Worldwide Epidemiology Study Results . The common data model will allow the use of one set of programming following creation of a standardised structure. Wherever feasible, all statistical programming will be independently reviewed by a second analyst, with oversight by a senior statistician. Key study documents, such as the ISAC Protocol, statistical analysis plan, and study reports will undergo quality-control checks and review by the Scientific Steering Committee. Archiving of the project materials will be performed in accordance with GSK SOPs for documentation and archiving of observational studies.

8.9. Limitations of the research methods

Sample size within a given timeframe is difficult to predict since it depends upon the rate of prescribing by primary care physicians and, hence, the study size and timelines are cautiously estimated.

Generalizability of the UK data to the other EU countries can represent a study limitation. GSK proposed this study in the UK environment, because of the presence of robust data and possibility to use a distributed design within one health-care system ensuring fast delivery. GSK will compare patient population characteristics (inclusive of gender, age, COPD severity and prior treatment) in patients identified in this retrospective study with patients prospectively enrolled in the multi-country European study. If a different patient profile or pattern of use for UMEC/VI or UMEC among patients with COPD is observed, GSK will initiate additional drug utilization study representing other countries within the EU with high quality medical records data available.

Data on new exposure to UMEC/VI, UMEC, or other LABD are based on records of prescribed medications, rather than dispensed data. Currently, information on prescriptions initiated in hospitals or secondary care are not accessible for analysis. As such, the

adherence measures proposed to be calculated in this study are not a "direct" measure of medication taking but rather reflect repeat prescribing.

We also assume that each prescribed medication will provide treatment for 30 days, which may introduce a bias, albeit one of a systematic nature, impacting on all medications.

As this study is primarily aimed to understand the rate of key patient outcomes specifically in new users of UMEC and UMEC/VI, the design of the study only assigns current and previously exposed follow-up time to only those users initiating one (or both) of these drugs in the identification period of July 1, 2014 to June 30, 2016. By this design, new users of Other LABD who may have switched to either UMEC or UMEC/VI after the identification period during the *one-year follow-up window* will not have that UMEC or UMEC/VI exposure time counted in this study. Despite this, we feel we still will have captured a broad cross section of new users of UMEC and UMEC/VI in the immediate post approval period for these mediations.

The final sets of databases, CPRD GOLD and THIN, are both based on the same GP software (Vision) and have comparable data structures and coding schemes. This reduces complexity in the analyses with PPD performing the bulk of the post-extraction data processing and analysis tasks. This provides the greatest control over standardisation and quality assurance of the analyses.

There are no routine databases available to researchers capturing for secondary and tertiary care prescribing in the UK. Hence, we will not be able to ascertain exposure start accurately in the cases where the UMEC/VI, UMEC, or other LABD was initially prescribed by a chest specialist or at discharge from the hospital. There is only one pilot project managed by the IMS Company providing data on prescribing in secondary/tertiary care, but the link to primary care data is available only for a small subset of CPRD GOLD practices only resulting in a total of only few hundreds of COPD patients.

The ascertainment of the pneumonia events from GP records may lead into issues with misclassification of the event. We will not be able to access chest x-ray results or analysis of sputum samples to confirm the diagnosis and, therefore, the resulting event rates will need to interpret with caution. Similarly, heart failure may be misclassified as undiagnosed COPD [Valk, 2015].

Using information recorded in secondary care (HES) and at the time of death (ONS mortality data) will enable better capture of pneumonia, heart failure and other outcomes, including acute exacerbations of COPD which may be under-recorded in GP records. However, better classification of these outcomes comes at a cost of reduced sample size as not all patients in the study will be eligible for linkage to HES and ONS.

8.9.1. Study closure/uninterpretability of results

If uptake of the UMEC/VI or UMEC is lower than expected and fewer than 500 patients per group is ascertained the descriptive information about off-label medication use and medication usage patterns may not be as robust. If identification of UMEC/VI patients

results in fewer patients than anticipated, GSK will consider either extending the patient identification period beyond two years and/or add additional databases to the study.

8.10. Other aspects

Not Applicable

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

CPRD and other similar EMR systems are databases of pseudonymised EMRs. Our approach to the study is naturalistic; we will not be conducting further diagnostic tests, alter disease management strategies, or collect data in addition to or above routine medical care. Where further information is likely to be helpful, for example for ascertaining cardiovascular endpoints, this will be sought from the patients' registered GP, usually via a structured questionnaire, and/or anonymised chart review (for example copies of hospital discharge letters). This is a well-established process co-ordinated and managed by a separate group within PPD to ensure that researchers and analysts with access to the EMR database cannot identify individual general practices or patients.

Linkage of the primary care databases to other datasets such as HES is undertaken by a trusted third party (the Health and Social Care Information Centre). The identifiers (date of birth, gender, NHS number, postcode of residence) required for linkage are sent directly from the originating general practice to the trusted third party. PPD holds only a local patient identifier which is meaningful only at the patients' registered general practice. This identifier is pseudonymised a second time before being made available to researchers and analysts with access to the database.

PPD processes have been reviewed by the Confidentiality Advisory Group (CAG) and approved by the Health Research Authority (HRA) and Secretary of State to process patient identifiable information without consent under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002. This effectively removes the obligation to obtain patient consent for the use of confidential patient information for conducting purely observational research using CPRD databases, and associated linked datasets. This approval is conditional on approval of a study protocol by the PPD Independent Scientific Advisory Committee (ISAC).

9.2. Subject confidentiality

CPRD and other EMR databases in the distributed network contain only fully de-identified patient data. No patient identifiable information will be available to the study team, or to GSK. All data held and processed by PPD and any other partners in the distributed

network will be done so in compliance with the relevant legal obligations including the Data Protection Act 1998.

All data will be held on a secure computer network, with access restricted to authorised users.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Based on the study objectives, it is unlikely that adverse events will be identified during this descriptive drug utilization study. Further, as the research utilises existing data sources of anonymised patient data, the minimum criteria needed to report serious and non-serious adverse events, pregnancy exposures, and other incidents related to a GSK product are not present in the data and thus there is no potential for reporting of adverse events, pregnancy exposures and other incidents in this study. The following minimum criteria for reporting are missing from the data sources: an identifiable patient.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

The final report of this Post-Authorization Safety Study will be provided to the European Medicines Agency and reported in appropriate regulatory documents in accordance with regulations. This study will also be submitted for consideration in the published literature.

11.2. Study reporting and publications

External communications

Interim and Final study reports will lead into development of peer-reviewed publications in collaboration with Scientific Committee.

Internal communications

Interim and Final reports will be circulated and archived according to GSK SOPs.

12. REFERENCES

Ashworth M, Latinovic R, Charlton J, Cox K, Rowlands G, Gulliford M. Why has antibiotic prescribing for respiratory illness declined in primary care? A longitudinal study using the General Practice Research Database. *J Public Health (Oxf)*. 2004; 26(3):268-274.

Bateman E, Nelson H, Bousquet J, Kral K, Sutton L, Ortega H et al. Meta-analysis: effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events. Ann Intern Med. 2008; 149(1):33-42.

Coloma PM, Valkhoff VE, Mazzaglia G, Nielsson MS, Pedersen L, Molokhia M et al. Identification of acute myocardial infarction from electronic healthcare records using different disease coding systems: a validation study in three European countries. BMJ Open. 2013; 3(6).

de Luise C, Lanes SF, Jacobsen J, Pedersen L, Sorensen HT. Cardiovascular and respiratory hospitalizations and mortality among users of tiotropium in Denmark. Eur J Epidemiol. 2007; 22(4):267-272.

DiSantostefano RL, Sampson T, Le HV, Hinds D, Davis KJ, Bakerly ND. Risk of Pneumonia with Inhaled Corticosteroid versus Long-Acting Bronchodilator Regimens in Chronic Obstructive Pulmonary Disease: A New-User Cohort Study. PLoS One. 2014; 9(5):e97149.

Gershon A, Croxford R, Calzavara A, To T, Stanbrook MB, Upshur R et al. Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease. JAMA Intern Med. 2013; 173(13):1175-1185.

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2018. Available at: https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/ Accessed 13/08/2018

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD. 2009. Available at: http://www.goldcopd.org/Guidelines/guideline-2010-gold-report.html. Accessed on 29/08/2014.

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD. 2018. Available at: https://goldcopd.org/gold-reports/ http://www.goldcopd.org/Guidelines/guidelines-resources.html. Accessed 13/08/2018

Glynn RJ, Buring JE. Ways of measuring rates of recurrent events. BMJ. 1996; 312(7027):364-367.

Glynn RJ, Stukel TA, Sharp SM, Bubolz TA, Freeman JL, Fisher ES. Estimating the variance of standardized rates of recurrent events, with application to hospitalizations among the elderly in New England. Am J Epidemiol. 1993; 137(7):776-786.

Hammad TA, McAdams MA, Feight A, Iyasu S, Dal Pan GJ. Determining the predictive value of Read/OXMIS codes to identify incident acute myocardial infarction in the General Practice Research Database. Pharmacoepidemiol Drug Saf. 2008; 17(12):1197-1201.

Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van ST et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ. 2013; 346:f2350.

Jara M, Lanes SF, Wentworth C, III, May C, Kesten S. Comparative safety of long-acting inhaled bronchodilators: a cohort study using the UK THIN primary care database. Drug Saf. 2007; 30(12):1151-1160.

Jara M, Wentworth C, III, Lanes S. A new user cohort study comparing the safety of long-acting inhaled bronchodilators in COPD. BMJ Open. 2012; 2(3).

Jenkins CR, Beasley R. Tiotropium Respimat increases the risk of mortality. Thorax. 2013; 68(1):5-7.

Mannino DM, Davis KJ, Kiri VA. Chronic obstructive pulmonary disease and hospitalizations for pneumonia in a US cohort. Respir Med. 2009; 103(2):224-229.

Millett ER, Quint JK, Smeeth L, Daniel RM, Thomas SL. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. PLoS One. 2013 Sep 11;8(9):e75131.

Morales DR. LABA monotherapy in asthma: an avoidable problem. Br J Gen Pract. 2013 Dec;63(617):627-8. doi: 10.3399

Mullerova H, Chigbo C, Hagan GW, Woodhead MA, Miravitlles M, Davis KJ et al. The natural history of community-acquired pneumonia in COPD patients: a population database analysis. Respir Med. 2012; 106(8):1124-1133.

Nelson HS. Long-acting beta-agonists in adult asthma: Evidence that these drugs are safe. Prim Care Respir J. 2006; 15(5):271-277.

Nissen F, Morales DR, Mullerova H, Smeeth L, Douglas IJ, Quint JK. Validation of asthma recording in the Clinical Practice Research Datalink (CPRD). BMJ open. 2017 Aug 1;7(8): e017474.

Quint JK, Mullerova H, DiSantostefano RL, Forbes H, Eaton S, Hurst JR et al. Validation of Chronic Obstructive Pulmonary Disease (COPD) recording in the Clinical Practice Research Datalink (CPRD_GOLD). BMJ Open. 2014.

Rothnie KJ, Müllerová H, Hurst JR, Smeeth L, Davis K, Thomas SL, et al. (2016) Validation of the Recording of Acute Exacerbations of COPD in UK Primary Care Electronic Healthcare Records. PLoS ONE 11(3): e0151357.

Ruigomez A, Martin-Merino E, Rodriguez LA. Validation of ischemic cerebrovascular diagnoses in the health improvement network (THIN). Pharmacoepidemiol Drug Saf. 2010; 19(6):579-585.

Sapey E and Stockley RA. COPD exacerbations. 2: aetiology. Thorax. 2006 Mar;61(3):250-8.

Sears MR. Safety of long-acting beta-agonists: are new data really required? Chest. 2009; 136(2):604-607.

Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. Chest. 2005; 128(4):2099-2107.

The Heath Improvement Network (THIN), https://www.iqvia.com/locations/uk-and-ireland/thin

Valk MJ, Broekhuizen BD, Mosterd A, Zuithoff NP, Hoes AW, Rutten FH. COPD in patients with stable heart failure in the primary care setting. International Journal of COPD. 2015;10:1219-1224.

van Staa TP, Cooper C, Leufkens HG, Lammers JW, Suissa S. The use of inhaled corticosteroids in the United Kingdom and the Netherlands. Respir Med. 2003; 97(5):578-585.

Verhamme KM, Afonso A, Romio S, Stricker BC, Brusselle GG, Sturkenboom MC. Use of tiotropium Respimat Soft Mist Inhaler versus HandiHaler and mortality in patients with COPD. Eur Respir J. 2013; 42(3):606-615.

Wise RA, Anzueto A, Cotton D, Dahl R, Devins T, Disse B et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Engl J Med. 2013; 369(16):1491-1501.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Tables

Complete list of Tables will be determined in a separate document of the Statistical analysis plan.

Figures

Complete list of Figures will be determined in a separate document of the Statistical analysis plan.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title:

WWE117397: Post-authorization safety Electronic Medical Records database retrospective cohort study of new users of inhaled UMEC/VI or new users of inhaled UMEC in the primary care setting

Study reference number:

EUPAS7761

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5
1.1.3 Study progress report(s)	☒	☐	☐	5
1.1.4 Interim progress report(s)	☒	☐	☐	5
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	6; 7
2.1.1 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)	☒	☐	☐	6.2
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	8.7.1.3
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	8.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	8.1
4.2.2 Age and sex?	☒	☐	☐	8.3.3
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☒	☐	☐	8.3.2.1
4.2.5 Duration of follow-up?	☒	☐	☐	8.3.1.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	8.3.1; 8.9
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	8.3.1.3
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	8.3.2; 8.9
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☒	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☐	☒	☐	

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	8.9
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.3.2
9.1.3 Covariates?	☒	☐	☐	8.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.3.2
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.3.2

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.3 Covariates?	☒	☐	☐	8.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	8.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	8.7.1
10.2 Are descriptive analyses included?	☒	☐	☐	8.7.1
10.3 Are stratified analyses included?	☒	☐	☐	8.7.1
10.4 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.5 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	8.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.2
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	11.1

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☒	☐	☐	8.9

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	8.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.2

Comments:

Ethical clearance is subject to approval of protocol by independent scientific advisory committee.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11.1
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11.2

Comments:

Name of main author of study protocol: PPD

Date: / /

Signature: _____