TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Study Protocol

Title:	Drug utilisation study of new users of fluticasone furoate / vilanterol (FF/VI) in the primary care setting: UK Clinical Practice Research Datalink (CPRD) study

Compound Number:	GW685698+GW642444
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Subject:	Drug Utilisation Study, Post-authorisation Safety Study, Chronic Obstructive Pulmonary Disease, asthma, Electronic Medical Records, Inhaled Corticosteroids, Long-Acting Beta-2-Agonists
Author(s):	[redacted]

PASS information

Title	Drug utilisation study of new users of fluticasone furoate / vilanterol (FF/VI) in the primary care setting: UK Clinical Practice Research Datalink (CPRD) study
Protocol version identifier	1.0
Date of last version of protocol	22 December 2016
EU PAS register number	TBC
Active substance	Fluticasone furoate/ vilanterol (FF/VI) ATC: R03AK10. Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics
Medicinal product	RELVAR ELLIPTA REVINTY ELLIPTA
Product reference	EU/1/13/886/001-006 EU/1/14/929/001-006
Procedure number	EMEA/H/C/002673 EMEA/H/C/002745
Marketing authorisation holder(s)	Glaxo Group Limited 980 Great West Road Brentford Middlesex, TW8 9GS UK
Joint PASS	No

Research question and objectives	In the 24-month period immediately following the availability of fluticasone furoate / vilanterol (FF/VI) in the United Kingdom, this study will identify new users of FF/VI or other inhaled-corticosteroid/long-acting beta-2-agonist (ICS/LABA) fixed dose combination (FDC) medications from a UK primary care Electronic Medical Records (EMR) database. Drug utilisation review will be performed with the following objectives: Objectives 1. Separately among new users of FF/VI and other ICS/LABA FDC, describe patient characteristics (including demographics, disease burden, selected comorbidities and respiratory medication use) and diagnosis group (asthma, COPD-including an asthma history stratification, other). 2. Among new users of FF/VI, describe off-label prescribing including prescription of: • FF/VI 200/25 (pre-dispensed doses; all doses in mcg) formulation in patients with evidence in the EMR database of a COPD diagnosis (only FF/VI 100/25 is licensed for use in patients with COPD) • FF/VI (any dose) in children <12 years of age (neither FF/VI 200/25 nor FF/VI 100/25 is licensed for use in children <12 years of age) 3. Among new users of FF/VI, describe the treatment patterns and adherence to therapy by diagnosis group (asthma, COPD-including an asthma history stratification, other).

Country(-ies) of study	United Kingdom
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MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Glaxo Group Limited 980 Great West Road Brentford Middlesex, TW8 9GS UK
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2. LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body mass index
CAG	Confidential Advisory Group
COPD	Chronic Obstructive Pulmonary Disease
CONSORT	CONsolidated Standards of Reporting Trials
CPRD	Clinical Practice Research Datalink
CPRD-GOLD	GP OnLine Database
EC	European Commission
EMA	European Medicines Agency
EMR	Electronic Medical Record
EU-RMP	European Union – Risk Management Plan
FDC	Fixed dose combination
FEV1	Forced expiratory volume in 1 second
FF	Fluticasone Furoate
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
GPRD	General Practice Research Database
GSK	GlaxoSmithKline
HES	Hospital Episode Statistics
HRA	Health Research Authority
ICS	Inhaled Corticosteroid
ISAC	Independent Scientific Advisory Committee
LABA	Long Acting Beta Agonist
LABD	Long-Acting Bronchodilator
LAMA	Long-Acting Anti-Muscarinic
MAH	Market Authorization Holder
MPR	Medication possession ratio
MRC	Medical Research Council
OCS	Oral Corticosteroids
PDC	Proportion days covered
SABA	Short-Acting Beta-Agonist
SABD	Short-Acting Bronchodilator
SAMA	Short-Acting Anti-Muscarinic
SD	Standard deviation
UK	United Kingdom
VI	Vilanterol

Trademark Information

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SAS
Stata

3. 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 and Therapy Area Head, Respiratory Epidemiology
Name: [redacted]

Address: GlaxoSmithKline Research & Development Ltd.

Study Coordination

The MAH intends to contract 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. Scientific advice will be sought to provide expert medical and epidemiological input and advice on the protocol and final report.

CPRD:
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SW1W 9SZ

SPONSOR SIGNATORY:

[redacted] **Date**

Senior Director and Respiratory TA Head

[redacted] **Date**

VP Real World Evidence & Epidemiology

SPONSOR INFORMATION PAGE

WWEpi Project Identifier: 205052 (GSK Epidemiology: PRJ2214)

Sponsor Legal Registered Address:

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Telephone: [redacted]

Sponsor Medical Monitor Contact Information: Not applicable

Regulatory Agency Identifying number(s): N/A

INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

[redacted]

Investigator Signature

Date

4. ABSTRACT

Title: Drug utilisation study of new users of fluticasone furoate / vilanterol (FF/VI) in the primary care setting: UK Clinical Practice Research Datalink (CPRD) study

Rationale and background: Fluticasone furoate/vilanterol (FF/VI) is a once-daily inhaled corticosteroid/long-acting beta-2 agonist (ICS/LABA) fixed dose-combination (FDC) medication which was approved in the EU for the treatment of asthma and COPD in November, 2013. This study will describe the patient population prescribed FF/VI and other fixed-dose inhaled corticosteroid / long-acting beta-2-agonist (ICS/LABA FDC) medications and will assess off label use of FF/VI. This study fulfils a voluntary commitment made in the European Union – Risk Management Plan (EU-RMP) for FF/VI to examine the utilisation (including off-label use) of FF/VI in a real-world, post-approval setting.

Research question and objectives: In the 24-month period immediately following the availability of fluticasone furoate / vilanterol (FF/VI) in the United Kingdom (UK), a drug utilisation review will be conducted with the following objectives: 1) separately among new users of FF/VI and other ICS/LABA FDC, describe patient characteristics and diagnosis group (asthma, COPD-including an asthma history stratification, other); 2) among new users of FF/VI, describe off-label prescribing including prescription of FF/VI 200/25 formulation in patients with a COPD diagnosis (as only the FF/VI 100/25 formulation is licensed for patients with COPD) and FF/VI (any dose) in children <12 years of age (as neither formulation of FF/VI is licensed for use in children <12 years of age), and 3) among new users of FF/VI, describe the treatment patterns and adherence to therapy by diagnosis group.

Study Design: Retrospective, longitudinal, non-interventional, observational study of patients newly prescribed FF/VI or other ICS/LABA FDC medications between January 1, 2014-December 31, 2015. A cross-sectional assessment of demographic and clinical characteristics will be performed using information available prior to and at the time of index prescription initiation. For new users of FF/VI, off-label prescribing, treatment patterns and adherence will also be assessed from index prescription date until the first of the following: 12 months post-index prescription date or censoring due to death or leaving GP practice.

Population: Patients newly prescribed FF/VI or other ICS/LABA FDC during the study period will be retrospectively identified based on prescription records. At least 12 months of recorded data prior to index prescription date will be required to assess baseline characteristics. New use will be ascertained using all available history (i.e. 12 months or more) to exclude previous users of FF/VI and other ICS/LABA FDC Patients will be described by diagnosis group, which represents the likely indication for treatment (Asthma, COPD-including a stratification by history of asthma, Other) as ascertained from diagnosis codes.

Variables: Study outcomes will include patient characteristics (including demographics, disease burden, select comorbidities and prior respiratory medication use) [Objective 1], off-label prescribing (including prescription of FF/VI 200/25 formulation in patients with

evidence of a COPD diagnosis, and FF/VI in children <12 years of age) [Objective 2], treatment patterns (including prescription frequency, continuous use, switching, dose escalation, dose reduction, augmentation or discontinuation) [Objective 3] and adherence to therapy (including Medication Possession Ratio (MPC) and Proportion of Days Covered (PDC) [Objective 3]. The study outcomes for Objective 1 will be described for both the FF/VI and other ICS/LABA FDC new user cohorts, while the Objective 2 and 3 outcomes will be explored in the FF/VI new user cohort only. No exposure/outcome associations will be explored.

Data sources: The study will be conducted in the UK Clinical Practice Research Database (CPRD)-GOLD, a primary care-based EMR database in the United Kingdom.

Study size: A preliminary review of CPRD GOLD to assess study feasibility identified 4,220 patients with a prescription for FF/VI during the period 01/01/2014 - 31/12/2015 whilst registered at a research quality (up to standard) practice; approximately 2,500 with a record of COPD (with or without asthma), 1,700 with a record of asthma and 235 without a record of either indication. While this study does not aim to test any specific hypothesis, this large number of patients initiating FF/VI will be sufficient to provide precise and meaningful 95% confidence intervals around a range of potential proportions of off label use.

Data analysis: Descriptive statistics (n, % or mean (SD)) will be generated for all outcomes.

Milestones:

Protocol Approval Date: December 22 2016

Statistical Analysis Plan Approved: December 31 2016

Analysis Start Date: March 1 2017

Analysis Complete Date: 15 June 2017

Study Report Approval date: 31 July 2017

5. AMENDMENTS AND UPDATES

None at this time

6. MILESTONES

Milestone	Planned date
Protocol Approval Date	22 December 2016
Statistical Analysis Plan Approved	31 December 2016
Analysis Start Date	1 March 2017
Analysis Complete Date	15 June 2017
Study Report Approval date	31 July 2017

7. RATIONALE AND BACKGROUND

7.1. Background

Bronchodilators, such as beta2-agonists, are central to improving lung function and managing symptoms in COPD. Long-acting agents are convenient and more effective at producing maintained symptom relief than short-acting ones. Regular treatment with ICS leads to reductions in the frequency of exacerbations, improves symptoms and quality of life and produces small improvements in lung function [Global Initiative for Obstructive Lung Disease (GOLD), 2016]. Although, long-term monotherapy treatment with ICS is not recommended, an ICS combined with a LABA is more effective than the individual components in managing stable COPD by reducing exacerbations and improving lung function and health status [Global Initiative for Obstructive Lung Disease (GOLD), 2016; Ferguson, 2008; Calverley, 2007; Kardos 2007; Sharafkhaneh, 2012].

In asthma, ICS are considered the most effective anti-inflammatory treatments for all severities of persistent asthma [GINA, 2014]. Treatment with ICS controls asthma symptoms, improves quality of life and lung function, decreases airway hyper-responsiveness, controls airway inflammation, and reduces the frequency and severity of asthma exacerbations, thereby reducing asthma mortality. The addition of a LABA to an ICS improves symptom scores, decreases nocturnal asthma symptoms, improves lung function and reduces the number of asthma exacerbations [Ducharme 2010] and is preferred to increasing the dose of ICS to achieve asthma control.

Fluticasone furoate/vilanterol (FF/VI) is a once-daily inhaled corticosteroid/long-acting beta-2 agonist (ICS/LABA) fixed dose-combination (FDC) product approved in the EU for the treatment of both asthma and COPD in November, 2013 with the following indications:

Asthma Indication: FF/VI 100/25 and 200/25 [all doses mcg pre-dispensed] are indicated for regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta-2 agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta-2 agonists.

COPD Indication: FF/VI 100/25 is indicated for symptomatic treatment of adults with COPD with a FEV1 < 70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

FF/VI was launched in the United Kingdom under the trade name Relvar® Ellipta® in January 2014.

In addition to FF/VI there are other ICS/LABA FDC medications that have been approved for use in asthma and/or COPD in Europe which include fluticasone propionate/salmeterol xinofoate, budesonide/formoterol, beclometasone/formoterol and fluticasone propionate/formoterol.

The safety and efficacy of ICS/LABA FDC combination therapy medications in asthma and COPD have been studied extensively for the past decade. During the FF/VI clinical studies, the safety experience for FF/VI was similar to that with other ICS/LABA FDC [Agusti, 2014; Dransfield, 2014; Lötvall, 2014]. However, there is potential for off-label use of FF/VI and thus as part of the European Union Risk Management Plan (EU-RMP) for FF/VI, GSK proposed to conduct this voluntary post-authorisation safety study (PASS) to monitor this potential safety concern. The present study is a drug utilisation study with the objective of examining potential off-label use, including use of the FF/VI 200/25 dose in COPD and use of FF/VI in children <12 years of age, in new users of FF/VI who initiated the medication within the first 24 months of drug availability in the UK.

7.2. Rationale

In accordance with the pharmacovigilance plan agreed for FF/VI, this study will provide information on the 'real-world' utilisation of FF/VI in the early post-approval period including potential off-label prescribing.

8. RESEARCH QUESTION AND OBJECTIVE(S)

In the 24-month period immediately following the availability of fluticasone furoate / vilanterol (FF/VI) in the United Kingdom, this study will identify new users of FF/VI or other inhaled-corticosteroid/Long-acting beta-2-agonist (ICS/LABA) fixed dose combination (FDC) medications from a UK primary care Electronic Medical Records (EMR) database and drug utilisation review will be performed with the following objectives:

Objectives:

Objective 1: Separately among new users of FF/VI and other ICS/LABA FDC, describe patient characteristics (including demographics, disease burden, select comorbidities and

respiratory medication use) and diagnosis group (asthma, COPD-including an asthma history stratification, Other).

Objective 2: Among new users of FF/VI, describe off-label prescribing including prescription of:

- FF/VI 200/25 (pre-dispensed doses; all doses in mcg) formulation in patients with evidence in the EMR database of a COPD diagnosis
- FF/VI (any dose) in children <12 years of age

Objective 3: Among new users of FF/VI, describe the treatment patterns and adherence to therapy by diagnosis group (asthma, COPD-including an asthma history stratification, Other).

9. RESEARCH METHODS

9.1. Study Design

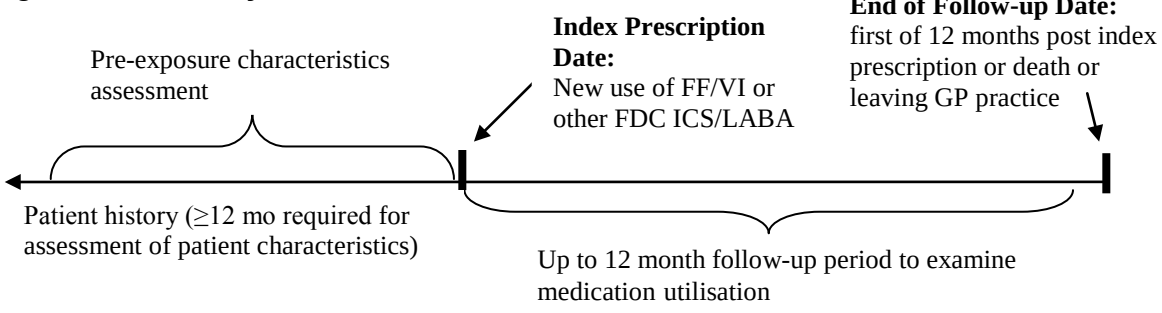
This study will take a naturalistic approach, capturing routine medical care using a retrospective longitudinal non-interventional observational design. All patients with a record of a new prescription for FF/VI or other ICS/LABA FDC during the inclusion period of January 1, 2014 through December 31, 2015 (corresponding to the period of 24 months from the start of FF/VI availability in the UK) will be identified and assessed for eligibility to be included in the study. The index date will be the date of new use of FF/VI or other ICS/LABA FDC prescription that occurs during the inclusion period.

The end date of the study will be December 31, 2016 (end of inclusion period on December 31, 2015 plus 12 months), thus allowing all patients the potential to contribute up to 12 months of follow-up time. Each patient will be followed starting on their index date and ending at the first of the following events:

1. 12 months post index medication date,
2. Death (Censored)
3. Leaving GP practice (Censored)

The study schematic is provided in Figure 1.

Figure 1 Study Schematic

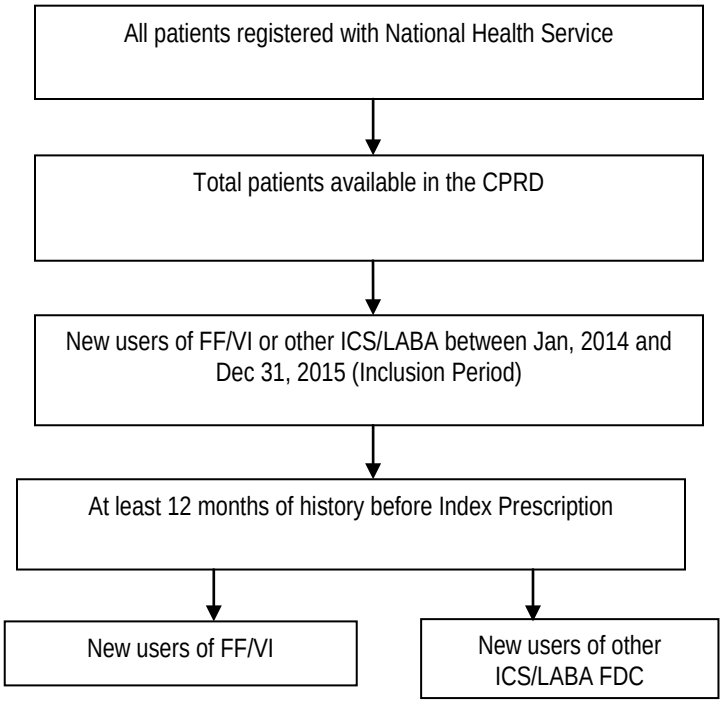


A minimum period of at least 12 months prior to index prescription date, defined as being registered with the practice for at least one year, is required to allow for a standardised period of history to describe selected patient demographics, disease burden, and previous respiratory medication use (Figure 1). NB. All available patient history will be used to ascertain new use with sufficient confidence.

A patient may contribute information on more than one treatment if they meet the "new user" definition for more than one medication during the inclusion period (for example, a patient who is newly prescribed FDC flucticasone propionate / salmeterol xinofoate and then FF/VI during the inclusion period could contribute information to both the FF/VI and 'other ICS/LABA FDC' cohorts). Similarly, patients who are prescribed FF/VI and later switch to FDC fluticasone propionate / salmeterol xinofoate, or patients prescribed FDC fluticasone propionate / salmeterol xinofoate who then later switch to another FDC ICS/LABA, will be allowed to contribute information for multiple cohorts.

The CONSORT diagram for the selection of patients is shown in Figure 2 [Schulz, 2010].

Figure 2 CONSORT Diagram Schematic: Cohort Selection



* A patient may contribute information on more than one treatment if they meet the "new user" definition for more than one medication during the inclusion period (for example, a patient who is newly prescribed FP/FOR and then FF/VI during the inclusion period could contribute information to both the FF/VI and 'other ICS/LABA FDC' cohorts).

9.2. Setting

9.2.1. Time period

This study will examine drug utilisation in patients initiating therapy with FF/VI or other ICS/LABA FDC during the first two-years of FF/VI availability in the United Kingdom (UK), January 1, 2014 through December 31, 2015. Patients initiating therapy will be followed for up to 12 months post index date (unless censored due to death or leaving practice).

9.2.2. Data Source

This study will use the Clinical Practice Research Datalink's (CPRD)-GP OnLine Database (CPRD-GOLD), a UK primary care electronic medical record (EMR) database. Approach to the study is naturalistic; capturing routine medical care.

Table 1 Summary of the characteristics of the CPRD-GOLD EMR database as of July 2016

EMR System	CPRD-GOLD
Database size: a) total patients b) current (or active) patients c) current (or active) practices	 a) 14.7M b) 2.8M c)330
Patient geographical coverage	UK
Regularity of data uploads	Monthly

For the purposes of complete capture of each patient's history of acute exacerbations of COPD (a descriptive variable in this study), primary care records of eligible patients may be linked, where possible, to additional datasets such as the Hospital Episode Statistics database (HES).

9.2.2.1. Study Populations

The main study population will consist of new users of FF/VI or other ICS/LABA FDC medications (see section 9.3.1 for details on exposure) with 'acceptable' data quality in CPRD-GOLD.

Inclusion criteria:

- Record of a new prescription of FF/VI or other ICS/LABA FDC during the inclusion period (January 1, 2014 through December 31, 2015).
- $\geq$ 12 months of registration at a practice with 'up to standard data' recording prior to index prescription date to allow for characterization of patient's status, demographics and clinical characteristics.

Exclusion criteria:

- Past record *ever in medical history* of prescription for the specific inclusion medication (prior use of another ICS/LABA FDC product will be permitted). (NB. All available data prior to the index date will be used to ascertain new use of FF/VI and other ICS/LABA FDC.)

From the main study population, a subset of patients eligible for HES linkage will be identified. HES data will be used in addition to GP data to delineate between moderate and severe exacerbations in this subset.

Diagnosis group classification

Patients meeting criteria for entry will be classified into diagnosis groups, based on evidence in the CPRD of a recorded diagnosis of: (a) COPD, (b) Asthma, (c) 'Other' (neither COPD nor asthma), as described below.

COPD diagnosis group: Patients will be considered to have COPD if they have a COPD diagnosis recorded any time in their CPRD history up to and including the index FF/VI or other ICS/LABA FDC prescription date through their end of follow-up date and were aged 35 years or older at the time of their first diagnosis code. COPD is not normally diagnosed in younger patients as symptoms do not often manifest until 35-40 years of age. Patients with a record of COPD at less than 35 years of age may have been misdiagnosed and we therefore want to exclude these patients from the COPD group to avoid misclassification. If these patients meet the criteria for inclusion in the Asthma diagnosis group (see below) they will be classified as such, otherwise they will be classified in the Other group. The codes to establish the COPD indication in this analysis have been validated in CPRD [Quint, 2014]. As this group may include patients with a mixed diagnosis history of COPD and asthma, a stratification of the COPD diagnosis group by asthma history will also be presented. A patient will be considered to have a history of asthma if they have an asthma diagnosis recorded at any time in their CPRD history up to and including the index FF/VI or other ICS/LABA FDC prescription date.

Asthma diagnosis group: Patients will be considered to have asthma if they do not meet criteria for inclusion in the COPD diagnosis group and (a) have an asthma diagnosis recorded any time in their CPRD history up to and including the index FF/VI or other ICS/LABA FDC prescription date through their end of follow-up date AND (b) are classified as "never smokers". Current and ex-smokers with a diagnosis of asthma will not be included in this group. Rather, they will be classified in the Other group. The asthma codelist will be reviewed by a clinician and this definition may change following publication of the results of an ongoing asthma validation study in CPRD.

Other diagnosis group (neither COPD nor asthma): Patients will be classified into this category if they did not meet the criteria for either the COPD or asthma diagnosis groups above. This group may include patients with evidence of possible asthma and/or possible COPD, but who smoke(d) and/or were aged less than 35 years at the time of first COPD record and therefore did not meet the strict criteria for inclusion in either the COPD or Asthma diagnosis groups.

9.3. Variables

9.3.1. Exposure definitions

9.3.1.1. New users of FF/VI and other ICS/LABA

We will identify all new users of FF/VI or other ICS/LABA FDC during the period of January 1, 2014 through December 31, 2015. New use is defined as never having had a prescription for FF/VI or the other ICS/LABA FDC ever recorded in the past. The first day of the first qualifying new use prescriptions will be in the index date. Prior or concomitant use of respiratory medications containing a combination of different active substances, or monotherapy use of the active substances in the qualifying new use medication, will be allowed.

Other LABA/ICS FDC includes fluticasone propionate/salmeterol xinofoate, budesonide/formoterol, beclometasone/formoterol and fluticasone propionate/formoterol. The other LABD FDC group will be analysed as a class; no other ICS/LABA drugs will be analysed individually.

All individual prescriptions will be assigned a default length of 30 days per container prescribed irrespective of whether they have a recorded value for script length (less than 0.2% are likely to have a duration value recorded in the CPRD record).

A single patient is able to contribute more than one qualifying index medication during the study if they meet the definition of new use for multiple medications.

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

9.3.1.2. Concomitant use of other medications at index date

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

We will search the patient record and flag instances when patients are receiving concomitant respiratory therapy at the time of the index prescription. Use of concomitant medication will be reported using summary statistics and will be used to define treatment patterns (Objective 3). Concomitant therapy will be defined as at least two continuous prescriptions for the other respiratory therapy which start either before, or up to 30 days after the index date, and overlap for at least 30 days with the index treatment. See Section 9.3.2.1 for a list of respiratory medications that will be considered.

9.3.1.3. Discontinuation

For Objective 3, new users of FF/VI will be followed for 12 months from the date of their index prescription in order to explore treatment patterns. Discontinuation of FF/VI prescribing will be considered to have occurred if there is either:

- A break of at least 91 days between prescriptions. The discontinuation date is set at 30 days after the prescription prior to the break.

  or

- Complete cessation in prescribing of the index medication. The discontinuation date is set at 30 days after the final prescription.

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

9.3.2. Outcome definitions

All codes and detailed algorithms to derive the variables below will be reviewed by a clinician and summarised in the detailed statistical analysis plan.

9.3.2.1. OBJECTIVE 1: Characteristics of New Users of FF/VI or other ICS/LABA FDC

The following characteristics will be described for both cohorts (new user of FF/VI and new user of other ICS/LABA FDC) by diagnosis group (Asthma, COPD - including a stratification by asthma history, Other). Note: characteristics will be described separately in the main study population (using GP data only) and in the subset of patients eligible for HES linkage (using GP data plus HES data on exacerbations).

- **Age at index prescription date**: Mean (SD) and categories of: <5, 6-11, 12-17, 18-44, 45-64, 65-79, ≥80 years.

- **Duration of follow up time until censoring:** 0-<3 months, 3-<6 months, 6-<9 months, 9-12 months

- **Gender**: % male, female

- **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. BMI 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.

- **Area based deprivation measures:** the most recently available version of each national index of multiple deprivation (IMD) 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. The IMD attempts to capture tangible deprivation (e.g. employment, living environment, income etc.) and is one of two measures of socio-economic deprivation available in CPRD.

- **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 at Index Date

- **COPD exacerbations:** COPD exacerbations will be calculated only for the COPD patients (regardless of whether they have a history of asthma).

  COPD exacerbations will be identified in the 12 months prior to index date. Exacerbations will be described as the rate per person year, and as a count of 0, 1 and 2+ events. COPD exacerbation events will be identified based on a validated algorithm for the CPRD [Rothnie, 2016].

  It is not possible to delineate exacerbation type (moderate versus severe) using GP data alone. However, in the subset of patients with the HES link, exacerbations will be further defined as moderate (treated with OCS and/or antibiotics) and severe (hospitalised).

- **Asthma exacerbations:** Asthma exacerbations will be calculated only for the subgroup of patients who meet the criteria for asthma. Asthma exacerbations will be identified in the 12 months prior to index date. Exacerbations will be described as the rate per person year, and as a count of 0, 1 and 2+ events (See algorithm in Stand Alone Document 2 for derivation of asthma exacerbations).

  It is not possible to delineate exacerbation type (moderate versus severe) using GP data alone. However, in the subset of patients with the HES link, exacerbations will be further defined as moderate (treated with OCS) and severe (hospitalised).

  Note: Exacerbations will not be described for the other group.

- **COPD severity** will be characterised in the COPD group (regardless of whether they have a history of asthma) by airflow limitation as measured by lung function test (spirometry) in the 12 months prior to index date (value nearest

prior to index date will be used). Lung function parameter of forced expiratory volume in one second, FEV1, 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 FEV1 ≥80% predicted for mild Grade 1, ≥50% to <80% FEV1 predicted for moderate Grade 2, ≥30% to <50% FEV1 predicted for severe Grade 3, and <30% FEV1 predicted for very severe Grade 4. Patients with missing values will be categorised as 'missing'. The count and percent of patients in each group will be reported.

Further, the value for FEV1/FVC ratio in the 12 months prior to index date (value nearest prior to index date will be used) will be flagged and expressed as Mean (SD) and categorised as less than 70%, equal or more than 70%, and missing.

Comorbidity

- **History (diagnosis records) of key comorbid conditions:** cardio-and cerebrovascular diseases, pneumonia, gastroesophageal reflux disease, diabetes, renal disease (acute and chronic) and cancer (each flagged yes/no) as recorded ever in the patients history prior to the index date. Each comorbidity will be listed separately, indicating the number/proportion of patients with and without a record for the comorbidity.

Prior use of COPD or asthma medication

Utilisation of other respiratory therapies in the 12 months prior to index date will be flagged and the count and percentage of patients with at least one prescription for that type of medication will be tabulated. The types of medications to be ascertained are outlined in Table 2 below.

For short-acting bronchodilators (SABD), the count and percent of patients with more than four prescriptions will be presented.

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

In the asthma diagnosis group, the dose of inhaled corticosteroids (alone or in combination with a LABA) will be classified as 'low, medium or high' according to the Global Initiative for Asthma (GINA) 2015 guidelines [GINA, 2015].

Table 2 Categories of COPD and asthma medications

Category	Description
SABD§	Short-Acting Beta2-Agonist (SABA), Short-Acting Anticholinergic (SAMA), Fixed Combinations of SABA/ Cromoglycate Fixed Combinations of SABA/SAMA
ICS and	Inhaled Corticosteroids

Category	Description
SABA/ICS*	OR Fixed Combination of Short-Acting Beta2-Agonist and Inhaled Corticosteroid
LABA	Long-Acting Beta2-Agonists
ICS/LABA*	Fixed Combination of Inhaled Corticosteroid and Long-Acting Beta2-Agonist OR 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 OR 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 OR Open combination of Inhaled Corticosteroid and Long-Acting Beta2-Agonist and Long-Acting Anticholinergic in three devices OR 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)
Oral corticosteroids*	

1. § Asthma medications categorized as "reliever"
2. *Asthma medications categorized as "maintenance"

9.3.2.2. OBJECTIVE 2: Ascertainment of Off-label Use

Off-label prescribing will be described for patients in the FF/VI new user cohort only including prescribing of:

- FF/VI 200/25 formulation in patients with evidence in the CPRD record of a COPD diagnosis (including an asthma history stratification). Only the FF/VI 100/25 formulation is licensed for use in patients with COPD.
- FF/VI (any dose) in children <12 years. Neither the 200/25 nor the 100/25 formulations of FF/VI are licensed for use in children <12 years of age.

9.3.2.3. OBJECTIVE 3: Treatment patterns and adherence

The treatment patterns and adherence in the FF/VI new user cohorts only will be described based on prescription records and will be presented by diagnosis group (Asthma, COPD - including an asthma history stratification [i.e. yes/no], Other). Treatment patterns will be considered in patients with 12 full months of follow-up after their index treatment. The follow-up period for these analyses is therefore the time from the index prescription to 12 months after the index prescription.

The specific treatment patterns and adherence measures to be assessed are described below.

Treatment patterns:

Three types of treatment patterns will be explored in different groups of patients:

- **FF/VI dose escalation/reduction (all patients):** The first occurrence of either an increase or a decrease in the FF/VI dose in the 12 months following the index date. Events will be categorized as follows:
  - **FF/VI dose escalation in patients with an index prescription for FF/VI 100/25:** step up from FF/VI 100/25 to 200/25, defined as at least 1 prescription for FF/VI 200/25 during follow-up
  - **FFI/VI dose reduction in patients with an index prescription for FF/VI 200/25:** step down from FF/VI 200/25 to 100/25, defined as at least 1 prescription for FF/VI 100/25 during follow-up

- **Treatment patterns during follow-up (patients who are not taking a concomitant inhaled maintenance therapy for COPD or asthma)**: Patients will be classified into mutually exclusive unique treatment pattern groups based on prescription records. The first change during the follow-up period will be described.

  Treatment patterns will not be described in patients who are censored between 31 and 90 days after their last prescription as it will not be possible to determine whether these patients have discontinued their index treatment.

  Unique treatment patterns are described below and outlined in Figure 3 and Figure 4:

  (1) Continuous use: No prescription for another inhaled COPD or asthma maintenance therapy, and continuous prescriptions (no break >90 days between prescriptions) throughout the 12 month period after the index date.

  (2) Augmentation: at least 1 prescription for another inhaled COPD or asthma maintenance therapy (Table 3) during period ≥31 days from index date and ≥31 days before the discontinuation date of the index treatment or the end of 12 months following the index date. The augmentation date will be defined as the date of first prescription for the new COPD or asthma maintenance therapy.

  (3) Immediate switching: at least 1 prescription for another inhaled COPD or asthma maintenance therapy (Table 3) within 12 months of the index date, and the new treatment starts ≤30 days before the discontinuation date for the index treatment, and ≤60 days after the discontinuation date for the index treatment. The switching date will be defined as the date of first prescription for the new COPD maintenance therapy.

  (4) Discontinuation: discontinuation of the index medication prior to 12 months after the index date and does not meet the definitions for continuous use,

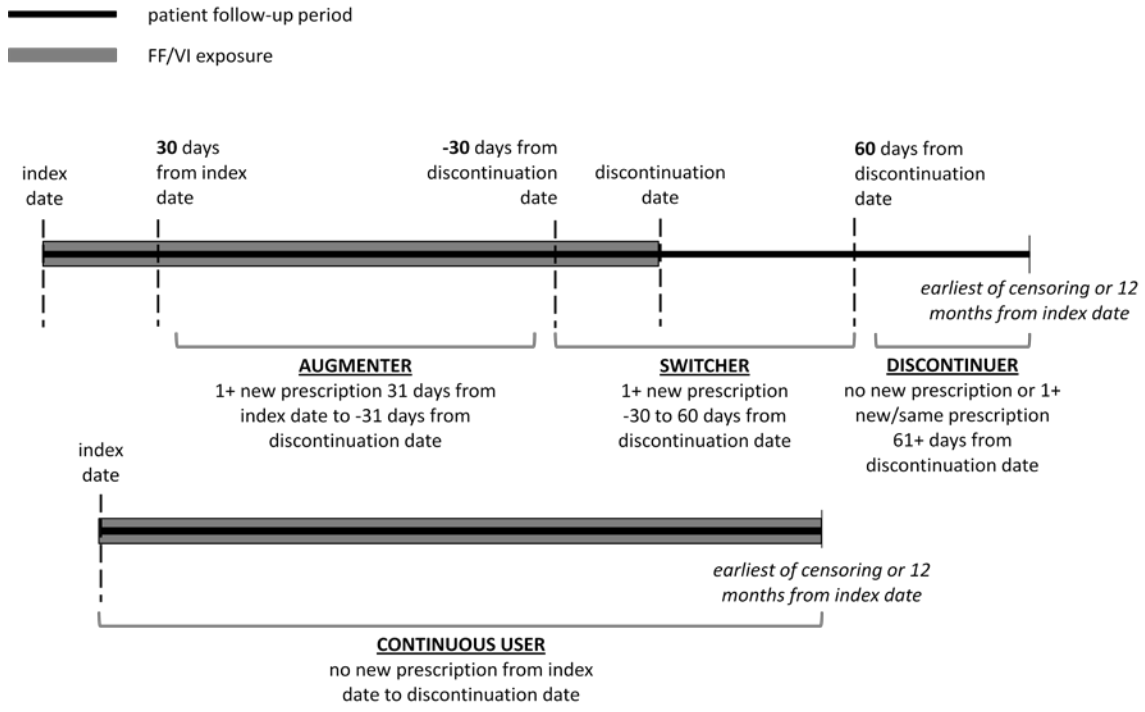
immediate switching and augmentation above. Patients who discontinue will be further categorised into those who restart their index therapy within the first 12 months after a break of ≥91 days ('discontinuation with drug hiatus'), those who do not restart their initial therapy in the first 12 months ('true discontinuation') and those who initiate a new therapy >60 days after discontinuation ('discontinuation with latent switch').

Table 3 Potential treatment switches or augmentations

Initial treatment	*Potential Treatment switches*	*Potential Treatment augmentation*
FF/VI	*ICS/LABA[1]*	*FF/VI+LAMA*
	ICS (or ICS/SABA) alone[1]	*FF/VI+LABA/LAMA*
	LABA alone[1]	
	LAMA alone	
	LAMA/LABA[3]	
	ICS/LAMA/LABA[1,4]	

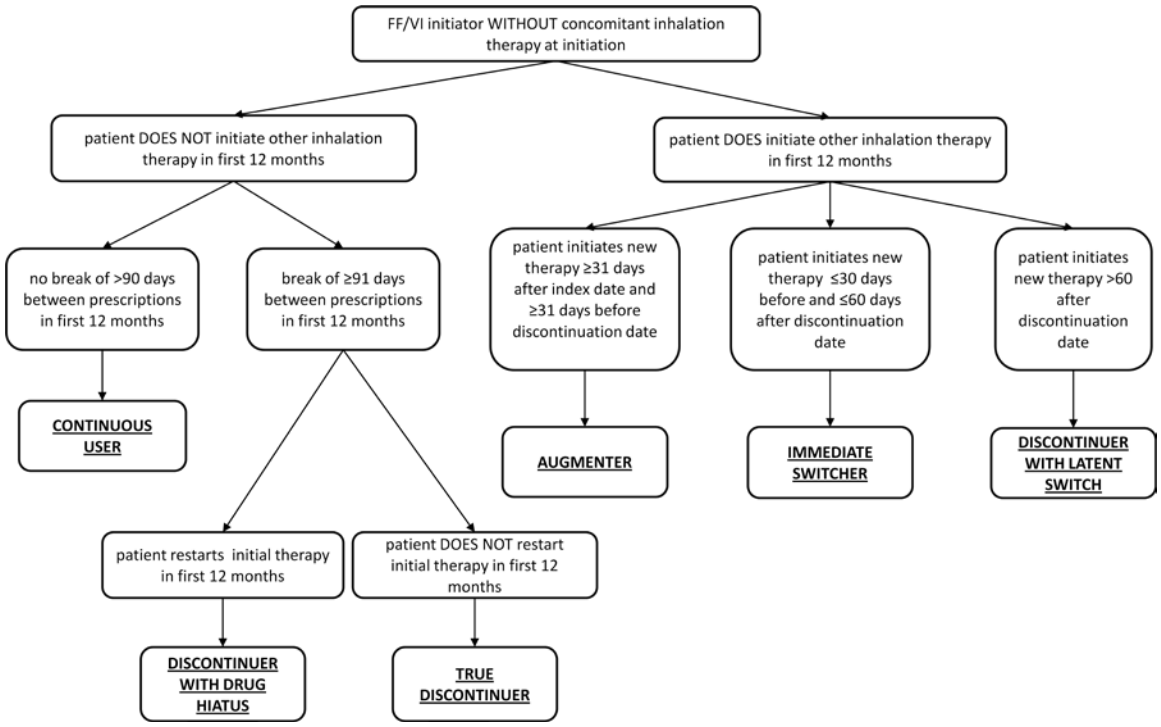
1. *ICS/LABA other than FF/VI (fixed dose or open combination in two devices)*
2. *Open combination of Inhaled Corticosteroid and Long-Acting Anticholinergic (Tiotropium) in two devices*
3. *Fixed dose or open combination in two devices*
4. *Open combination in 2 or more devices; ICS/LABA components other than FF/VI*

Figure 3 Treatment patterns for patients who are not taking a concomitant COPD or asthma maintenance therapy at index date



NB. 'new' prescriptions mean prescriptions for a 'new' inhalation therapy which is different from the index therapy. 'same' prescriptions refer to repeat prescriptions of the index therapy.

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



- **Treatment pattern during follow-up <u>(patients with concomitant inhaled maintenance therapy for COPD or asthma)</u>**: For patients who are taking a concomitant COPD (inhalation) maintenance therapy at the time of the index prescription, similar mutually exclusive treatment patterns will be defined (continuous use, augmentation, immediate switching, and discontinuation). Patients who discontinue or switch will be required to stop both the index medication and the concomitant maintenance therapy on the same day. Patients who augment must continue to take both the index medication and the concomitant therapy at the time of augmentation. Two additional types of discontinuers will be defined to classify patients who discontinue either the index medication or the concomitant therapy. We will only describe the first change within the 12 month period following initiation.

<u>Adherence measures:</u>

- **Medication possession ratio (MPR):** will be calculated only in those with 12 complete months of follow-up from the index date and at least one additional FF/VI prescription (at any dose) after the index FF/VI prescription. Calculated as follows:

$$\frac{\text{Number of days in possession of FF/VI (at any dose) between last prescription date and index date}}{\text{Total number of days between index date and last prescription date}}$$

Where number of days in possession is calculated by multiplying the number of prescriptions in the period (minus the last prescription) by the assumed duration of 30 days and where last prescription date is the last prescription date recorded before the end of the follow-up period or discontinuation date, whichever occurs first. Additions to FF/VI are allowed as long as the patient is still exposed to FF/VI.

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

- **Proportion of days covered (PDC)** will be calculated in patients with 12 complete months of follow-up from the index date Calculated as follows:

$$\frac{\text{Number of days in possession of FF/VI (at any dose) over 12 month follow-up period}}{\text{365 days}}$$

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

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 365 days) to a maximum of 100% (had medication available every day for the 365 day study period). Additions to FF/VI are allowed as long as the patient is still exposed to FF/VI.

The PDC will also be dichotomised, with nonadherence defined as PDC <80% and adherence defined as PDC ≥80%.

9.3.3. Confounders and effect modifiers

Not applicable. No assessment of exposure-outcome relationship will be performed as part of this study.

9.4. Data sources

Primary care data

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.

CPRD-GOLD contains the anonymised, longitudinal medical records of patients registered with contributing primary care practices across the UK. As of July 2016 there were 701 GP practices and 14.2M acceptable (research quality) patients in GOLD, of

which 2.8M are active (still alive and registered with a contributing practice). Data has been collected 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. Prescribing data are coded based on the NHS dictionary of medicines and devices (dm+d). Coded clinical data are recorded using the Unified 5-byte Version 2 Read code set.

The CPRD-GOLD database has been used previously for descriptive drug utilisation studies for prescription medications in respiratory diseases [Ashworth, 2014; van Staa, 2003; Coloma, 2013; DiSantostefano, 2011]. 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 such as Hospital Episodes Statistics (HES) is possible for a subset of around 1.4 million patients currently registered with the 153 consented English practices that actively participate in the linkage scheme. 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.

Description of validated diagnoses

Where possible code lists and disease algorithms that are validated in the CPRD and published will be utilized. Details of all code lists will include review with at least one physician currently practicing in the UK and will be outlined in the detailed statistical analysis plan.

9.5. Study size

A preliminary review of CPRD GOLD to assess study feasibility identified 4,220 patients who had a prescription for FF/VI during the period 01/01/2014 - 31/12/2015 whilst registered at a research quality (up to standard) practice.

Of these 4,220 patients, the following counts were obtained when looking at a time period of at any time within the patient’s record before and up to 01/01/2016:

- 1,079 have a record of both asthma and COPD
- 1,504 have a record of asthma but not COPD
- 1,402 have a record of COPD but not asthma
- 235 do not have a record of COPD or asthma

These expected counts were used to estimate the confidence interval width around a range of potential proportions of (NCSS PASS: Confidence Interval for One Proportion).

- FF/VI 200/25 formulation in patients with evidence in the CPRD record of a COPD diagnosis (including an asthma history stratification)

Assuming approximately 2,400 patients with COPD (with or without asthma) will meet all eligibility criteria and a confidence level (1-alpha) of 95%, the two sided confidence interval for a range of off label use (from 0.1% to 20%) is shown below:

Estimated proportion off label	Two sided confidence interval
0.1%	0%, 0.3%
1%	0.6%, 1.5%
10%	8.8%, 11.3%
20%	18.4%, 21.7%

- FF/VI (any dose) in children <12 years

Assuming approximately 1,700 patients in the asthma and Other diagnosis groups will meet all eligibility criteria and a confidence level (1-alpha) of 95%, the two sided confidence interval for a range of off label use (from 0.1% to 20%) is shown below:

Estimated proportion off label	Two sided confidence interval
0.1%	0%, 0.4%
1%	0.6%, 1.6%
10%	8.6%, 11.5%
20%	18.1%, 22.0%

9.6. Data management

Data will be collected retrospectively from CPRD-GOLD. 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.

9.6.1. Data handling conventions

Definitions and data handling conventions are described in other sections.

9.6.2. Resourcing needs

GSK intends to 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.

9.6.3. Timings of Assessment during follow-up

The proposed analysis design is descriptive using retrospective EMR cohorts of patients prescribed FF/VI or other ICS/LABA FDC. As this study is purely observational without any intervention, there are no specific assessments.

9.7. Data analysis

9.7.1. Essential analysis

A detailed Statistical Analysis Plan outlining algorithms and coding lists will be created and approved initialing the analyses below. For all analyses, cell counts of 5 or fewer patients will be suppressed in the interests of patient confidentiality.

9.7.1.1. Describing the exposure cohorts

Descriptive statistics (mean (SD); median (range)) on the duration of time until censoring and the reasons for censoring for the main study population and the subset of patients eligible for HES linkage will be described. These statistics will be described by index medication (FF/VI 200/25, FF/VI 100/25 and other ICS/LABA FDC).

For patients with an index prescription for FF/VI 100/25 or FF/VI 200/25, descriptive statistics on the number (mean (SD)) and distribution of prescriptions (n, % with 0, 1, 2, 3, 4, 5, 6, 7, ≥8) will be also described. Prescription frequency for the 100/25 or 200/25 doses will be described separately.

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

Further, the proportion of FF/VI users that were flagged as taking concomitant maintenance therapy for COPD or asthma at the index date (see section 9.3.1.2 for definition) will be calculated and the type of concomitant drug described.

9.7.1.2. OBJECTIVE 1: Characteristics of New Users of FF/VI or Other ICS/LABA FDC

The patient demographic, comorbidity and disease history characteristics of new users of FF/VI or other ICS/LABA FDC at date of index prescription will be summarised (See Section 9.3.2.1 for variable description) by diagnosis group. Characteristics will be described as mean (SD) for quantitative variables and n, % for categorical variables.

The analysis of characteristics of FF/VI and other ICS/LABA FDC users will be repeated using the subset of patients eligible for linkage with HES data.

For the group that is characterised as "Other", we will explore diagnosis codes that were recorded on the index date to try to understand if these patients have some other respiratory disease. We acknowledge that this group may also include patients with possible asthma and possible COPD, but who did not meet the strict definition for inclusion in the COPD or Asthma diagnosis groups.

9.7.1.3. OBJECTIVE 2: Description of Off-label Use of FF/VI

Use of FF/VI 200/25 formulation in patients with evidence in the CPRD record of a COPD diagnosis

Use of FF/VI 200/25 formulation in FF/VI new users in the COPD diagnosis group (with or without asthma) will be described during follow-up as follows:

- **Proportion of COPD patients with a prescription for FF/VI 200/25 on the index date**
  This is the primary measure of off-label FF/VI use. The measure will include all COPD patients who are prescribed FF/VI 200/25 as their index prescription, regardless of whether they receive further prescriptions for FF/VI 200/25 or FF/VI 100/25. The proportion will be calculated as:

  $$\frac{\text{\# patients with COPD (with or without asthma) with index presc. of FF/VI 200/25}}{\text{\# patients with COPD (with or without asthma)}}$$

- **Proportion of COPD patients with prescription for FF/VI 200/25 at any time during follow-up**
  This is a secondary, and conservative measure of off-label FF/VI use. The measure will include all COPD patients who are prescribed FF/VI 200/25 on their index date, and all COPD patients who initiate on FF/VI 100/25 but then receive a prescription for FF/VI 200/25 during follow-up. The proportion will be calculated as:

  $$\frac{\text{\# patients with COPD (with or without asthma) that receive 1+ FF/VI 200/25 presc. during follow-up}}{\text{\# patients with COPD (with or without asthma)}}$$

- **Proportion of FF/VI prescriptions which are FF/VI 200/25 in a COPD patient**

As an indication of persistent off label use, the proportion of all prescriptions that were off label for each patient will be calculated. These data will be presented as a histogram and as distinct categories which represent increasing frequency of off label use: <25%, 25-50%, 50-75%, ≥75%. Proportion will be calculated for each patient as follows:

$$\frac{\text{\# FF/VI 200/25 prescriptions for patient X with COPD (with or without asthma)}}{\text{\# FF/VI (any dose) prescriptions for patient X with COPD (with or without asthma)}}$$

Use of FF/VI (any dose) in children <12 years of age

Use of FF/VI (any dose) in children <12 years of age will be described during follow-up as follows:

- **Proportion of patients in the Asthma or Other diagnosis group age <12 at index prescription for FF/VI (any dose)**
  This is the primary measure of off-label use in children, who by definition, cannot be in the COPD diagnosis group. This measure is conservative, because (a) it excludes patients in the COPD diagnosis group and (b) it is recognised that some children may initiate FF/VI at age 11 but then turn 12 shortly after initiation but the index prescription is still not per label. The proportion will be calculated as:

  $$\frac{\text{\# patients in Asthma and Other diagnosis groups aged <12 years at index date}}{\text{\# patients in Asthma and Other diagnosis groups}}$$

  Additionally, for patients in the Asthma and Other diagnosis groups aged <12 at the time of their index prescription, the distribution of their ages (in years) at the index date will be described and presented as a histogram. For children aged ≥11 and <12 at the time of their index prescription, the distribution of their ages in years and months will also be presented.

- **Proportion of FF/VI (any dose) prescriptions issued to children <12 years**
  As an indication of persistent off label use, the proportion of all prescriptions that were off label for each patient in Asthma and Other diagnosis groups will be calculated. This will be calculated for each patient and presented as a histogram and as distinct categories which represent increasing frequency of off label use: <1, 1-5%, ≥5%. Note: For this measure of off-label, if a child is 11 years of age at index but becomes 12 during the study period, only those prescriptions that occurred while aged 11 will be considered as off label. Proportion will be calculated for each patient as follows:

  $$\frac{\text{\# FF/VI (any dose) prescriptions in patient X (in the Asthma or Other diagnosis group) <12 years at time of prescription}}{\text{\# FF/VI (any dose) prescriptions for patient X (in the Asthma or Other diagnosis group)}}$$

9.7.1.4. OBJECTIVE 3: Treatment patterns and adherence

Treatment patterns

The following measures will be described for new users of FF/VI with 12 complete months of follow-up after the index date, by diagnosis group (Asthma, COPD-including a stratification by asthma history, Other) during follow-up.

- First FF/VI dose escalation or reduction
    - FF/VI dose escalation**:** step up to 200/25 for a patient with an index dose of 100/25 (n, %)
    - FF/VI dose reduction**:** step down to 100/25 for a patient with an index dose of 200/25 (n, %)
- Classification of treatment pattern during follow-up in those with no concomitant use of inhaled maintenance therapies for COPD or asthma at Index Date
    - continuous use, augmentation, immediate switching, discontinuation (n,%)
    - time (days) to augmentation, immediate switching or discontinuation (mean, SD)
- Description of the inhaled maintenance therapies for COPD or asthma identified in augmentation or switching during follow-up
- Classification of treatment pattern during follow-up in those with no concomitant use of inhaled maintenance therapies for COPD or asthma at Index Date
    - continuous use, augmentation, immediate switching, discontinuation (n,%)
    - time (days) to augmentation, immediate switching or discontinuation (mean, SD)

Adherence:

MPR and PDC will be calculated as described in Section 9.3.2.3 for new users of FF/VI with at least 12 months of follow-up, by diagnosis group:

- MPR: distributions (mean (SD), min, max, median) and ≥80% (n,%)
- PDC: distributions (mean (SD), min, max, median) and ≥80% (n,%)

9.7.2. Exploratory analysis

Additional analyses may be conducted to explore:

- Use of an alternative time window for identifying eligibility for the COPD or asthma diagnoses groups: record of diagnosis ever in history up to and including index date (instead of the time window specified in Section 9.2.2.1 which was

ever in history prior to index medication date or until end of follow-up or censoring).

- The characteristics of COPD patients identified as being off-label at index date (yes/no) and off-label at any point (yes/no) will be described in terms of demographics, disease burden (including COPD severity), select comorbidities and respiratory medication use at baseline.

9.8. Quality control

CPRD has been used previously for descriptive drug utilisation studies for prescription medications in respiratory diseases [Ashworth, 2004; van Staa, 2003; DiSantostefano, 2011].

The standard operating procedures of CPRD 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. Archiving of the project materials will be performed in accordance with GSK SOPs for documentation and archiving of observational studies.

9.9. Limitations of the research methods

Observational study designs allow for the understanding of the natural history of disease as well as medication utilisation patterns using electronic or medical claims data in a real-world versus interventional setting. However, these studies have their strengths and limitations.

Study advantages:

- Representative base sample of asthma and/or COPD primary care patient populations in England
- Unlike in a clinical trial, patients are not excluded from the study based on co-morbidities or lack of consent. This allows identification and characterisation of ALL patients newly prescribed FF/VI in a real world setting.
- Routine collection of demographic and clinical characteristics in COPD patients (e.g. spirometry, dyspnoea) will be collected in this study that are not typically available in other large linked healthcare databases.

Study limitations:

- Sample size within a given timeframe is difficult to predict since it depends upon the rate of prescribing by primary care physicians.
- Results apply to off-label use and utilisation patterns for the United Kingdom and may not reflect patterns in other countries. Further, new users of a new drug (e.g. FF/VI) may be a skewed population. More severely diseased patients may be channelled towards FF/VI relative to other FDC ICS/LABA. We recognise this as a limitation of the study and consequence of conducting the study in immediate period following market authorisation.
- Analysis of respiratory and other co-morbidities include only diagnosed diseases that are recorded in EMR by the general practice practitioner. Medication use is based on prescribed medications recorded by the general practitioner, which might not have been dispensed at the pharmacy or ultimately utilized by the patient. Currently, information on prescriptions initiated in hospitals or secondary care are not accessible for analysis.
- There is the potential to misdiagnose COPD as asthma (or vice versa), particularly in patients forty and older [Tinkelman, 2006]. In addition, there may be patients with asthma which had progressed to COPD. Further, we may find a small number of patients with COPD who are younger than would be expected (<35 years of age). Additionally, in our stratification of COPD patients with and without a history of asthma, we will not be able to distinguish between patients with a history of asthma, those with an initial asthma diagnosis that progressed to COPD, and those with active, concurrent asthma. We accept limitations of our disease algorithms, particularly for mixed disease, and note the potential for some misclassification as would be expected in electronic medical records.

We 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. Despite the limitations, this observational study will provide insights into off-label prescribing of FF/VI and medication usage patterns among new users of FF/VI in the United Kingdom.

9.9.1. Study closure/uninterpretability of results

If uptake of the recently approved FF/VI is lower than expected in the United Kingdom and recruits fewer than 500 patients in asthma and/or COPD, the descriptive information about off-label medication use and medication usage patterns may not be as robust. If identification of FF/VI patients results in fewer patients than anticipated, GSK will consider extending the patient identification period beyond two years and/or add additional databases to the study. GSK will communicate with the European Medicines Agency on any adjustments required to achieve adequate sample size.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Ethical approval and subject consent

CPRD and other similar EMR systems are databases of pseudonymised EMRs. Our approach to the study is naturalistic; we will not be conducting further diagnostic tests, alter disease management strategies, or collect data in addition to or above routine medical care.

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).

10.2. Subject confidentiality

CPRD and linked HES data contain only fully de-identified patient data. No confidential information is available to the study team, and GSK does not have any access to patient identifiers.

All data held and processed by CPRD 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.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Based on the study objectives, it is unlikely that adverse events will be identified during this study. Further, as the research utilises existing data sources of anonymised patient data, the minimum criteria needed to report serious and non-serious adverse events, pregnancy exposures, and other incidents related to a GSK product are not present in the

data and thus there is no potential for reporting of adverse events, pregnancy exposures and other incidents in this study. The following minimum criteria for reporting are missing from the data sources: an identifiable patient.

12. EXTERNAL COMMUNICATIONS

The final report of this Post-Authorization Safety Study will be submitted to the European Medicines Agency to the timelines agreed in the EU-RMP. This study may also be submitted for consideration in the published literature.

13. INTERNAL COMMUNICATIONS

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

14. REFERENCES

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