# 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 |

**Compound Number:** GSK573719, GW642444

**Development Phase** IV

**Effective Date:** 01-SEP-2014

**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):** [redacted]

## PASS information

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|---|---|
| **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** | 0.1 |
| **Date of last version of protocol** | 6 June 2014 |
| **EU PAS register number** | Study not yet registered |
| **Active substance** | Umeclidinium bromide/Vilanterol trifenatate (UMEC/VI)<br>ATC R03AL03: Adrenergics in combination with anticholinergics<br><br>Umeclidinium bromide (UMEC)<br>ATC R03BB07: Anticholinergics |
| **Medicinal product** | UMEC (Incruse™/Laventair™) , UMEC/VI (Anoro™)<br>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:<br>Tiotropium<br>Glycopyrronium<br>Glycopyrronium/Indacaterol<br>Aclidinium<br>Indacaterol<br>Formoterol<br>Salmeterol |

| | |
|---|---|
| **Product reference** | The EU Marketing Authorisation numbers are:<br>Anoro<br>EU/1/14/898/001<br>EU/1/14/898/002<br>EU/1/14/898/003<br>Laventair:<br>EU/1/14/899/001<br>EU/1/14/899/002<br>EU/1/14/899/003<br>Incruse:<br>EU/1/14/922/001<br>EU/1/14/922/002<br>EU/1/14/922/003 |
| **Procedure number** | Incruse: EMEA/H/C/002809<br>Anoro: EMEA/H/C/002751/0000/<br>Laventair: EMEA/H/C/003754 |
| **Marketing authorisation holder(s)** | GlaxoSmithKline Research & Development Limited<br>980 Great West Road,<br>Brentford<br>Middlesex,<br>TW8 9GS<br>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:<br><br>Objective 1: In *all* new users of UMEC/VI, UMEC, or other LABD report the proportion of patients with possible off-label use 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, COPD or asthma medication use, and health care resource utilization.<br><br>Objective 2: In new users of UMEC/VI, UMEC, or other LABD *diagnosed with COPD*, quantify incidence of major cardiovascular and cerebrovascular events, mortality, pneumonia /lower respiratory tract infections, and exacerbations of COPD during follow-up.<br><br>Objective 3: In new users of UMEC/VI or UMEC, *diagnosed with COPD*, describe treatment patterns (time to discontinuation, switch or augmentation) and adherence including Medication Possession Ratio and Proportion of Days Covered during follow-up. |
| **Country(-ies) of study** | United Kingdom |
| **Author** | [redacted]<br>Director, Respiratory Epidemiology<br>R&D Projects, Clinical Platforms & Sciences GlaxoSmithKline<br>Building 9, Iron Bridge Road,<br>Stockley Park West,<br>Uxbridge, Middlesex,<br>UB11 1BT<br><br>Tel. [redacted] |

# MARKETING AUTHORISATION HOLDER(S)

| | |
|---|---|
| **Marketing authorisation holder(s)** | GlaxoSmithKline Research & Development Limited<br>980 Great West Road,<br>Brentford, Middlesex, TW8 9GS<br>UK |
| **MAH contact person** | [redacted]<br>Senior Director, Respiratory Therapeutic Group Global Regulatory Affairs<br>GlaxoSmithKline Research & Development Ltd |

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# 1. LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AMI | Acute Myocardial Infarction |
| ATB | Antibiotics |
| CHF | Coronary Heart Failure |
| CI | Confidence Interval |
| COPD | Chronic Obstructive Pulmonary Disease |
| CPRD | Clinical Practice Research Datalink |
| CV | Cardiovascular |
| CVD | Cardiovascular Disease |
| DUR | Drug Utilization Review |
| EMR | Electronic Medical Records |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| FEV1 | Forced Expiratory Volume (in one second) |
| FVC | Forced Vital Capacity |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| GP | General Practitioner |
| GSK | GlaxoSmithKline |
| HCU | Health-Care Utilization |
| HES | Hospital Episodes Statistics |
| ICS | Inhaled Corticosteroids |
| LABA | Long-Acting Beta2-Agonists |
| LABD | Long-Acting Bronchodilator |
| LAMA | Long-Acting Muscarinics Antagonist |
| LRTI | Lower Respiratory Tract Infections |
| MACE | Major Adverse Cardiac Events |
| 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 |
| OR | Odds Ratio |
| RR | Risk Ratio |
| SAE | Serious Adverse Event |
| UK | United Kingdom |
| UMEC | Umeclidinium bromide |
| VI | Vilanterol trifenatate |

## Trademark Information

| Trademarks of the GlaxoSmithKline group of companies |
|---|
| Anoro |
| Incruse |
| Laventair |

| 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: Senior Director, Respiratory Therapeutic Group, Global Regulatory Affairs

Name: [redacted]

Address: GlaxoSmithKline Research & Development Ltd.

**Study Coordination**

The MAH has contracted with Clinical Practice Research Datalink (CPRD), 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 CPRD 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.

CPRD:
5th Floor,
151 Buckingham Palace Road,
London,
SW1W 9SZ

**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 two GSK employees, and two representatives from the CPRD. This group is assisting with protocol development, and will develop and review the statistical analysis plan, provide technical input during study development, assist with interpretation and dissemination of study results. Further clinical and methodological advice can be sought with other members of academia on 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**

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

[redacted] (Professor, Department of Epidemiology, Erasmus MC University Medical Center Rotterdam, The Netherlands)

Dr. [redacted] (Consultant in Chest medicine and Lecturer, Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine)

**CPRD Members**

Dr. [redacted] (Scientific Head, CPRD)

[redacted] (CPRD, WWE117397 Project Epidemiologist)

**GSK Members**

[redacted] (Senior Director, Respiratory Therapeutic Area Lead, Worldwide Epidemiology)

[redacted] (WWE117397 Project Epidemiologist and Director, Worldwide Epidemiology)

## SPONSOR SIGNATORY:

[redacted] 1-9-2014

Primary Author/ Project officer **Date**

[redacted] 1-9-2014

Therapy Area Leader **Date**

[redacted] 1-9-2014

VP, Worldwide 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: [redacted]

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: [redacted]
Fax: [redacted]

**Regulatory Agency Identifying Number(s):** PENDING

# 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.

Tim Williams

| | |
|---|---|
| Investigator Signature | Date |

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 evaluate feasibility of undertaking potential future risk-benefit studies.

**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 *all* new users of UMEC/VI, UMEC, or other LABD report the proportion of patients with possible off-label use 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, COPD or asthma medication use, and health care resource utilization.

Objective 2: In new users of UMEC/VI, UMEC or other LABD *diagnosed with COPD*, quantify incidence of major cardiovascular and cerebrovascular events, mortality, pneumonia/lower respiratory tract infections, and exacerbations of COPD during follow-up.

Objective 3: In new users of UMEC/VI or UMEC, *diagnosed with COPD*, describe treatment patterns (time to discontinuation, switch or augmentation) and adherence including Medication Possession Ratio and Proportion of Days Covered during follow-up.

**Study design**

Retrospective longitudinal non-interventional observational study of patients identified based on a new prescription (index prescription date) for UMEC/VI, UMEC, or other LABD and followed-up for up to 24 months from their index prescription date until censoring at death, leaving practice, index medication discontinuation, or end of follow-up at earliest of 730 days of follow-up or October 1, 2017.

**Population**

To address Objective 1, all new users of UMEC/VI, UMEC or other LABD will be included. To address Objective 2, these patients will be further limited to patients with diagnosis of COPD, identified based on occurrence of a record for at least one medical code for COPD in their history (including the day of the index prescription date). To address Objective 3, patients included in the Objective 2 will be further limited to new users of UMEC/VI or UMEC only.

**Variables**

*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 prior to and including index date with (a) COPD with or without concurrent asthma, (b) asthma only or (c) neither COPD nor asthma. For Objective 2 we will quantify incident events of cardiac ischaemia, heart failure, or stroke in patients at risk during the follow-up period based on their available history. Further, events of death, pneumonia/lower respiratory tract infections, and exacerbations of COPD will be counted. For Objective 3 we will describe treatment patterns including adherence with therapy.

*Exposures*

During the patient identification period, between July 1, 2014 and June 30, 2016, patients initiating UMEC/VI or UMEC will be defined by their first prescription for either UMEC/VI or UMEC. At the end of the patient identification period, we will also identify all new users of other LABD who did not initiate UMEC/VI or UMEC during the overall identification period (July 1 2014-June 30 2016). New other LABD use is defined as a prescription for a medication containing a new active substance of LAMA, LABA or a combination of LAMA/LABA that was never prescribed (recorded) in the past 12 months. 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. The other LABD group will be stratified as new use of LAMA, LABA, and LAMA/LABA containing medications based on the index prescription.

The new UMEC/VI, UMEC, or other LABD users will be followed from the date of their first ever new UMEC/VI, UMEC, or other LABD prescription (index date) until censoring at death, leaving practice, index medication discontinuation, or end of follow-up at earliest of 730 days of follow-up or October 1, 2017.

**Data sources**

Data will be derived from the distributed network of EMR databases, including the Clinical Practice Research Datalink (CPRD)-GOLD database and up to three other EMR databases. A distributed network of databases using a common data model is being considered.

**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 off-label use 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 for a respiratory diagnosis record [(a) COPD with or without concurrent asthma, (b) asthma only or (c) neither COPD nor asthma], and described by their demographics, co-morbidity, disease burden, COPD or asthma medication use, and health care resource utilization 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, UMEC, or other LABD with COPD, we will further enumerate count and incidence (new events/person-time) of cardiac ischaemia, heart failure, or stroke as well as events of death, pneumonia/lower respiratory tract infections, and exacerbations of COPD during follow-up. All analyses will be descriptive.

Objective 3: Among new user UMEC/VI or UMEC with COPD, we will describe treatment patterns (discontinuation, switching and augmentation) 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. 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.

**Milestones**

Start of periodic data evaluation: March 2015

Statistical and Operational analysis plan finalized: July 2015

Interim report: March 2017 (off-label use, interim analysis of follow-up)

Final report completed: Q4 2019

# 4. AMENDMENTS AND UPDATES

None.

# 5. MILESTONES

| Milestone | Planned date |
|---|---|
| Start of data collection | March 2015 |
| End of data collection | October 2017 or earlier if sufficient # of patients identified |
| Registration in the EU PAS register | To be registered |
| Interim report 1 (Drug Utilization) | March 2017 |
| Final report of study results (up to 24 months follow-up: treatment patterns, adherence, incidence of events of interest, linkages with HES and ONS mortality databases) | 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 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. LAMA/LABA fixed-dose combinations are identified in the treatment guidance document for COPD, when severity warrants the use of both medications [GOLD, 2014]. Currently, one other fixed-dose LAMA/LABA combination medication (glycopyrronium/indacaterol) is 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 monocomponent 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, 2014]. As there are fewer approved fixed dose LAMA/LABAs less is known about their risk/benefit profile.

There is a potential for off-label use 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, 2011]. 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]. They 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. 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, 2011].

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 randomized 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 10000 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 without prior exposure to UMEC/VI or UMEC. There is no apriori hypothesis to be tested.

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 comparing the distribution of comorbidities in the three cohorts at the time of index prescription.

Another specific focus is on quantifying and characterizing off-label use 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, UMEC, or other LABD as well as report on the incidence of events of pneumonia/lower respiratory tract infections (LRTI).

We will also describe patterns of use (e.g. adherence, discontinuation, switch or augmentation) among new users UMEC/VI and UMEC with a COPD diagnosis.

# 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 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 *all* new users of UMEC/VI, UMEC, or other LABD report the proportion of patients with a possible off-label use 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, COPD or asthma medication use, and health care resource utilization.

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

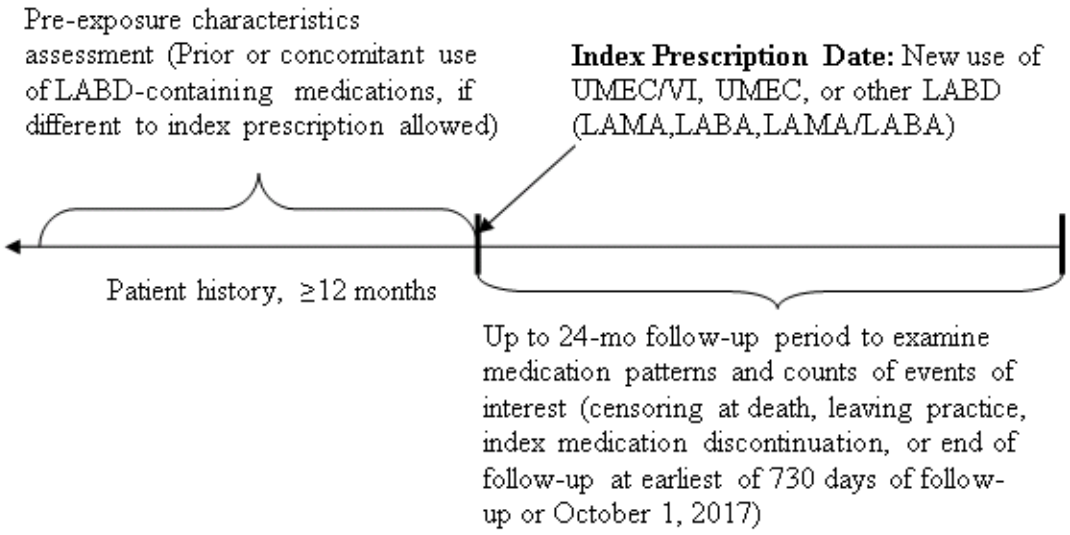
*Objective 3:* In new users of UMEC/VI or UMEC *diagnosed with COPD*, describe treatment patterns (time to discontinuation, switch or augmentation) and adherence including Medication Possession Ratio and Proportion of Days Covered during follow-up.

# 8. RESEARCH METHODS

## 8.1. Study Design

Retrospective longitudinal non-interventional observational study of patients identified based on a new prescription (index prescription date) for UMEC/VI, UMEC, or other LABD and followed-up from their index prescription date until censoring at death, leaving practice, index medication discontinuation, or end of follow-up at earliest of 730 days of follow-up or October 1, 2017 (Figure 1). Further, the definition of censoring at the index medication discontinuation will be explored. Our approach to the study is naturalistic, capturing routine medical care.

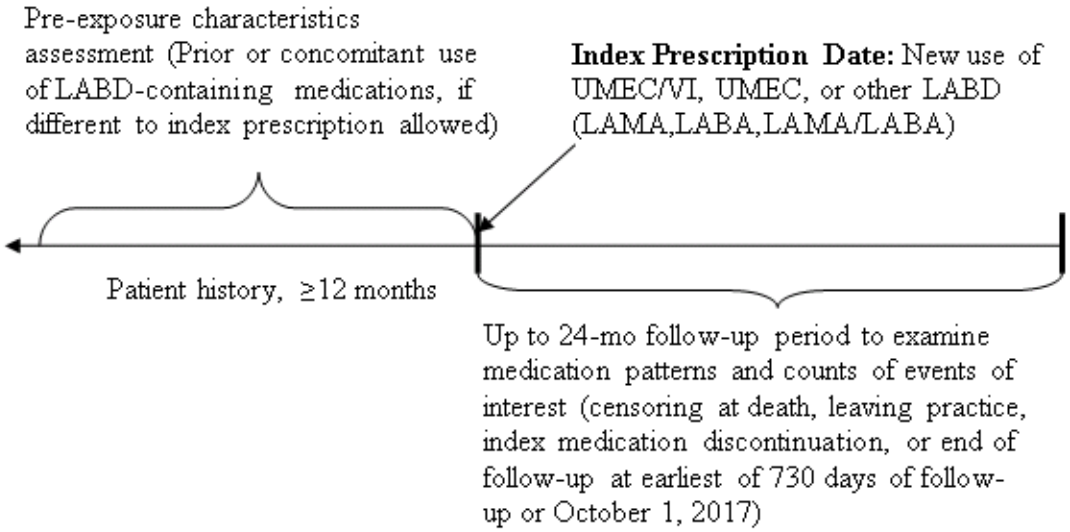
To evaluate Objective 1, all patients newly prescribed UMEC/VI, UMEC, or other LABD between July 1, 2014 and June 30, 2016 will be identified in UK-based distributed network of EMR databases. This time period was selected to correspond to the period of up to 24 months of UMEC/VI or UMEC availability in the UK (UMEC/VI launched on 9th June 2014 with availability to prescribers starting in July 2014; Figure 2).




Prior or concomitant use, from 12 month prior up to and including index date, of a LABD-containing medication, *different to the one being initiated*, will be allowed. To address Objective 2, these patients will be further limited to patients with diagnosis of COPD, identified based on occurrence of a record for at least one medical code for COPD in their history (including the day of the index prescription date). To address

Objective 3, patients included in the Objective 2 will be further limited to new users of UMEC/VI or UMEC only.

During the patient identification period (July 1, 2014 and June 30, 2016), patients initiating UMEC/VI or UMEC will be defined by their first prescription for either UMEC/VI or UMEC. At the end of the patient identification period, we will identify all new users of other LABD who did not initiate UMEC/VI or UMEC during the identification period (Section 8.3.2) New other LABD use is defined as a prescription for a new active substance of LAMA, LABA, or a combination of LAMA/LABA that was never prescribed (recorded) in the past 12 months (Section 8.3.2). Further the other LABD group will be stratified, where appropriate, as new use of LAMA, LABA, and LAMA/LABA containing medications (Figure 2).




The new UMEC/VI, UMEC, or other LABD users will be described from the date of their first ever new UMEC/VI, UMEC, or other LABD prescription during the patient identification period until censoring (Figure 1). Any change of LABD during this follow-up period will be described.

**Figure 1 Study Schematic: Individual patient history assessment**

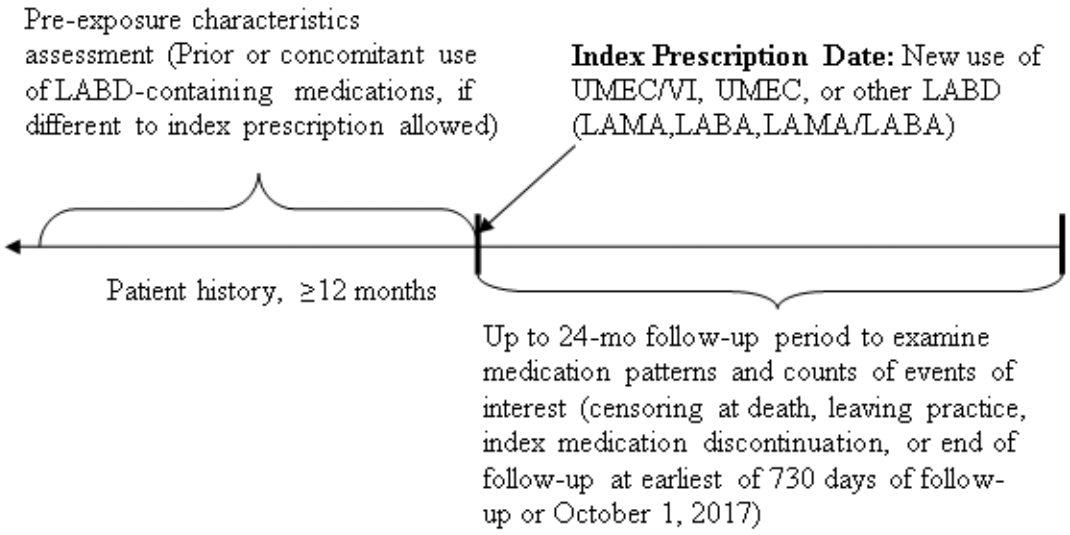
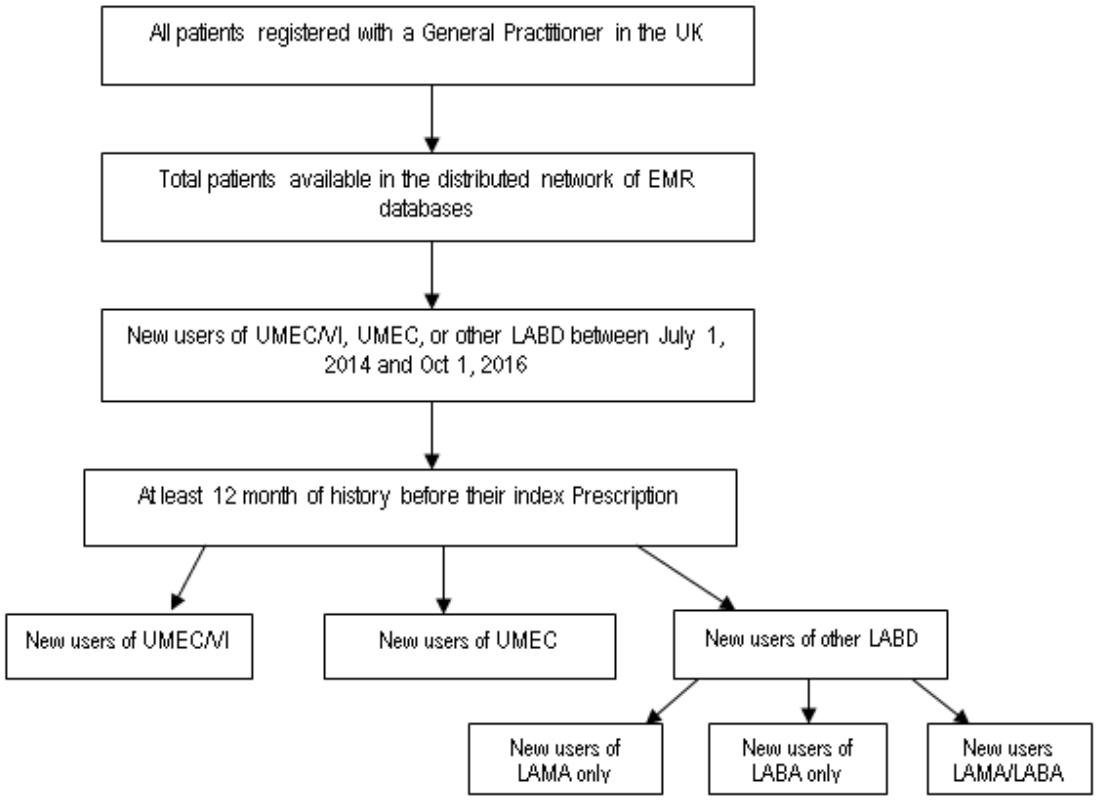



**Figure 2 Consort Diagram Schematic: Cohort Selection**



## 8.2. Setting

The study population will be identified from several UK Primary Care EMR databases.

The Clinical Practice Research Datalink GOLD database (referred to hereafter as CPRD-GOLD) will serve as the main database for development and benchmarking of analyses. However the required sample size is likely to substantially exceed that available in CPRD-GOLD or any other single UK Primary Care database currently available. It will therefore be necessary to combine data from more than one database. Each database currently comprises EMR data from a single vendor system, and we will consider for inclusion those databases which contain data from the three main systems which currently cover over 85% of UK general practices. These include: Vision from In Practice Systems (InPS); EMIS Web from Egton Medical Information Systems; and SystmOne from The Phoenix Partnership (TPP). An overview of candidate databases is provided in Table 3. As the co-coordinating centre for the study, CPRD will identify, evaluate and select additional databases for inclusion, using criteria agreed in advance with GSK.

We will ensure the 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 will be linked to additional datasets to obtain richer information about study outcome events where possible due to a substantial lag of 12-18 months between the CPRD or other EMR data availability and HES. These supplemental sources of medical information are including (but not limited to):

- Hospital Episodes Statistics (HES)
- Office for National Statistics (ONS) death registration dataset
- Clinical audit databases managed by the National Institute for Cardiovascular Outcomes research (NICOR): including the Myocardial Infarction National Audit Program (MINAP), and Cardiac Rhythm Management database

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

**Table 3 Summary of the characteristics for the EMR databases proposed to be included in the distributed network**

| | CPRD-GOLD | CPRD-EMIS | CPRD-TPP | THIN | QRESEARCH | ResearchOne |
|---|---|---|---|---|---|---|
| **EMR System** | **Vision (InPS)** | **EMIS Web (EMIS)** | **SystmOne (TPP)** | **Vision (InPS)** | **EMIS (EMIS)** | **SystmOne (TPP)** |
| **Database size:**<br>**a) total patients**<br>**b) current patients**<br>**c) total practices**<br>**d) current practices** | a) 13.5M<br>b) 5.7M<br>c) 684<br>d) 520 | d) 49 practices with a further 115 ready to start. Extensive recruitment over next 12-24 months. | Extensive recruitment over next 12-24 months. | a) 11.1M<br>b) 3.7M<br>c) 578<br>d) n/k | b) 5.1M<br>c) 754<br>d) 607 | c) approx 350 |
| **Patient geographical coverage** | UK | England (initial phase) | England (initial phase) | UK | UK | n/k |
| **Linked data available** | For a subset of English practices: HES, ONS, NICOR (MINAP) | Likely for a subset of English practices | Likely for a subset of English practices | A small subset of practices have been linked to HES | For a subset of practices: based on pseudonymised NHS number | |
| **Regularity of data uploads** | Monthly | Monthly | Monthly | Monthly | | |
| **Allows obtaining further evidence from GP practice medical records** | Yes (subset of practices) | Likely (for subset of practices) | Likely (for subset of practices) | Yes | | |
| **Further specifications** | | | | ~50% of flagged practices overlap with the CPRD. | | |

**Study time period:** Regular data uploads will be used to identify patients newly initiating LABD from July 1, 2014 until June 30, 2016 to evaluate LABD uptake, including UMEC/VI and UMEC. We will pilot various time intervals of data uploads depending on the upload frequency in each database participating in the distributed network. A minimum period of 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 standardized period of history to describe selected patient demographics, disease burden, previous respiratory medication use, and health care resource utilization. New users will be followed-up for up to 24 months from their index prescription date (censoring at death, leaving practice, index medication discontinuation, or end of follow-up at earliest of 730 days of follow-up or October 1, 2017).

### 8.2.1. Study Populations

The study population will consist of new users of LABD treatment.

During the patient identification period between July 1, 2014 and June 30, 2016, patients initiating UMEC/VI or UMEC will be defined by their first prescription for either UMEC/VI or UMEC. At the end of the patient identification period, we will identify all new users of other LABD who did not initiate UMEC/VI or UMEC during the identification period. New other LABD use is defined as a prescription for a new active substance of LAMA, LABA, or a combination of LAMA/LABA that was never taken (recorded) in the past 12 months (Section 8.3.2). Prior or concomitant use, from 12 month prior up to and including index date, of a LABD-containing medication, *different to the one being initiated*, will be allowed.

#### 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.
2. Have at least one year of data prior to index prescription date to allow characterization of patient's status, demographics and clinical characteristics.

#### 8.2.1.2. Exclusion Criteria

1. Having a prescription for the same substance of LABD during the period of at least 12 months prior to index date.

To address Objective 1, all new users of UMEC/VI, UMEC or other LABD will be included. To address Objective 2, these patients will be further limited to patients with diagnosis of COPD, identified based on occurrence of a record for at least one medical code for COPD in their history (including the day of the index prescription date). The clinical diagnosis of COPD will be further supported by a requirement of minimum age of 35 years at the first ever recorded COPD medical diagnosis code.

To address Objective 3, patients included in the Objective 2 will be further limited to new users of UMEC/VI or UMEC only.

## 8.3. Variables

### 8.3.1. Outcome definitions

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

#### 8.3.1.1. Objective 1

For Objective 1 to estimate a possible off-label use at index date all new users of UMEC/VI, UMEC, or other LABD will be further split by a diagnosis of: (a) COPD with or without concurrent asthma, (b) asthma only, or (c) neither COPD nor asthma, as

described below. Descriptive statistics of patient characteristics of each of these diagnosis groups will then be populated.

**1. Asthma only**

Among patients without a record for a prior COPD medical diagnosis any time in the available history, we will define two sub-categories of asthma only:

1.1. Current Asthma: Patients will be considered to have current asthma if (a) at least two medical codes for asthma diagnosis are recorded in the 12 months up to and including the index UMEC/VI, UMEC, or LABD prescription date AND (b) a record of one or more prescription for asthma medications (either maintenance or reliever, See section 8.3.3 and Table 4 for list of medications) in the 12 months up to and including the index date.

1.2. Probable Asthma: Patients will be considered to have probable asthma if they either (a) have a record for asthma diagnosis anytime in their history, but do not fulfil the definition of "current asthma" above, OR (b) have a record for four or more prescriptions for asthma maintenance therapy (See Section 8.3.3 and Table 4 for list of medications) in the 12 months up to and including the index date regardless if they ever had a record for asthma anytime time in their history.

2. **COPD:** Patients will be considered to have COPD if they have a COPD diagnosis any time in their available history up to and including the index UMEC/VI, UMEC, or other LABD prescription date and were age 35 years or older at the time of their first ever COPD medical code. COPD patients will be further stratified as being diagnosed with (a) COPD only or (b) COPD with history of asthma diagnosis. COPD patients with history of asthma will be further split by concurrent or past history of asthma, the latter category being defined by a presence of one or more diagnosis for asthma in the available history prior to prescription index date, but not fulfilling the current asthma definition, as defined above.

3. **Neither COPD nor asthma (i.e. Other Diagnosis):** Patients will be classified into this category if they (a) have a record for a respiratory diagnosis different to COPD or Asthma categories as defined above, OR (b) have an absence of any respiratory diagnosis. We will search all available history and ascertain presence of diagnoses for a selection of respiratory diseases or syndromes inclusive of COPD diagnosed before age of 35 years, chronic bronchitis, lower respiratory tract infections, wheeze, bronchiectasis, alpha1-antiprypsin deficiency, lung cancer, chronic cough, respiratory symptoms like sputum or phlegm production, and wheezing.

#### 8.3.1.2. Objective 2

For *Objective 2*, in new users of UMEC/VI, UMEC and other LABD with COPD, we will enumerate during the follow-up period, from index prescription date until censoring the frequency of the following incident events:

**1. Myocardial infarction, Heart failure, Stroke**

We will derive diagnoses for these events using ReadCode 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]. For heart failure, we will focus on recorded diagnoses of (a) newly diagnosed heart failure, i.e., first ever congestive heart failure diagnosis in the available history after the index date or (b) acute worsening of heart failure in patient with a prior diagnosis of heart failure. Worsening of heart failure will be defined as an un-scheduled (emergency) hospital admission with a primary reason of heart failure. Further, in a subset of eligible patients, we will conduct a linkage with supplemental sources of medical information, inclusive of HES and MINAP registry, to obtain richer information about outcome events where possible due to a substantial lag of 12-18 months between the CPRD or other EMR data availability and HES [Herrett, 2013].

**2. Combined event of Pneumonia/Lower Respiratory Tract Infections (LRTI)**

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

*Pneumonia/LRTI* will be defined based on a recorded diagnosis in the GP record, further supplemented with HES record, where available. Distinctions will be made between episodes of severe and non-severe pneumonia/LRTI.

Non-Severe pneumonia/LRTI will be classified as an episode of that was treated in the community and did not result in hospitalization or death. The subset of severe events will be defined (1) an episode of for pneumonia or LRTI that included a record for hospitalization or death.

Exacerbations of COPD are lower respiratory tract infections. These events are captured systematically as a separate outcome.

**3. Death**

The event of death will be primarily derived from EMR databases using ReadCode lists or specifics flags, depending on the database. Where available, for GP practices located in England, a linkage in ONS Mortality statistics will be used to confirm event and date of death.

**4. Episodes of moderate-to-severe COPD exacerbations**

The count and exacerbation rate per person year will be calculated. We will define the COPD exacerbation events based on the ongoing validation study in the CPRD (GSK protocol: WEUSKOP5893; CPRD ISAC protocol: 13_116) reporting in Q3 2014. Provisionally, we define Moderate-to-Severe COPD exacerbations as episodes that can be split into two types (1) severe episodes are associated with a hospital admissions for COPD and (2) moderate episodes are based on a record in the database for COPD-

specific antibiotics together with oral corticosteroids and/or diagnosis of COPD exacerbation without a reference to hospital admission.

**5. Health-care utilization events**

5.1. Visits to the general practice will be flagged using specific practice contacts variables where available. The visit type will be further stratified as (a) administrative and (b) clinical (patient's visit to GP, nurse, out-of-hours visits, home visits) encounters. Events will be counted and standardized per 365.25 days.

5.2. Emergency (i.e., non-scheduled) hospitalizations for causes other than COPD (i.e., excluding hospital admissions for COPD exacerbations) will be flagged. Additionally, in a subset of patients eligible for linkage of data with HES, we will ascertain hospital admission events using HES only and derive number of days of hospital stay.

#### 8.3.1.3. Objective 3

For *Objective 3*, we will describe treatment patterns and adherence in new users of UMEC/VI and UMEC diagnosed with COPD using the following measures. All measures will allow for a pre-defined "permissible gap" of < 30 days in use. Gaps in therapy of <30 days will be considered to be continuous treatment (handling of missing values is described in Section 8.3.2. Treatment discontinuation).

1. **Discontinuation** from the initial prescription of UMEC/VI or UMEC during follow-up and the time to the last prescription (in days) will be defined as follows:

    1.1 Never have another of UMEC/VI or UMEC prescription respectively, after the baseline prescription.
    1.2 Received only one further prescription of the same of UMEC/VI or UMEC and did not have a switch or addition between the two prescriptions.

2. **Treatment switching and augmentation** of medications for COPD

The first occurrence of either switch or augmentation during follow-up will be described.

2.1 Switches from UMEC/VI alone or UMEC alone to other COPD medication(s) and the time to the first treatment switch (in days).

Switching will be considered in the cases where another COPD maintenance therapy is either started after the end of the initial therapy (within the follow-up period) or prior to the end of the initial therapy and continued to 60 days post the final initial therapy prescription. To account for censoring, we will evaluate the time between the initial therapy end date and the end of the follow-up period. If this time was greater than the average gap between the initial therapy

prescriptions then the patient was considered to have switched to the new therapy.

The date of the switch will therefore be first date of the new COPD maintenance therapy.

2.2 Addition (augmentation) of COPD medications to UMEC/VI alone or UMEC alone at the time of index prescription and the time to the first treatment addition (in days)

Any therapy that continuously overlapped with the initial therapy for more than 30 days post initial therapy index will be considered an augmentation. If there were less than 30 days of continuous overlap, the total period of the initial therapy (from start of the initial prescription to the end of the last prescription) will be examined to determine if there was another prescription for the therapy and if so, it will be also classified as an augmentation.

The date of the augmentation will therefore be first date of the new COPD maintenance therapy.

The following treatment switches or augmentations may possibly occur:

| Initial treatment | Treatment switch | Treatment addition |
|---|---|---|
| UMEC | LAMA[1] | ICS |
| | LABA | LABA |
| | ICS | ICS/LABA[3] |
| | ICS/LABA[3] | Roflumilast |
| | ICS/LAMA[2] | |
| UMEC/VI | ICS | ICS |
| | LABA | ICS/LABA[3] |
| | LAMA | Roflumilast |
| | LAMA/LABA[1] | |
| | ICS/LAMA[2] | |
| | ICS/LABA[3] | |

1. LAMA and LAMA/LABA different to the index medication
2. Open combination of Inhaled Corticosteroid and Long-Acting Anticholinergic (Tiotropium) in two devices
3. Fixed Combination of Inhaled Corticosteroid and Long-Acting Beta2-Agonist, OR, Open combination of Inhaled Corticosteroid and Long-Acting Beta2-Agonist in two devices

## 3. Treatment adherence

To asses treatment adherence during follow-up, we will assume that the patient began using the UMEC/VI or UMEC on the day the medication was prescribed and used it daily for the number of days supplied.

3.1 **Medication possession ratio (MPR)** calculated by summing the number of days of being exposed (see Exposure Section 8.3.2) for all but the last prescription over the patients total follow-up before the patient switched, augmented, or discontinued the index medication and divided by the number of days between

the first and last prescription (Note: each patient will have a unique denominator). Additions to the 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%. A patient must have at least two prescriptions for the index medication without a switch or augmentation between them in order to be included in the MPR calculation.

3.2 **Proportion of days covered (PDC)** will be calculated as the number of days with a drug on hand divided by the number of days in the specified time period of 364.25 days for the 0-12 month time period. The numerator for the PDC is the number of days for which the patient had possession of the initially prescribed medication, or any regimen which contains the initially prescribed medication (i.e. an addition), while the denominator is always 364.25. All 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 month time period, PDC values will range from a minimum of 8% (only had one index prescription over 364.25 days) to a maximum of 100% (had medication available everyday for the 364.25 day study period). The PDC will also be dichotomized, with nonadherence defined as PDC <80% and adherence defined as PDC ≥80%.

### 8.3.2. Exposure definitions

All patients newly prescribed UMEC/VI, UMEC, or other LABD will be identified in UK-based distributed network of EMR databases between July 1, 2014 and June 30, 2016, corresponding with a period up to 24 months of UMEC/VI or UMEC availability to prescribers in the UK (Figure 1 and Figure 2). Prior or concomitant use, from 12 month prior up to and including index date, of a LABD-containing medication, containing a *different active substance to the one being initiated*, will be allowed.

First, during the patient identification period, between July 1, 2014 and June 30, 2016, patients initiating UMEC/VI or UMEC will be defined by their first prescription for either UMEC/VI or UMEC.

Second, we will identify all new users of other LABD who did not initiate UMEC/VI or UMEC during the identification period. New *other LABD* use is defined as a prescription for a new active substance of LAMA, LABA, or a combination of LAMA/LABA that was never taken (recorded) in the past 12 months. The use of other LABD includes but is not limited to medications containing: tiotropium, glycopyrronium, glycopyrronium/aclidinium, aclidinium, indacaterol, salmeterol, and formoterol, according to the availability. This list may need to be further modified depending on newly authorized medications in the class. Further the other LABD group will be stratified, where appropriate, as new users of LAMA, LABA, and LAMA/LABA containing medications (Table 4).

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.

For the duration of each individual prescription, all prescriptions will be given a *default length of 30 days per container prescribed*, irrespective of them having a recoded value for script length (less than 1% had a value recorded).

As concomitant use of an ICS is of particular interest for Objective 1, an ICS-containing medication use which overlaps with the index date of the UMEC/VI, UMEC, or other LABD prescription by at least one day, regardless of whether the ICS initiated before or after the index prescription, will be flagged.

### 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, COPD or asthma medication use, and health care resource utilization. The subpopulations derived for Objectives 2 and 3 will also be described by these baseline characteristics.

**Demographics**

- **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 anytime 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 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 the area in which their practice is located. A subset of patients will also be classified according to the deprivation level of their own area of residence.

- **Region**: patients will be classified according to the region of their registered general practice. A regional geography will be selected to correspond with health administrative boundaries while providing an appropriate level of granularity to capture geographical variation in health outcomes.

**Disease burden**

- **Moderate-to-severe 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 moderate to severe exacerbations will be described. (See Section 8.3.1.2 for definition)
- **Hospitalized exacerbations** (a subset of Moderate-to-Severe 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 hospitalized exacerbations will be described. (See Section 8.3.1.2 for definition)
- **Dyspnea** will be identified as having a code for Medical Research Council (MRC) dyspnea in the 12 months prior to index date and will be characterized 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 characterized by airflow limitation as measured by lung function test (spirometry) in the 12 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 $FEV_1$ ≥80% predicted for mild Grade 1, ≥50% to <80% $FEV_1$ predicted for moderate Grade 2, ≥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 categorized 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 nearest prior to index date will flagged and expressed as Mean (SD) and categorized as less than 70%, equal or more than 70%, and missing.

  Further classification of COPD severity using the 2013 GOLD groups A, B, C, and D or 'missing' (MRC or lung function data missing) will be derived using airflow limitation, dyspnoea, and history of moderate-to-severe exacerbations 12 months prior to index date [GOLD, 2014].

**Comorbidity**

- **Other concomitant respiratory conditions** that affect diagnosis and treatment of COPD will be flagged in all available history prior to index date (Yes/No for each group of conditions inclusive of alpha-1-antiprypsin deficiency, cystic fibrosis, and bronchiectasis).

- **Charlson score** will be defined by diagnosis codes and will be searched using all available history prior to the index date (index score). The Charlson comorbidity index as published will be adjusted by removing COPD. Individual diseases listed in the Charlson's comorbidity index disease will also be searched as separate entities (Yes/No) with the addition of Depression, Anxiety, Pneumonia, Gastro-oesophageal reflux, and Asthma.

- **Past history of cardio-and cerebrovascular diseases** will be flagged (Yes/No) in all available history prior to index date (See Section 8.3.1.2 for definition). In addition to diseases captured by Charlson comorbidity score, prevalence of arrhythmias will be explored.

- **Pneumonia/LRTI** events will be flagged (Yes/No) in all available history prior to index date and the rate (per person-year) and 95% confidence interval in the past 12 months only will be calculated (See Section 8.3.1.2 for definition).

**COPD or asthma medication use**

Utilization of other COPD 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 flagged. Further, the total number of prescriptions of each type of drug will be described.

For SABD, we will also describe the count and percent of patients with more than four prescriptions. The types of COPD therapies to be ascertained was outlined in Table 4 below

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.

Oxygen use will used as a marker of disease severity understanding the limitation of the CPRD-GOLD in respect to only capturing a subset of all oxygen prescriptions.

**Table 4 Categories of COPD and asthma medications**

| Category | Description |
|---|---|
| SABD§ | Short-Acting Beta2-Agonist (SABA),<br>Short-Acting Anticholinergic (SAMA),<br>Fixed Combinations of SABA/ Cromoglycate<br>Fixed Combinations of SABA/SAMA |
| ICS and SABA/ICS* | Inhaled Corticosteroids<br>OR<br>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<br>OR<br>Open combination of Inhaled Corticosteroid and Long-Acting Beta2-Agonist in two devices (LABA script overlaps with ICS by at least one day) |
| LAMA | Long-Acting Anticholinergics |
| ICS/LAMA* | Open combination of Inhaled Corticosteroid and Long-Acting Anticholinergic in two devices |
| LAMA/LABA | Fixed Combination of Long-Acting Beta2-Agonist along with a Long-Acting Anticholinergic<br>OR<br>Open combination of Long-Acting Beta2-Agonist and Long-Acting Anticholinergic in two devices |
| "Open triple" of ICS, LABA, and LAMA* | Fixed Combination of Inhaled Corticosteroid and Long-Acting Beta2-Agonist along with a Long-Acting Anticholinergic in two devices<br>OR<br>Open combination of Inhaled Corticosteroid and Long-Acting Beta2-Agonist and Long-Acting Anticholinergic in three devices<br>OR<br>Fixed combination of Long-Acting Beta2-Agonist and Long-Acting Anticholinergic along with Inhaled Corticosteroid in two devices |
| Theophylline* | Theophylline and its derivates |
| Roflumilast | Roflumilast (Oral PDE4 inhibitor) |
| LTRA* | Leukotriene Receptor Antagonist (montelukast, zafirlukast) |
| Anti-IgE* | Anti Immunoglobulin E (omalizumab) |
| Home oxygen therapy* | |
| Oral corticosteroids* | |

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

**Health care resource use**

- V**isits to the GP surgery** during 12 months prior to index date will be flagged and expressed as total counts by type. Only one event per day will be counted. Availability of information for specific types of GP office visit, e.g. clinical consultation, repeat prescription, respiratory nurse appointment will be explored. Phone calls to the GP office will not be included.

- **Hospitalizations for causes other than COPD** will be flagged in the 12 months prior to index date and the rate (per person-years) and 95% confidence interval will be calculated. Further, the total number of hospitalizations will be described.

## 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 patients 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 8.5% of the UK population, including practices in England, Northern Ireland, Scotland and Wales. As of May 2014 there were 684 GP practices and 13.5M acceptable (research quality) patients in GOLD, of which 5.7M are active (still alive and registered with the GP practice). Data has been collected from GP practices since 1987.

CPRD-GOLD contains 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 contains 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. Other coding systems in use in UK primary care EMR systems include Clinical Terms (The Read Codes) Version 3, used in TPP SystmOne, and SNOMED CT, used in EMIS Web. The UK Terminology Centre maintains and distributes all 3 code sets as well as cross mappings between them (http://systems.hscic.gov.uk/data/uktc/readcodes).

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 CPRD, including validation of physician-recorded COPD diagnosis [Quint, 2014] and evaluation of COPD co-morbidities [Soriano, 2005].

*Linked data*

Linkage of CPRD-GOLD data to other patient level datasets including HES, ONS, NICOR is possible for a subset of around 7.2 million patients registered with the 375 English practices that have consented to participate in the linkage scheme.

- 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)

- Clinical audit databases managed by the National Institute for Cardiovascular Outcomes research (NICOR): including the Myocardial Infarction National Audit Program (MINAP). Further information about these datasets is available at: http://www.ucl.ac.uk/nicor/audits

*Description of validated diagnoses*

All codes lists will be agreed with data partners across the distributed network of EMR databases and include review with a at least one physician currently practicing in the UK Where possible code lists already validated and published will be utilized. Further, an ongoing validation study in the CPRD (GSK project WEUSKOP5893; collaborative project with London School of Hygiene and Tropical Medicine) will provide validated definitions of COPD diagnosis and COPD exacerbations for this study [Quint, 2014].

Availability of some validated code lists is indicated in the Section 8.3.1. 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 CPRD. 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 CPRD.

### 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 and analysis plan will be prepared and managed by the CPRD and agreed with GSK and Scientific Committee.

### 8.7.1. Essential analysis

#### 8.7.1.1. Objective 1

*In all new users of UMEC/VI, UMEC, or other LABD report the proportion of patients with possible off-label use 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, COPD or asthma medication use, and health care resource utilization.*

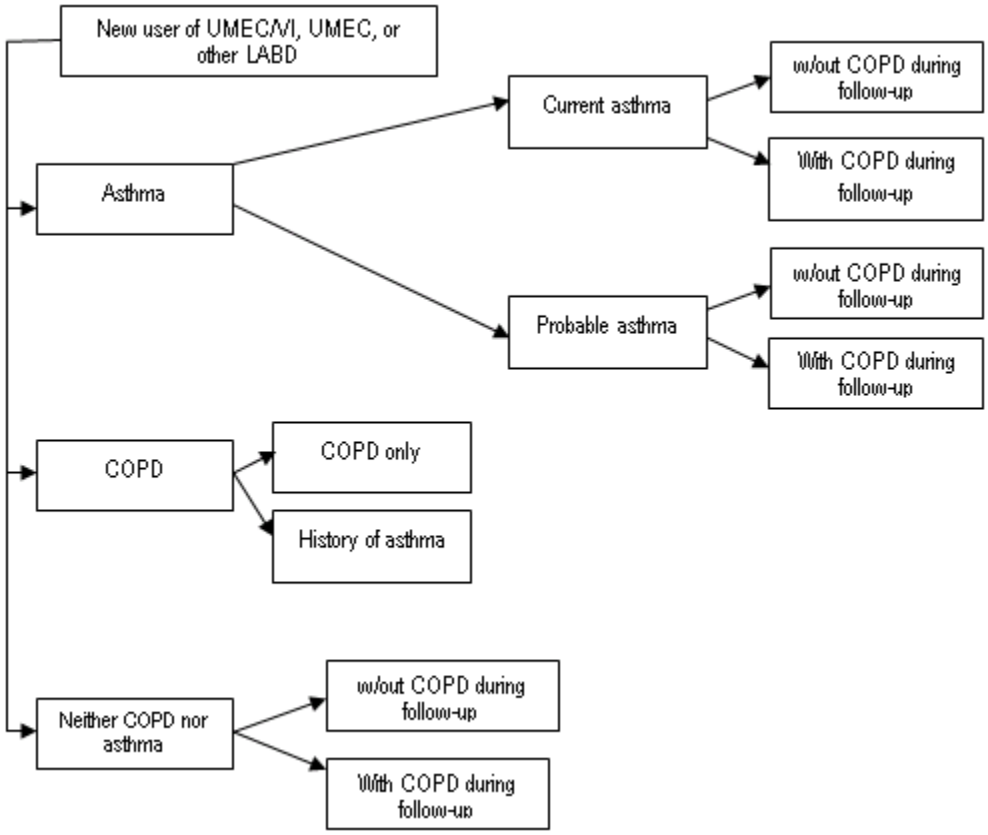
This objective will be explored among all new users combined and for each cohort UMEC/VI, UMEC, or other LABD for the time period up to and including the index prescription date. The only exception will be the further determination of prospective COPD diagnosis for patients categorized as asthma where information from the available history post index date will be utilized. 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 Asthma, COPD, and neither COPD nor asthma (Section 8.3.1. Outcome definitions) and frequencies tabulated. All three disease categories will be further stratified by concomitant prescription of ICS-containing

medications at index date if counts allow. Further stratifications, specific to the Asthma and neither COPD or asthma groups are described in Figure 3.

Descriptive analysis using traits specified in Section 8.3.3. will be repeated for each of the three main disease categories of Asthma, COPD, and neither COPD nor asthma with count and percentage for categorical variables and mean (SD) for continuous variables. The total count of moderate-to-severe exacerbations (and hospitalized exacerbations) and non-COPD hospital admissions will be categorized as described in Section 8.3.3. and a summary per category tabulated. As well, the exacerbation rate (expressed per person-years) 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.

**Figure 3 Stratification of new users of UMEC/VI, UMEC, or other LABD by diagnosis category; each category will be expressed as N (% based on new user category total)**




### 8.7.1.2. Objective 2

*In new users of UMEC/VI, UMEC, or other LABD diagnosed with COPD, quantify incidence of major cardiovascular and cerebrovascular events, mortality,*

*pneumonia/lower respiratory tract infections, and exacerbations of COPD during follow-up.*

In COPD patients, we will further enumerate count and incidence (new events/person-time) of pre-defined events (See Section 8.3.1 for a description of events) within each of the new user cohorts of UMEC/VI, UMEC, or other LABD during the follow-up from their index prescription date until censoring at death, leaving practice, index medication discontinuation, or end of follow-up at earliest of 730 days of follow-up or October 1, 2017. All analyses will be descriptive. Further, all analyses will be split by concomitant ICS-containing medications use at index date.

For myocardial infarction we will flag all events from the index date until censoring and summarize their distribution per new user group. 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 visualized using Kaplan-Meier plot. The incidence rate accompanied with 95% confidence interval will be calculated as follows: numerators consist of the count of first events of myocardial infarction; denominator will be composed of person-time from index date until first event of myocardial infarction or censoring. 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. Identical analysis will be conducted for the event of stroke and a combined event of serious pneumonia/LRTI. 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. For the event of an acute worsening of heart failure only patients with prior heart failure diagnosis will be considered and their time from index date until the date of acute worsening will contribute to denominator.

Death will be flagged and summarized as a proportion of patients who died within each new user category. 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 visualized using Kaplan-Meier plot.

Count of exacerbations of COPD during the follow-up period from index date until censoring will be summarized and exacerbation rate accompanied with 95% confidence interval calculated as total count of exacerbation events divided by total person-time during follow-up and standardized per person year. Further, due exacerbation rate frequently being higher than 1 event per person year, negative binomial regression will be also considered to produce the rates as well as 95% confidence intervals [Glynn, 1993; Glynn, 1996].

Visits to the general practice will be counted standardized per 365.25 days and further stratified into pre-defined practice visit type categories.

Count of non-COPD hospitalizations during the follow-up period from index date until censoring will be summarized and exacerbation rate accompanied with 95% confidence interval calculated as total count of exacerbation events divided by total person-time during follow-up and standardized per person year.

#### 8.7.1.3. Objective 3

*In new users of UMEC/VI or UMEC, diagnosed with COPD, describe treatment patterns (time to discontinuation, switch or augmentation) and adherence including Medication Possession Ratio and Proportion of Days Covered during follow-up.*

The following analyses will be undertaken separately for new users of UMEC and new users of UMEC/VI.

Calculate the count and percentage of patients who have a switch in medication as described in Section 8.3.1.3 during follow-up. Only the first switch will be described among patients with at least one switch that did not have an augmentation before the switch. The mean (SD) time (in days) to the first treatment switch from the prescription initiation date during follow-up period will be reported. A Kaplan-Meier plot of time until first treatment switch among patients with at least one switch will also be created.

Calculate the count and percentage of patients who have a treatment augmentation as described in Section 8.3.1.3 during follow-up. Only the first augmentation will be described among patients with at least one augmentation that did not have a switch before the augmentation. The mean (SD) time (in days) to the first treatment augmentation from the prescription initiation date during follow-up period will be reported. A Kaplan-Meier plot of time until first addition (excluding additions that result in triple therapy) among patients with at least one addition will also be created.

Calculate the count and percentage of patients that discontinue the initially prescribed therapy during follow-up as described in Section 8.3.1.3.

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 8.3.1.3. As well as cut offs of >=80% for the MPR and PDC, the mean (SD) of these variables during follow-up will also be calculated.

The calculation of MPR requires that patients received at least two prescriptions during the follow-up; the PDC can be calculated with only one prescription and requires a fixed follow-up period 0-12 months. Therefore the denominator 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 0-12 months of follow-up. Patient demographics, co-morbidity, disease burden, other COPD and asthma medications, and health care resource utilization (as defined in Section 8.3.3) will be described for adherent and non-adherent patients 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

Following exploratory analyses are being planned:

1. An impact of censoring at index exposure discontinuation on rate of study outcomes addressed in Objective 2 will be explored. Varying period of discontinuation assumption will be tested including 30, 60, or 90 days after the last prescription.

2. Completeness of dosing instructions will be described.

3. An overlap of records for asthma and COPD diagnosis prior to index date will be explored by describing the pattern of records for asthma diagnosis as well as asthma maintenance medication in a period of 12 months prior to index date among patients who fulfill COPD definition.

### 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 CPRD 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 standardized 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.

If prescribing of UMEC/VI or UMEC is preferential to patients with more severe COPD, relative to new users of other LABD then interpretation of any differences across new user groups will not be feasible.

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.

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.

Distributed network design will increase the sample size; however, it will also increase the complexity of data analysis considering different coding procedures and classification across the final set of collaborating database centres. Maximally integrated model will be preferred with CPRD 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, but also leads to high complexity, needing to ensure comparability of event and exposure coding as well as availability of the same descriptors across the databases.

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 and LRTI events from GP records may lead into issues with miss-classification of the event presence as well as the severity type (non-severe vs. severe). 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.

### 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 pseudonymized 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 CPRD 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. CPRD 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.

CPRD's 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 CPRD 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 CPRD 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. However, any adverse events attributable to a GSK medication would be reported as described below.

If, during the study, an adverse event (serious or non serious) is identified as explicitly attributed to any GSK product (including products not covered in the specific study objective), this will be reported. The study epidemiologist must forward the report to GSK central safety department within 24 hours of first becoming aware of the event as per SOP 52214 (Reporting and Disclosing Information from Observational Safety Studies and Analyses of Epidemiology Data).

When conducted by a third party, the adverse event must be faxed to GSK Global Clinical Safety and Pharmacovigilance at 919-483-5404 within 24 hours of receiving the information.

# 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.

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# 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

| **Section 1: Research question** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 1.1 Does the formulation of the research question clearly explain: | | | | |
| 1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | 18 & 21 |
| 1.1.2 The objectives of the study? | ☒ | ☐ | ☐ | 21 |
| 1.2 Does the formulation of the research question specify: | | | | |
| 1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 27 |
| 1.2.2 Which formal hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 1.2.3 if applicable, that there is no *a priori* hypothesis? | ☒ | ☐ | ☐ | 21 |

Comments:

| |
|---|
| |

| **Section 2: Source and study populations** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 2.1 Is the source population described? | ☒ | ☐ | ☐ | 27 |
| 2.2 Is the planned study population defined in terms of: | | | | |
| 2.2.1 Study time period? | ☒ | ☐ | ☐ | 27 |
| 2.2.2 Age and sex? | | | | |

| **Section 2: Source and study populations** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 2.2.3 Country of origin? | ☒ | ☐ | ☐ | 27 |
| 2.2.4 Disease/indication? | ☒ | ☐ | ☐ | 25 |
| 2.2.5 Co-morbidity? | ☒ | ☐ | ☐ | 27 |
| 2.2.6 Seasonality? | ☐ | ☐ | ☒ | |
| | ☐ | ☐ | ☒ | |
| 2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 22 & 27 |

Comments:

| |
|---|
| |

| **Section 3: Study design** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated? | ☒ | ☐ | ☐ | 27 |
| 3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design) | ☒ | ☐ | ☐ | 22 |
| 3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year) | ☒ | ☐ | ☐ | 40 |
| 3.4 Is sample size considered? | ☒ | ☐ | ☐ | 39 |
| 3.5 Is statistical power calculated? | ☒ | ☐ | ☐ | 39 |

Comments:

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| **Section 4: Data sources** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc) | ☒ | ☐ | ☐ | 37 |
| 4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc) | ☒ | ☐ | ☐ | 37 |
| 4.1.3 Covariates? | ☒ | ☐ | ☐ | 37 |
| 4.2 Does the protocol describe the information available from the data source(s) on: | ☒ | ☐ | ☐ | 32 |
| 4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 27 |
| 4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 33 |
| 4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.) | | | | |
| 4.3 Is the coding system described for: | | | | |
| 4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10) | ☒ | ☐ | ☐ | 37 |
| 4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events) | ☒ | ☐ | ☐ | 37 |
| 4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical | ☒ | ☐ | ☐ | 37 |

| **Section 4: Data sources** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| (ATC)Classification System) | | | | |
| 4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other) | ☒ | ☐ | ☐ | 37 & 39 |

Comments:

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| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure) | ☒ | ☐ | ☐ | 32 |
| 5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study) | ☒ | ☐ | ☐ | 37 |
| 5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use) | ☐ | ☐ | ☒ | |
| 5.4 Is exposure classified based on biological mechanism of action? | ☐ | ☐ | ☒ | |
| 5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured? | ☐ | ☐ | ☒ | |

Comments:

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| **Section 6: Endpoint definition and measurement** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 6.1 Does the protocol describe how the endpoints are defined and measured? | ☒ | ☐ | ☐ | 27 |
| 6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study) | ☒ | ☐ | ☐ | 27 & 37 |

Comments:

| **Section 7: Biases and Effect modifiers** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 7.1 Does the protocol address:<br>7.1.1 Selection biases?<br>7.1.2 Information biases?<br>(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods) | ☐<br>☐ | ☐<br>☐ | ☒<br>☒ | |
| 7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders) | ☒ | ☐ | ☐ | 33 |
| 7.3 Does the protocol address known effect modifiers?<br>(e.g. collection of data on known effect modifiers, anticipated direction of effect) | ☒ | ☐ | ☐ | 33 |
| 7.4 Does the protocol address other limitations? | ☒ | ☐ | ☐ | 45 |

Comments:

| **Section 8: Analysis plan** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 8.1 Does the plan include measurement of absolute effects? | ☐ | ☐ | ☒ | This is a descriptive study. |
| 8.2 Is the choice of statistical techniques described? | ☒ | ☐ | ☐ | 40 |
| 8.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | 40 |
| 8.4 Are stratified analyses included? | ☒ | ☐ | ☐ | 40 |
| 8.5 Does the plan describe the methods for identifying: | | | | |
| 8.5.1 Confounders? | ☒ | ☐ | ☐ | 33 |
| 8.5.2 Effect modifiers? | ☒ | ☐ | ☐ | 33 |
| 8.6 Does the plan describe how the analysis will address: | | | | |
| 8.6.1 Confounding? | ☒ | ☐ | ☐ | 40 |
| 8.6.2 Effect modification? | ☒ | ☐ | ☐ | 40 |

Comments:

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| **Section 9: Quality assurance, feasibility and reporting** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 39 |

| **Section 9: Quality assurance, feasibility and reporting** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| | | | | |
| 9.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 39 |
| 9.3 Does the protocol describe quality issues related to the data source(s)? | ☒ | ☐ | ☐ | 39 |
| 9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment) | ☒ | ☐ | ☐ | 39 |
| 9.5 Does the protocol specify timelines for | | | | |
| 9.5.1 Start of data collection? | ☒ | ☐ | ☐ | 18 |
| 9.5.2 Any progress report? | ☒ | ☐ | ☐ | 18 |
| 9.5.3 End of data collection? | ☒ | ☐ | ☐ | 18 |
| 9.5.4 Reporting? (i.e. interim reports, final study report) | ☒ | ☐ | ☐ | 18 |
| 9.6 Does the protocol include a section to document future amendments and deviations? | ☒ | ☐ | ☐ | 18 |
| 9.7 Are communication methods to disseminate results described? | ☒ | ☐ | ☐ | 47 |
| 9.8 Is there a system in place for independent review of study results? | ☒ | ☐ | ☐ | 10 & 47 |

Comments:

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| **Section 10: Ethical issues** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 10.1 Have requirements of Ethics Committee/Institutional Review Board approval | ☒ | ☐ | ☐ | 46 |

| **Section 10: Ethical issues** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| been described? | | | | |
| 10.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☐ | ☒ | The Ethics approval is pending post the protocol finalization. |
| 10.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 47 |

Comments:

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Name of main author of study protocol: [redacted]

Date: / /

Signature: _____