In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Final Study Report
Control: Non-Interventional

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
Phase:	IV
Compound Number:	GW685698+GW642444 (GSK2285997)
Effective Date:	27-SEP-2017
Description:	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 prescribing) of FF/VI in a real-world, post-approval setting.

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): PPD

Indication Studied: COPD, Asthma

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
Version identifier of the final study report	1.0
Date of last version of the final study report.	DD-MMM-YYYY
EU PAS register number	EUPAS17720
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-months following the availability of fluticasone furoate / vilanterol (FF/VI) in the United Kingdom, 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 perform the following objectives:
	• Describe patient characteristics (demographics, disease burden, comorbidities, respiratory medication use) and diagnosis group (COPD-including asthma history stratification, Asthma, Other) of new users of FF/VI and other ICS/LABA FDC.
	• Describe off-label prescribing of FF/VI 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)
	• Describe the treatment patterns and adherence to FF/VI by diagnosis group.

Country(-ies) of study	United Kingdom
Author	PPD Clinical Practice Research Datalink (CPRD) MHRA, 151 Buckingham Palace Road London SW1W 9SZ UK Email: PPD

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Glaxo Group Limited 980 Great West Road Brentford Middlesex, TW8 9GS UK
MAH contact person	PPD Senior Director and Therapy Area Head, Respiratory Epidemiology R&D Projects, Clinical Platforms & Sciences GSK Stockley Park West, 1-3 Ironbridge Road, Uxbridge, Middlesex, UB11 1BT, UK Email: PPD

SPONSOR SIGNATORY SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of the study PRJ2214 / 205052.

PPD

Name of Project Officer: Wilhelmine Meeraus

Title of Project Officer: Manager, Respiratory Epidemiology

Signature: PPD

Date: 26 / SEPT / 2017

Name of Therapy Area Head: Sarah Landis

Title of Therapy Area Head: Senior Director and Therapy Area Head

Signature: PPD

Date: 26 / Sept / 2017

INVESTIGATOR SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge Study PRJ2214 / 205052 *was carried out as described in this GlaxoSmithKline Report*

Name of Investigator: Daniel Dedman

Affiliation: Clinical Practice Research Datalink (CPRD)

Signature of Investigator: PPD

Date: 27 September 2017

PPD

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1 LIST OF ABBREVIATIONS

AE	Adverse Event
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
CAG	Confidential Advisory Group
CI	Confidence Interval
CONSORT	CONsolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
CPRD-GOLD	GP OnLine Database
EMR	Electronic Medical Records
EU-RMP	European Union – Risk Management Plan
FDC	Fixed dose combination
FEV_1	Forced Expiratory Volume (in one second)
FF	Fluticasone Furoate
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Obstructive Lung Disease
GP	General Practitioner
GSK	GlaxoSmithKline
HES	Hospital Episodes Statistics
HRA	Health Research Authority
ICS	Inhaled Corticosteroids
IQR	Interquartile Range
ISAC	Independent Scientific Advisory Committee
LABA	Long-Acting Beta2-Agonists
LAMA	Long-Acting Muscarinic Antagonist
LTRA	Leukotriene Receptor Antagonists
MAH	Marketing Authorization Holder
MPR	Medication Possession Ratio
MITT	Multiple Inhaler Triple Therapy
OCS	Oral Corticosteroids
ONS	Office for National Statistics
PASS	Post Authorisation Safety Study
PDC	Proportion of Days Covered
PDE4	Phosphodiesterase-4
SABA	Short-Acting Beta-Agonist
SABD	Short-Acting Bronchodilator
SAMA	Short-Acting Anti-Muscarinic
SD	Standard Deviation
UK	United Kingdom
VI	Vilanterol trifenatate

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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 and Therapy Area Head, Respiratory Epidemiology

Name: PPD

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.

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

CPRD Members

Dr. PPD (Senior Researcher CPRD)

PPD (Senior Researcher, CPRD)

Dr. PPD (Researcher CPRD)

3 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

Keywords

Chronic Obstructive Pulmonary Disease, Asthma, Electronic Medical Records, Inhaled Corticosteroids, Long-acting Beta-2-Agonists

Rationale and background

FF/VI is a once-daily inhaled corticosteroid/long-acting beta-2 agonist (ICS/LABA) fixed dose-combination (FDC) medication that was approved in the EU for the treatment of asthma and COPD in November, 2013. 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 prescribing) of FF/VI in a real-world, post-approval setting.

Research questions and objectives

In the 24-month period immediately following the availability of FF/VI in the United Kingdom (UK), a drug utilisation review was conducted with the following objectives:

1. Separately among new users of FF/VI and other ICS/LABA FDC, describe patient characteristics and diagnosis group (COPD-including an asthma history stratification, Asthma, Other);
2. Among new users of FF/VI, describe off-label prescribing including prescription of FF/VI (any dose) in children <12 years of age (as neither FF/VI 100/25 nor 200/25 is licensed for use in children) and FF/VI 200/25 in patients with a COPD diagnosis (only FF/VI 100/25 is licensed for treatment of COPD); and
3. Among new users of FF/VI, describe 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.

Setting

UK primary care

Subjects and study size, including dropouts

Patients newly prescribed FF/VI or other ICS/LABA FDC during the study period were identified based on prescription records. At least 12 months of recorded data prior to the index prescription date was required to assess baseline characteristics. Prior use of another ICS/LABA FDC product was permitted. In total, 52,817 new users were included.

Variables and data sources

Study outcomes included patient characteristics (demographics, disease burden, comorbidities, prior respiratory medication use), off-label prescribing (FF/VI in children <12 years of age, and prescription of FF/VI 200/25 in patients with evidence of a COPD diagnosis), treatment patterns (dose escalation and reduction, continuous use, switching, augmentation or discontinuation) and adherence to therapy (Medication Possession Ratio, MPR, and Proportion of Days Covered, PDC). Diagnosis groups were defined sequentially with patients first considered for COPD, then Asthma if they did not meet criteria for COPD and then Other if not meeting the inclusion criteria for COPD or Asthma.

Data were derived from the Clinical Practice Research Datalink (CPRD) database, a primary care-based EMR database in the UK. Additional patient-level data on secondary care was obtained from linked Hospital Episode Statistics (HES) data held by CPRD.

Results

Of the total sample of 52,817 new users of FF/VI and other ICS/ LABA FDCs, 34.0% were in the COPD diagnosis group; 55.3% in the Asthma diagnosis group, and 10.7% had neither a COPD nor an asthma diagnosis (Other group). Half the patients in the COPD diagnosis group had a history of asthma in their electronic medical record (N=7,343, 44.2%).

In the post-approval period of up to 24 months from the start of FF/VI availability in the UK, 4,373 patients initiated FF/VI; 77.3% at the lower dose (100/25) and 22.7% at the higher dose (200/25). In that same period 48,444 patients initiated other ICS/LABA FDCs.

Patient characteristics

Mean age of new users of FF/VI or other ICS/LABA FDC ranged from 68.1 to 69.4 years in the COPD diagnosis group, 47.0 to 53.1 years in the Asthma diagnosis group and 58.6 to 63.8 years in the Other diagnosis group. Females comprised around half of new users of FF/VI 100/25 (50.1%), FF/VI 200/25 (46.65%) and other ICS/LABA FDC (50.43%) in the COPD diagnosis group. The Asthma diagnosis group had a higher proportion of females than the COPD group (FF/VI 100/25 64.7%; FF/VI 200/25 66.5%; other ICS/LABA FDC 61.2%). In the Other diagnosis group, the proportion of females was similar for new users of FF/VI 100/25 (57.7%) and other ICS/LABA FDC (56.1%), but higher among new users of FF/VI 200/25 (65.1%).

The proportion of current smokers was highest in the COPD diagnosis group without a history of asthma (range 39.9-43.4%), followed by COPD patients with a history of asthma (range 32.8-35.7%), and lowest among patients in the Asthma diagnosis group (range 17.8-24.3%). In the Other diagnosis group, the proportion of current smokers was low in new users of FF/VI 200/25 (14.3%) compared with new users of FF/VI 100/25 (36.1%) and new users of FF/VI 200/25 (23.4%).

In the COPD diagnosis group, rates of moderate exacerbations in the year prior to the index date were higher in new users of FF/VI than in new users of other ICS/LABA FDC (FF/VI 100/25: 1.36 per person year FF/VI; 200/25: 1.53 per person year; other ICS/LABA FDC: 1.13 per person year). COPD patients newly using FF/VI (any dose) also had greater dyspnoea burden than COPD patients newly using another ICS/LABA FDC suggesting channelling of FF/VI (particularly the high dose) to patients with more severe COPD. Amongst patients in the Asthma diagnosis group, the highest rates of OCS treated exacerbations in the year prior to index date were observed in the new users of FF/VI 200/25 (0.20 per person year), followed by new users of FF/VI 100/25 (0.09 per person year) and new users of other ICS/LABA FDC (0.08 per person year).

Off-label prescribing

Prescribing of FF/VI (any dose) in children <12 years was very low (<0.29%). In total, 16.9% of COPD patients were prescribed FF/VI 200/25 as their index FF/VI prescription. As some COPD patients escalated from FF/VI 100/25 to FF/VI 200/25 during the 12-month study period, the proportion of the COPD diagnosis group with FF/VI 200/25 at any time during follow up was 20.2%. When considering prescriptions of FF/VI 200/25 to COPD patients with a history of asthma as not being off-label, the proportion of off-label prescribing was 7.5% for an index prescription of FF/VI 200/25 or 9.3% for prescribing of FF/VI 200/25 at any time during the 12-month study period.

Treatment patterns and adherence

More patients in the COPD diagnosis group reduced their dose of FF/VI (26.2%) than increased their dose (4.5%). In the Asthma diagnosis group, there were similar numbers of patients escalating (11.5%) and reducing (15.0%) their dose of FF/VI.

Treatment patterns were assessed among 3,312 new users of FF/VI who contributed data for the full 12 months after initiation (i.e. not censored due to death, leaving the GP practice, etc.). The most common treatment pattern in the COPD diagnosis group (with and without concomitant maintenance therapy at initiation) was to remain a continuous user in the first 12 months. A higher proportion of COPD patients with a concomitant LAMA maintenance therapy were continuous users of both drugs (FF/VI 100/25: 66.8%, FF/VI 200/25: 65.9%) than COPD patients without any concomitant therapy (FF/VI 100/25: 58.3%, FF/VI 200/25: 54.7%).

The majority of asthma patients with no concomitant use of a maintenance therapy were continuous users for both doses of FF/VI (FF/VI 100/25: 68.3%, FF/VI 200/25: 69.0%). Asthma patients with concomitant use of LTRA were also highly likely to continuously use both drugs (FF/VI 100/25: 59.7%, FF/VI 200/25: 55.4%).

MPR was assessed among 2,874 new users of FF/VI who contributed data for the full 12 months of follow up and who had 2+ prescriptions for the index FF/VI. The median MPR was 0.92 (IQR 0.63-1.05) for the COPD diagnosis group, marginally higher than the 0.82 (IQR 0.58-1.01) for patients in the Asthma diagnosis group and the 0.86 (IQR 0.60-1.00) for patients in the Other diagnosis group. The median PDC for all new users of FF/VI contributing a full 12 months of follow up (N=3,312) was 0.74 (IQR 0.41-0.99) for COPD patients and 0.66 (IQR 0.25-0.90) for patients in the Asthma diagnosis group. The PDC was lower for patients in the Other diagnosis group (median 0.25; IQR 0.08-0.74).

Discussion

This study demonstrates that use of FF/VI is rare in children under 12 years of age in the UK. As such, no risk minimisation measures or amendments to the labelling are required relating to paediatric off-label use. Some COPD patients in the UK have possibly been prescribed FF/VI 200/25 off-label (estimates range from 7.5% of COPD patients with a first prescription at the higher dose and no history of asthma to 20.2% of COPD patients with a high dose prescription at any time, with or without an asthma history). These data suggest that potential off-label prescribing of the higher dose formulation in the UK is highly linked to historical or concurrent asthma and, in addition, channelled to patients with more severe COPD and prior treatment with high-dose steroids. No amendments to the labelling for FF/VI 200/25 are proposed.

4 AMENDMENTS AND UPDATES

Amendments are described in Section 5 of the study protocol.

5 MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	01-JAN-2014	01-JAN-2014	NA
End of data collection	31-DEC-2015	31-DEC-2015	NA
Registration in the EU PAS register	01-MAR-2017	07-FEB-2017	NA
Final report of study results	31-JUL-2017	27-SEPT-2017	The report and study results were delivered by the vendor on 31-JUL-2017, but the report required review and finalisation within GSK, hence the delay between planned and actual dates.

6 RATIONALE AND BACKGROUND

6.1 Background

Bronchodilators, such as long-acting beta-2-agonists (LABA), are central to improving lung function and managing symptoms in COPD. Regular treatment with inhaled corticosteroids (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 2017)]. 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 [GOLD 2017; 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 [Global Initiative for Asthma [GINA 2017]. 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 ICS/LABA fixed dose-combination (FDC) product approved in the EU for the treatment of both COPD and asthma in November, 2013 with the following indications:

- COPD indication: FF/VI 100/25 is indicated for symptomatic treatment of adults with COPD with a FEV_1 < 70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.
- 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 (LABA and ICS) is appropriate:
    - patients not adequately controlled with ICS and 'as needed' inhaled short acting beta-2 agonists (SABA).

FF/VI was launched in the United Kingdom under the trade name RELVAR™ ELLIPTA™ in January 2014.

The safety and efficacy of ICS/LABA FDC combination therapy medications in COPD and asthma have been studied extensively for the past decade. The registration clinical development programme for FF/VI indicated that the safety profile for FF/VI was similar to that of other ICS/LABA FDC [Agusti 2014; Dransfield 2014; Lötvall 2014, Woodcock 2013; Busse 2016]. 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 prescribing, including prescribing of FF/VI (any dose) in children <12 years of age, and prescribing of the FF/VI 200/25 dose in COPD , in new users of FF/VI who initiated the medication within the first 24 months of drug availability in the United Kingdom (UK).

6.2 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.

7 RESEARCH QUESTION AND OBJECTIVES

In the 24-month period immediately following the availability of FF/VI in the UK, this study identifies new users of FF/VI or other ICS/LABA FDC medications from a UK primary care electronic medical records (EMR) database. A drug utilisation review was performed with the following 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 (COPD-including an asthma history stratification, Asthma, Other).
- Objective 2: Among new users of FF/VI, describe off-label prescribing including prescription of:
  - FF/VI (any dose) in children <12 years of age
  - FF/VI 200/25 (pre-dispensed doses; all doses in mcg) formulation in patients with evidence in the EMR database of a COPD diagnosis
- Objective 3: Among new users of FF/VI, describe the treatment patterns and adherence to therapy by diagnosis group.

8 RESEARCH METHODS

8.1 Study design

This study took 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) were identified and assessed for eligibility to be included in the study. The index date was the date of new use of FF/VI or other ICS/LABA FDC prescription that occurred during the inclusion period.

The end date of the study was 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

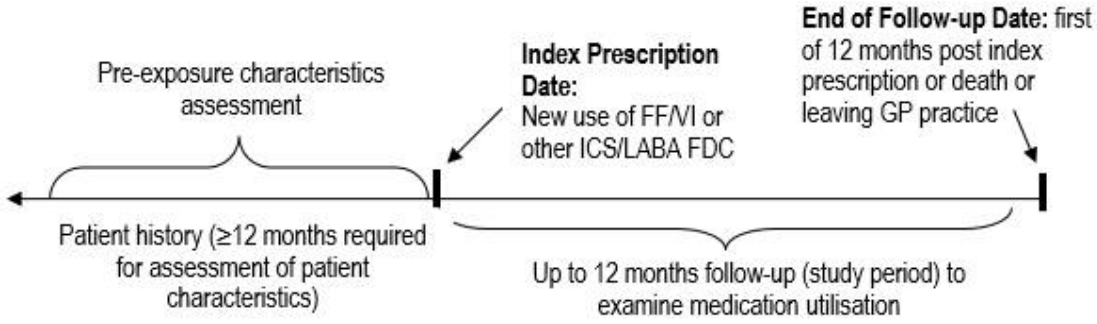
months of follow-up time. Each patient was followed starting on their index date and ending at the first of the following events:

- 12 months post index medication date,
- Death (Censored),
- Leaving GP practice (Censored)

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, was required to allow for a standardised period of history to describe selected patient demographics, disease burden, and previous respiratory medication use.

The study schematic is provided in Figure 1.

Figure 1 Study schematic



A patient could have contributed information on more than one treatment if they met the "new user" definition for more than one medication during the inclusion period (for example, a patient who was newly prescribed a fixed dose combination of fluticasone propionate / salmeterol xinofoate and then FF/VI during the inclusion period contributed information to both the FF/VI and ICS/LABA FDC cohorts).

8.2 Study population and setting

The main study population consisted of new users of FF/VI or other ICS/LABA FDC medications with 'acceptable' data quality in CPRD-GOLD. Patients are labelled as 'acceptable' if they have continuous follow up and do not meet criteria for poor data recording.

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).
- ≥ 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. Data are considered 'up to standard' when the GP practice has continuous high quality data fit for use in research.

Exclusion criteria:

- Patients were excluded if they had ever had a prescription for the same specific inclusion medication prior to the index prescription. Prior use of another ICS/LABA FDC product was permitted. All available data prior to the index date was used to ascertain new use of FF/VI and other ICS/LABA FDC. Concomitant use of respiratory medications was allowed.

From the main study population ('full CPRD sample'), a subset of patients eligible for Hospital Episode Statistics (HES) linkage was identified ('HES-linked sample'). HES data was used in addition to GP data to capture severe COPD exacerbations and hospitalised asthma exacerbations in this subset.

8.2.1 Diagnosis group classification

Patients meeting criteria for entry were classified into diagnosis groups sequentially, based on evidence in CPRD of a recorded diagnosis of: (a) COPD, (b) Asthma, (c) 'Other' (neither COPD nor asthma), as described below. The process for placing patients into their diagnosis groups began with COPD so that we would obtain a pure asthma group that didn't include patients with COPD. A sensitivity analysis using an alternative time period to that described below was also conducted (see Section 8.6.3).

COPD diagnosis group: Patients were considered to have COPD if they had 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 to 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 excluded these patients from the COPD group to avoid misclassification. If these patients met the criteria for inclusion in the Asthma diagnosis group (see below) they were classified as such, otherwise they were 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 was also presented. We defined a history of asthma as any 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. We also calculated the time in days between the index date and the earliest asthma record prior to the index date.

Asthma diagnosis group: Patients were considered to have asthma if they did not meet criteria for inclusion in the COPD diagnosis group and had 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 through to their end of follow-up date. The codes to establish the asthma indication in this analysis have been validated in CPRD [Nissen 2017].

Other diagnosis group (neither COPD nor asthma)**:** Patients were 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 (i.e. but who never received a coded diagnosis), and patients with a coded COPD diagnosis who were aged less than 35 years at the time of first COPD record and therefore did not meet the strict criteria for inclusion in the COPD diagnosis group.

8.2.2 Exposure definitions

8.2.2.1 New users of FF/VI and other ICS/LABA

We identified all new users of FF/VI or other ICS/LABA FDC during the period of January 1, 2014 through December 31, 2015. New use was 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 was the index date. A single patient could contribute more than one qualifying index medication during the study if they met the definition of new use for multiple medications.

All individual prescriptions of FF/VI and other LABA/ICS FDC were assigned a default length of 30 days per container prescribed irrespective of whether they had a recorded value for script length. Other LABA/ICS FDC includes fluticasone propionate/salmeterol xinofoate, budesonide/formoterol, beclometasone/formoterol and fluticasone propionate/formoterol. The other ICS/LABA FDC group was analysed as a class; no ICS/LABA drugs other than FF/VI were analysed individually.

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.

8.2.2.2 Concomitant use of other respiratory medications at index date

Given the naturalistic nature of the study design, it is possible that some patients will have initiated FF/VI or other ICS/LABA FDC while on other respiratory medications. In some instances, these patients will have been 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 searched the patient record and flagged instances when the patients were receiving concomitant respiratory therapy at the time of the index prescription. Concomitant therapy was defined as at least two continuous prescriptions for the other respiratory therapy which started either before, or up to 30 days after the index date, and overlapped for at least 30 days with the index treatment. See Section 8.2.3.1 for a list of respiratory medications that were considered.

8.2.2.3 Discontinuation of FF/VI

Discontinuation of FF/VI prescribing was considered to have occurred if there was either:

- A break of at least 91 days between prescriptions. The discontinuation date was set at 30 days after the prescription prior to the break. GPs may prescribe several months of drug supply at a time, either as a single prescription, or as multiple batch/repeat prescriptions, particularly for patients with stable chronic conditions.

Gaps of 90 days or less between prescriptions are considered acceptable given the patient population in this study.

or

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

It was not possible to determine whether a patient discontinued FF/VI if they were censored between 31 and 90 days after their last prescription

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

8.2.3 Outcome definitions

8.2.3.1 OBJECTIVE 1: Characteristics of new users of FF/VI or other ICS/LABA FDC

The following variables were defined to describe characteristics of new users of FF/VI and other ICS/LABA FDC. Full definitions for how these variables were created are available in the full study protocol.

Demographic variables

- Age at index prescription
- Gender
- Smoking status (current, ex-smoker, no, never smoker)
- Body mass index (BMI, Kg/m^2)
- Area based deprivation (based on the index of multiple deprivation (IMD) quintile, of the patient or GP practice postcode)
- Geographical region of the GP practice

COPD disease burden variables

Defined for patients in the COPD diagnosis group only.

- Acute exacerbations of COPD (AECOPD) in the 12 months prior to the index date defined using a validated algorithm [Rothnie 2016]. It was not possible to delineate exacerbation type (moderate versus severe) using primary care data (CPRD) alone. However, in the subset of patients with the HES link, severe exacerbations were also able to be defined and a further refinement of AECOPD by type is presented.
- Forced expiratory volume in one second, FEV_1, percent predicted based on most recent lung function test in 24 months prior to index date categorised based on GOLD 2006 classification of airflow limitation [GOLD 2009] as $FEV_1 \geq 80\%$ predicted for mild Grade 1, $\geq 50\%$ to $<80\%$ FEV1 predicted for moderate Grade

2, ≥30% to <50% FEV1 predicted for severe Grade 3, <30% FEV1 predicted for very severe Grade 4, or missing.

- FEV1/FVC ratio based on most recent lung function test in 24 months prior to index date, categorised as less than 70%, equal or more than 70%, and missing.
- MRC dyspnoea score in 12 months prior to the index date categorised as Grade 1, Grade 2, Grade 3, Grade 4, Grade 5, or missing.

Asthma disease burden variables

Defined for patients in the Asthma diagnosis group only.

- Asthma exacerbation based on OCS and/or healthcare utilisation were identified in the 12 months prior to index date.
  - OCS treated exacerbations identified based on asthma related OCS prescriptions recorded in primary care using CPRD data. Asthma related OCS prescriptions were defined based on an asthma diagnosis code within ± 14 days of the OCS prescription.
  - Healthcare utilisation defined exacerbations identified based on asthma related hospitalisations and A&E visits were identified based on CPRD data and linked HES data. Asthma related events were defined based on asthma being the primary cause of an episode of care during a hospitalisation (in HES) or any asthma related hospital referrals, A&E visit, or hospitalisation with a discharge diagnosis of asthma (in CPRD).

Comorbidity variables

History (diagnosis records) of key comorbid conditions as recorded ever (flagged yes/no) in the patients' history prior to the index date:

- cardio-and cerebrovascular diseases
- pneumonia
- gastroesophageal reflux disease
- diabetes
- renal disease (acute and chronic)
- cancer
- beta blocker prescribing (in the year prior to the index date only)

Prior use of COPD or asthma medication variables

- Prescriptions for the respiratory therapies (classified according to categories in Table 1) issued within the 12 months prior to index date
- ICS dose (calculated only for patients with 1+ prescription for an ICS containing medication in the 12 months prior to the index date, classified based on highest dose within the 12 month period using GINA conversion guidelines [GINA 2017] as high, medium or low)

Table 1 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 (Categories for 1+ and 4+ prescriptions.)
ICS and SABA/ICS	Inhaled Corticosteroids OR Fixed Combination of Short-Acting Beta2-Agonist and Inhaled Corticosteroid
LABA	Long-Acting Beta2-Agonists
ICS/LABA	Fixed Combination of Inhaled Corticosteroid and Long-Acting Beta2-Agonist
LAMA	Long-Acting Anticholinergics
LAMA/LABA	Fixed Combination of Long-Acting Beta2-Agonist along with a Long-Acting Anticholinergic
Theophylline	Theophylline and its derivates
Roflumilast	Roflumilast (oral phosphodiesterase-4 [PDE4] inhibitor)
LTRA	Leukotriene Receptor Antagonist (montelukast, zafirlukast)
Oral corticosteroids	(Chronic use defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days.)

8.2.3.2 OBJECTIVE 2: Ascertainment of off-label prescribing

Off-label prescribing of FF/VI was defined as:

- FF/VI (any dose) in children <12 years.
- FF/VI 200/25 formulation in patients with evidence in the CPRD record of a COPD diagnosis (including an asthma history stratification) assessed in two ways:
    - COPD patients 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.
    - COPD patients who are prescribed FF/VI 200/25 at any time during follow-up.

8.2.3.3 OBJECTIVE 3: Treatment patterns and adherence

Treatment patterns and adherence were defined in a subset of new users of FF/VI with a full 12 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 (with the exception of the dose escalation/reduction, which was also calculated among all patients regardless of length of follow-up).

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

Dose escalation/reduction of FF/VI:

- 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:

Treatment patterns during follow-up were explored for FF/VI new users only and were stratified by concomitant maintenance therapy and by diagnosis group.

Patients were classified into mutually exclusive unique treatment pattern groups based on prescription records. The first change during the follow-up period was described. Treatment patterns were not described in patients who were censored between 31 and 90 days after their last prescription as it was not possible to determine whether these patients discontinued their index treatment.

Treatment patterns for patients without any concomitant therapy:

- Continuous use: No prescription for another inhaled COPD or asthma maintenance therapy, and continuous prescriptions (no break >90 days between prescriptions) for FF/VI (any dose) throughout the follow-up period after the index date.
- Augmentation: at least 1 prescription for another inhaled COPD or asthma maintenance therapy during period ≥31 days from index date and ≥31 days before the discontinuation date of FF/VI (any dose) or the end of the follow-up period following the index date. The augmentation date was defined as the date of first prescription for the new COPD or asthma maintenance therapy.
- Immediate switching: at least 1 prescription for another inhaled COPD or asthma maintenance therapy within 12 months of the index date, and the new treatment starts ≤30 days before the discontinuation date of FF/VI (any dose) , and ≤60 days after the discontinuation date for the index treatment. The switching date was defined as the date of first prescription for the new COPD maintenance therapy.
- Discontinuation: discontinuation of FF/VI (any dose) , or a concomitant inhaled maintenance therapy, prior to 12 months after the index date and does not meet the definitions for continuous use, immediate switching and augmentation above. Patients who discontinued were 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').

Treatment patterns for patients with concomitant therapy at index date:

Treatment patterns as discussed above (with the exception of switching) were also explored for patients with the most common concomitant inhaled maintenance therapies for each diagnosis group. This included LAMA for patients in the COPD diagnosis group and LTRA for patients in the Asthma diagnosis group (see Section 8.6.2.3 for further definition of the treatment patterns).

Adherence measures:

- Medication possession ratio (MPR): 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. The MPR provides information on adherence during the period a patient is actively prescribed FF/VI.

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

  Where number of days in possession was 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 was the last prescription date recorded before the end of the follow-up period or discontinuation date, whichever occurred first. Additions to FF/VI were allowed as long as the patient was still exposed to FF/VI.

  The MPR was expressed as a percentage, with values greater than 100% allowed. Nonadherence was defined as MPR <80% and adherence defined as MPR ≥80%.

- Proportion of days covered (PDC): calculated for all patients regardless of the number of prescriptions. The PDC provides information on adherence during a set period of one year after initiating FF/VI, which may also include periods of time when a patient is not actively prescribed FF/VI (i.e. after discontinuation).

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

  Where number of days in possession was 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 was the last prescription date recorded before the end of the follow-up period or discontinuation date, whichever occurred first.

  The PDC was expressed as a percentage. For the 0-12 month time period, PDC values ranged 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). Values of greater than 100% were not allowed, and were truncated at 100%.

8.2.4 Confounders and effect modifiers

N/A

8.3 Data Sources

This study utilized the Clinical Practice Research Datalink's (CPRD)-GP OnLine Database (CPRD-GOLD), a UK primary care electronic medical record (EMR) database. Additional patient-level data on secondary care was obtained from linked Hospital Episode Statistics (HES) data held by CPRD.

8.3.1 Primary care data

CPRD-GOLD contains data extracted from Vision Primary Care EMR systems, and contains the anonymised, longitudinal medical records of patients registered with contributing primary care practices across the UK. Further detail on CPRD-GOLD is provided in the study protocol. As of October 2016 there were 711 GP practices and 14.6 Million acceptable (research quality) patients in GOLD, of which 5.4M are active (still alive and registered with the GP practice). Data has been collected from GP practices since 1987.

8.3.2 Linked data

Linkage of CPRD-GOLD data to other patient level datasets such as Hospital Episodes Statistics (HES) currently includes patients from 407 practices. These linkages cover approximately 75% of contributing CPRD GOLD practices in England, and roughly 57% of contributing CPRD GOLD practices in the UK. Further information is available at: http://content.digital.nhs.uk/hes.

8.3.3 Description of validated diagnoses

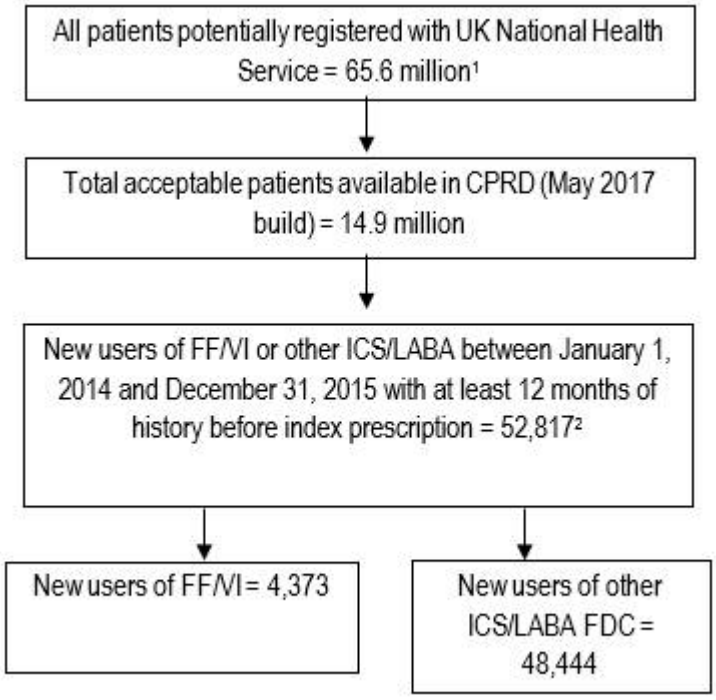
All codelists were agreed with GSK and CPRD. Where possible code lists already validated and published were utilised, for example COPD diagnosis [Quint 2014], COPD exacerbations [Rothnie 2016] and asthma diagnosis [Nissen 2017]. All codelists used in the analysis are provided in study protocol.

8.4 Study size

The CONSORT diagrams for selection of patients into the full CPRD sample and the smaller HES-linked sample are shown in Figure 2 and Figure 3 [Schulz 2010].

In total, 52,817 patients were included in the full CPRD sample and 26,005 in the HES-linked sample. A small number of patients, approximately 5.5% in the full sample and 7.2% in the linked sample, met the inclusion criteria as both new users of FF/VI and other ICS/LABA FDC during the period January 1, 2014 and December 31, 2016.

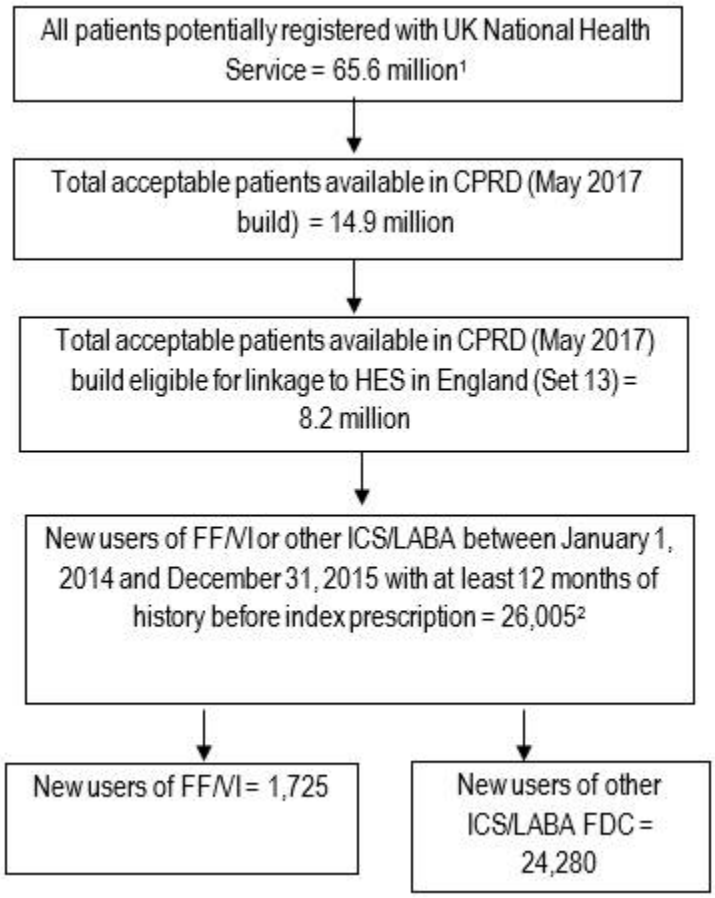
Figure 2 CONSORT diagram for the full CPRD sample



1 United Kingdom population mid-year estimate 2016, Office for National Statistics, https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates

2 Patients contributed information on more than one treatment if they met the "new user" definition for more than one medication during the inclusion period (for example, a patient newly prescribed fluticasone propionate/formoterol fumarate and then FF/VI during the inclusion period would contribute information to both the FF/VI and the other ICS/LABA FDC exposure cohorts).

Figure 3 CONSORT diagram for the HES-linked sample



1 United Kingdom population mid-year estimate 2016, Office for National Statistics, https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates

2 Patients contributed information on more than one treatment if they met the "new user" definition for more than one medication during the inclusion period (for example, a patient newly prescribed fluticasone propionate/formoterol fumarate and then FF/VI during the inclusion period would contribute information to both the FF/VI and the other ICS/LABA FDC exposure cohorts).

8.5 Data Management

8.5.1 Data transformation (data handling conventions)

Data was collected retrospectively from CPRD-GOLD. All programming was performed using Stata (StataCorp. College Station, TX).

8.5.2 Resourcing needs

GSK have outsourced this study to CPRD. GSK have closely collaborated and monitored the deliverables including finalization of the study protocol, and development of programs and conducting the analysis, and finalizing the study report.

8.6 Data analyses

8.6.1 Describing the participants

8.6.1.1 Diagnosis groups

The number and proportion of patients in the three main diagnosis groups (COPD, Asthma, Other) were reported. For the COPD diagnosis group, the number and proportion of patients with and without a history of asthma was also described. For patients in the COPD diagnosis group who had a history of asthma, the mean (SD) and median (IQR) time from earliest recorded (prior) asthma diagnosis to the index date was also reported.

For the group characterised as "Other", we explored diagnosis codes that were recorded in the year prior to (and including) the index date to try to understand if these patients had some other respiratory condition for which they may be receiving medication. We acknowledge that this group could include patients with COPD that did not meet the age requirement, or patients with COPD and/or asthma without a coded diagnosis in their available medical record.

8.6.1.2 Exposure cohorts

The FF/VI 100/25, FF/VI 200/25 and other ICS/LABA FDC exposure cohorts are described separately, and further stratified by disease group: COPD (with a history of asthma stratification), Asthma, Other. Descriptive analyses were conducted for the full CPRD sample and the HES-linked sample separately.

All patients

- Mean (SD) and median (IQR) duration of time in days until censoring
- Number (%) of patients censored for death, leaving GP practice, last collection from GP practice, and reaching the end of the full 12-month study period (n, %)

FF/VI new users only

- Mean (SD) and median (IQR) number of prescriptions of the index FF/VI dose per patient, as well as number (%) of patients with 1, 2, 3, 4, 5, 6, 7 or 8+ prescriptions
- Number (%) of patients contributing more than one index drug, and for these patients, mean (SD) and median (IQR) 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) and median (IQR) time during which the two index medications overlap (in cases where the medication do overlap)
- Number (%) of patients taking concomitant maintenance therapy for COPD or asthma at the index date (see Section 8.2.2.2 for definition), overall and by type of concomitant drug

8.6.2 Essential analyses

8.6.2.1 OBJECTIVE 1: Characteristics of new Users of FF/VI or Other ICS/LABA FDC

Patient demographic, comorbidity and disease history characteristics of new users of FF/VI 100/25, FF/VI 200/25 or other ICS/LABA FDC at date of index prescription were summarised separately, and further stratified by disease group. The variables assessed for this objective were listed in Section 8.2.3.1, and described in detail in the study protocol.

Characteristics were described as mean (SD) and median (IQR) for quantitative variables and n, % for categorical variables. Where data were missing, the numbers of patients with missing data were reported, and summary statistics were calculated only for patients without missing data.

The analysis of characteristics of FF/VI and other ICS/LABA FDC users was conducted using the full CPRD sample and then repeated using the subset of patients in the HES-linked sample.

8.6.2.2 OBJECTIVE 2: Description of off-label prescribing of FF/VI

Off-label prescribing of FF/VI (any dose) in children <12 was calculated as follows:

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

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

Per protocol analyses to examine age at index date were not performed due to small numbers of children prescribed FF/VI.

Off-label prescribing of FF/VI 200/25 in COPD was calculated using the following two measures. These calculations were repeated excluding COPD patients with a history of asthma from the numerator as GPs might reasonably prescribe FF/VI 200/25 to asthma patients who also have a diagnosis of COPD and prescribing in such patients would not be considered off-label.

Proportion of COPD patients with a prescription for FF/VI 200/25 **on the index date**:

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

Proportion of COPD patients with prescription for FF/VI 200/25 **at any time**

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

To understand the persistency of potential off-label prescribing in COPD, we also calculated the following measure:

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

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

This was presented for the whole COPD diagnosis group, and separately for COPD patients with a history of asthma and for those without history of asthma. Data were reported using histograms with distinct categories representing increasing frequency of off-label prescribing (<25%, 25-50%, 50-75%, ≥75%; and deciles (10%)).

8.6.2.3 OBJECTIVE 3: Treatment patterns and adherence

Treatment patterns during follow-up were explored for FF/VI new users only and were stratified by concomitant maintenance therapy. The COPD diagnosis group was further stratified by asthma history.

Treatment patterns were calculated for the subgroup of patients with a full 12 months of follow up (unless otherwise indicated). Full definitions for treatment patterns and measures of adherence are available in Section 8.2.3.3.

- Number (%) of new users of FF/VI escalating or reducing their dose of FF/VI during the full 12 months reported by diagnosis group. This analysis was additionally repeated for the full cohort regardless of whether they had a full 12 months of follow up.
- Mean (SD) time in days to first treatment change, and number (%) of patients with the following first changes in treatment. The following treatment changes were characterized:

  COPD patients with no concomitant inhaled maintenance therapy:
  - Continuing FF/VI for the full study period
  - Discontinuing FF/VI
  - Switching to another ICS/LABA, LAMA, LABA alone or LABA/LAMA
  - Augmenting by adding LAMA to FF/VI

  COPD patients with concomitant LAMA maintenance therapy:
  - Continuing both FF/VI and LAMA for the full study period
  - Discontinuing LAMA and continuing FF/VI
  - Discontinuing FF/VI and continuing LAMA
  - Discontinuing both FF/VI and LAMA at the same time
  - Switching to another ICS/LABA and continuing LAMA
    Patients were allowed to change the type of LAMA and still be considered as continuing LAMA.

  Asthma patients with no concomitant maintenance therapy:
  - Continuing FF/VI for the full study period
  - Discontinuing FF/VI
  - Switching to another ICS/LABA, ICS alone or LTRA

- Augmenting by adding LAMA or LTRA to FF/VI

Asthma patients with concomitant LTRA maintenance therapy:

- Continuing both FF/VI and LTRA for the full study period
- Discontinuing LTRA and continuing FF/VI
- Discontinuing FF/VI and continuing LTRA
- Discontinuing both FF/VI and LTRA at the same time
- Switching to another ICS/LABA and continuing LTRA
- Augmenting by adding LAMA to FF/VI and LTRA
  Patients were allowed to change the type of LTRA and still be considered as continuing LTRA.

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

8.6.3 Exploratory analyses

An additional analysis explored the use of an alternative time window for identifying eligibility for the COPD or Asthma diagnoses groups for Objective 2. Here, diagnosis groups were assigned based on a record of diagnosis ever in history up to and including index date (as opposed to assigning diagnosis group based on a record ever in history or prior to or after the index medication date until end of follow-up or censoring).

8.6.4 General considerations for data analyses

A detailed Statistical Analysis Plan outlining algorithms and coding lists was created and approved before initiating the analyses below.

8.6.5 Amendments to the statistical analysis plan

The following amendments to the statistical analysis plan were made:

- Due to CPRD small cell rules, which prohibit presentation of data in small numbers for confidentiality purposes, cell counts of five or fewer were suppressed for categorical variables were adapted to prevent re-identification. For example, the 0-<5, 6-11, and 12-17 age groupings were collapsed into one 0-17 age grouping.
- Geographical regions in England were combined (from 8 regions to 5 regions) to aid interpretation of trends.
- Analyses on the age distribution of children prescribed FF/VI 'off-label' were not performed due to small numbers of children prescribed FF/VI during the study period.
- The proportions of patients with a dose escalation or reduction were calculated using the number of patients eligible for a change as opposed to the total number of patients initiating on FF/VI 100/25 or FF/VI 200/25. For dose escalation, the denominator (number of eligible patients) was the number of patients initiated on FF/VI 100/25 with at least two prescriptions of FF/VI (any dose). For dose

reduction, the denominator (number of eligible patients) was the number of patients initiated on FF/VI 200/25 with at least two prescriptions of FF/VI (any dose).

8.7 Quality control and quality assurance

CPRD-GOLD has been used previously for descriptive drug utilisation studies for prescription medications in respiratory diseases [DiSantostefano 2014; Ashworth 2004; van Staa 2003]. The COPD and asthma codelists used in this study have been validated and published [Quint 2014, Nissen 2017; Rothnie 2016].

The standard operating procedures of CPRD 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 are required to have data of acceptable research quality according to CPRD standards.

Wherever feasible, all statistical programming was independently reviewed by a second analyst. Key study documents, such as the protocol for obtaining study approval from the Independent Scientific Advisory Committee (ISAC, the 'ISAC Protocol'), statistical analysis plan, and study reports underwent quality-control checks and review by CPRD and GSK Real World Evidence & Epidemiology staff.

9 PROTECTION OF HUMAN SUBJECTS

9.1 Ethical approval and subject consent

CPRD is a database of pseudonymised EMR. Our approach to the study was naturalistic; we did not conduct further diagnostic tests, alter disease management strategies, or collect data in addition to or above routine medical care.

CPRD's processes have been reviewed by the Confidentiality Advisory Group (CAG) and approved by the Health Research Authority (HRA) and Secretary of State in the UK 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 ISAC. ISAC approval for this study was obtained on 8th December 2016, ISAC protocol number 16_229R.

9.2 Subject confidentiality

CPRD contains only fully de-identified patient data. No patient identifiable information were available to the CPRD study team, or to GSK. All data were held and processed by CPRD in compliance with the relevant legal obligations including the Data Protection Act 1998. All data were held on a secure computer network, with access restricted to authorised users.

10 RESULTS

10.1 Participants

10.1.1 Diagnosis groups

Of the total sample of new users of FF/VI and other ICS/ LABA FDCs, 34.0% (N=16,629) were in the COPD diagnosis group; 55.3% (N=27,051) the Asthma diagnosis group, and 10.7% (N=5,250) had neither a COPD or asthma diagnosis (Other group). Nearly half the patients in the COPD diagnosis group had a history of asthma in their electronic medical record (N=7,343, 44.2%). Among the COPD patients with a history of asthma,the median time between the earliest recorded diagnosis of asthma and the index date was 8.8 years (IQR: 3.5- 11.9 years).

To further understand the Other diagnosis group, the frequency of all respiratory diagnoses and symptoms were identified in the year prior to initiation of FF/VI or other ICS/LABA FDC. Out of 5,250 patients in this group, 3,719 had a respiratory code recorded within the year prior to their index date. The top ten most commonly occurring codes nearest to the index date are shown in Table 2.

Table 2 Ten most frequently recorded respiratory codes nearest to the index date for patients in the Other diagnosis group

Read term	Count of patients with code
Chest infection NOS	844
Chest infection	498
Upper respiratory infection NOS	256
Lower respiratory tract infection	256
Upper respiratory tract infection NOS	238
Acute bronchitis	162
Bronchiectasis	147
Acute sinusitis	123
Respiratory tract infection	108

NOS: not otherwise specified. *Source Table: Obj 1-RespCodes_ClosestIndex*

10.1.2 Exposure cohorts

In the post-approval period of up to 24 months from the start of FF/VI availability in the UK, 4,373 patients initiated FF/VI; 3,380 (77.3%) at the lower dose (100/25) and 993 (22.7%) at the higher dose (200/25). In that same period 48,444 patients initiated other ICS/LABA FDCs.

Table 3 Descriptive statistics on exposure to FF/VI and other ICS/LABA, by diagnosis group, for all patients in the full CPRD sample

COPD diagnosis group (N=16,629)[1]		FF/VI 100/25 N=2,205 No. (%)[2]		FF/VI 200/25 N=448 No. (%)[2]		Other ICS/LABA FDC N=15,576 No. (%)[2]	
Time to censoring in (days)	Mean (SD)	328.17	85.9	323.48	92.34	318.84	94.8
	Median (IQR)	365	365 - 365	365	365 - 365	365	356 - 365
Reason for censoring	Death	128	5.8	22	4.91	906	5.82
	Left GP practice	34	1.54	6	1.34	387	2.48
	Last collection from GP practice	338	15.33	83	18.53	2,779	17.84
	Full 12 months of follow-up	1,705	77.32	337	75.22	11,504	73.86
Total prescriptions	Mean (SD)	5.84	2.71	4.63	2.96		
	Median (IQR)	8	3 - 8	5	1 - 8	Not calculated	
	Min, Max	1, 20		1,16			

Asthma diagnosis group (N=27,051)[1]		FF/VI 100/25 N=1,052 No. (%)[2]		FF/VI 200/25 N=502 No. (%)[2]		Other ICS/LABA FDC N=27,573 No. (%)[2]	
Time to censoring in (days)	Mean (SD)	323.45	87.78	333.28	81.95	327.65	86.22
	Median (IQR)	365	353 - 365	365	365 - 365	365	365 – 365
Reason for censoring	Death	21	2	6	1.2	218	0.79
	Left GP practice	29	2.76	13	2.59	1,042	3.78
	Last collection from GP practice	231	21.96	87	17.33	4,809	17.44
	Full 12 months of follow-up	771	73.29	396	78.88	21,504	77.99
Total prescriptions	Mean (SD)	4.91	2.89	5.08	2.95		
	Median (IQR)	5	2 - 8	6	2 - 8	Not calculated	
	Min, Max	1, 18		1, 17			

Other diagnosis group (N=5,250)[1]		FF/VI 100/25 N=123 No. (%)[2]		FF/VI 200/25 N=43 No. (%)[2]		Other ICS/LABA FDC N=5,461 No. (%)[2]	
Time to censoring in (days)	Mean (SD)	284.08	122.97	321.88	92.44	310.43	103.89
	Median (IQR)	365	189 - 365	365	361 - 365	365	325 - 365
Reason for censoring	Death	10	8.13	5	11.63	334	6.31
	Left GP practice	5	4.07			197	3.72
	Last collection from GP practice	36	29.27	7	16.28	969	18.30
	Full 12 months of follow-up	72	58.54	31	72.09	3,795	71.67
Total prescriptions	Mean (SD)	4.28	4.14	4.60	4.17		
	Median (IQR)	2	1 - 6	2	1 - 8		
	Min, Max	1, 14		1, 14		Not calculated	

1. Patients can qualify for more than one qualifying index medication which is reflected in the higher number of records when summing across the exposure cohorts. 2. Unless otherwise specified. *Source Tables: ExposureCohorts-T1_COPD; ExposureCohorts-T1_Asthma; ExposureCohorts-T1_Other*

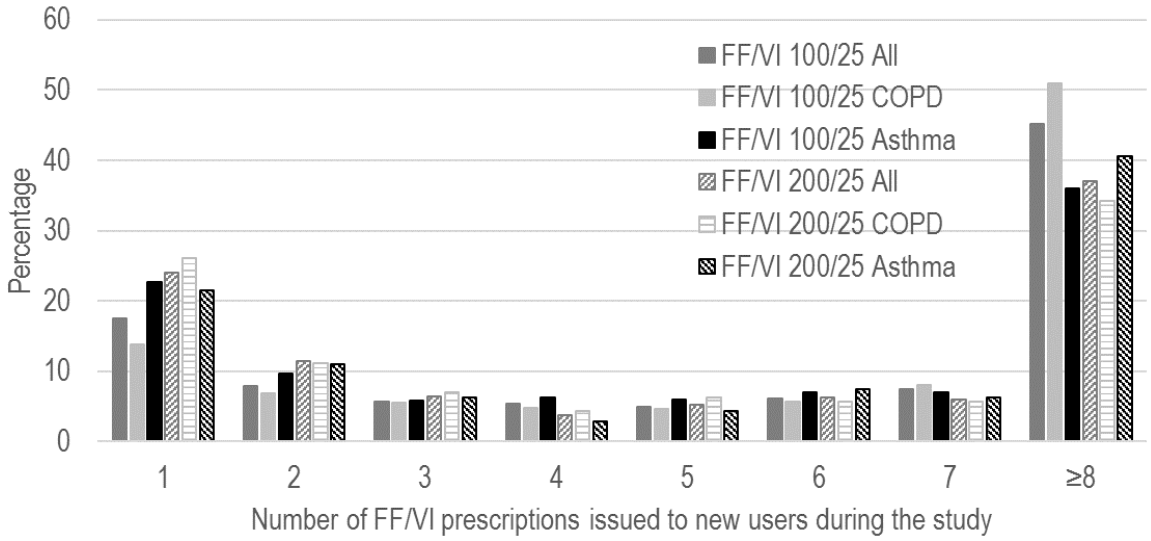
The FF/VI dose received varied by diagnosis group. For example, the proportion of COPD patients initiating FF/VI 100/25 was 83.1% (Table 3). This proportion was 67.7% in the Asthma group and 75% in the Other group (Table 3).

Following initiation, over three quarters of patients contributed data for the full 12-month study period (75.4% of FF/VI 100/25 new users, 77.0% of FF/VI 200/25 new users and 76.0% of other ICS/LABA FDC new users) with similar proportions observed within the diagnosis groups (Table 3). Censoring due to death was highest among patients in the COPD (5.8% among all patients) and Other (6.4% among all patients) diagnosis groups.

The median number of prescriptions issued during the study period for FF/VI 100/25 was 7 (IQR 2-8) and for FF/VI 200/25 was 5 (IQR 2-8). Between a fifth and a quarter of new users had only one occurrence of their index FF/VI prescription recorded during the study; however, a large proportion of patients (45.2% FF/VI 100/25; 37.1% FF/VI 200/25) received eight or more prescriptions of their index FF/VI over the 12-month period (Figure 4).

Among COPD patients, those initiating on FF/VI 200/25 were more likely to receive just one prescription, compared to those initiating on FF/VI 100/25 (26.1% versus 13.7%, respectively.) For asthma patients, the proportion of FF/VI 100/25 and FF/VI 200/25 initiators with just one prescription was similar (22.6% and 21.5%, respectively).

Figure 4 Number of prescriptions issued during the study period in the full CPRD sample



Source Tables: ExposureCohorts-T1; ExposureCohorts-T1_COPD; ExposureCohorts-T1_Asthma

As a subset of the full CPRD sample, the HES-linked sample (of English patients only) included fewer new users of FF/VI (N=1,725; 78.1% on FF/VI 100/25 and 21.9% on FF/VI 200/25) and other ICS/LABA FDC (N=24,280). Amongst the diagnosis groups, the proportions of FF/VI new users who initiated on the lower dose (FF/VI 100/25) was highest among patients with COPD (82.6%) and lower among patients in the asthma and other groups (70.3% and 70.5% respectively). The numbers of patients contributing data

for the full 12-month study period were lower in the HES-linked sample than in the full CPRD sample (excel source tables in ANNEX 1) and consequently the proportions of new users with only one prescription were higher (FF/VI 100/25 20.3%; FF/VI 200/15 28.8%). Exposure characteristics were generally similar in the HES linked sample to those described earlier for the full CPRD sample (excel source tables in ANNEX 1).

10.1.2.1 Concomitant use of other respiratory medications at index date

Among patients in the COPD diagnosis group, SABD and LAMA were the most commonly prescribed concomitant medications at the index date. SABD prescribing was high (>60%) and similar across the exposure cohorts (Table 4). However, concomitant LAMA prescribing was greatest in new users of FF/VI 100/25 (59.7%), followed by new users of FF/VI 200/25 (51.8%) and new users of other ICS/LABA FDC (45.5%). Similar patterns and levels of concomitant prescribing were observed in the COPD groups with and without a history of asthma (Table 4).

In the Asthma diagnosis group, SABD concomitant prescribing was around 50% in the three drug exposure cohorts (Table 4). The second most common concomitant medication was LTRA, with the greatest prescribing in the FF/VI 200/25 exposure cohort (17.9%).

A small proportion of patients in the COPD and Asthma diagnosis groups appear to have been prescribed concomitant LABA and ICS. This prescribing is most likely an artefact of the algorithm used to identify concomitant prescribing and reflects the real-world nature of the data.

Table 4 Concomitant prescribing at new use of FF/VI or other ICS/LABA, by COPD and Asthma diagnosis groups, for patients in the full CPRD sample

Diagnosis group[1]	Concomitant medication[2]	FF/VI 100/25 No. (%)[3]		FF/VI 200/25 No. (%)[3]		Other ICS/LABA FDC No. (%)[3]	
All COPD	Any	1,845	83.67	361	80.58	11,952	76.73
	SABD	1,460	66.21	284	63.39	9,845	63.21
	LAMA	1,317	59.73	232	51.79	7,068	45.38
	LABA/LAMA	21	0.95	<5	<1.11	18	0.12
	LABA	22	1.00	5	1.12	245	1.57
	ICS	33	1.50	10	2.23	378	2.43
	Theophylline	104	4.72	29	6.47	520	3.34
	LTRA	74	3.36	28	6.25	486	3.12
COPD with history of Asthma	Any	846	85.11	206	82.40	5,337	78.84
	SABD	693	69.72	168	67.20	4,588	67.78
	LAMA	575	57.85	120	48.00	2,827	41.76
	LABA/LAMA	7	0.70	0	0.00	7	0.10
	LABA	6	0.60	<5	<2.00	118	1.74
	ICS	23	2.31	6	2.40	254	3.75

Diagnosis group[1]	Concomitant medication[2]	FF/VI 100/25 No. (%)[3]		FF/VI 200/25 No. (%)[3]		Other ICS/LABA FDC No. (%)[3]	
	Theophylline	58	5.84	24	9.60	338	4.99
	LTRA	65	6.54	25	10.00	431	6.37
COPD without a history of Asthma	Any	999	82.49	155	78.28	6,615	75.11
	SABD	767	63.34	116	58.59	5,257	59.69
	LAMA	742	61.27	112	56.57	4,241	48.15
	LABA/LAMA	14	1.16	<5	<2.53	11	0.12
	LABA	16	1.32	<5	<2.53	127	1.44
	ICS	10	0.83	<5	<2.53	124	1.41
	Theophylline	46	3.80	<5	<2.53	182	2.07
	LTRA	9	0.74	<5	<2.53	55	0.62
Asthma	Any	616	58.56	315	62.75	14,761	53.53
	SABD	564	53.61	278	55.38	13,376	48.51
	LAMA	33	3.14	31	6.18	483	1.75
	LABA	6	0.57	<5	<1.00	219	0.79
	ICS	41	3.90	21	4.18	1,546	5.61
	Theophylline	14	1.33	12	2.39	255	0.92
	LTRA	100	9.51	90	17.93	2,382	8.64

1. Concomitant prescribing not evaluated for the Other diagnosis group. 2. Data on roflumilast not presented as less than 0.1% of patients had evidence of concomitant prescribing with roflumilast. 3. Unless otherwise specified
SABD: short acting bronchodilator; LAMA: long-acting muscarinic antagonist; LABA: long-acting beta2-agonist; LTRA: leukotriene receptor antagonists. *Source Tables: Obj 1-T1_COPD; Obj 1-T1_COPD_NoAst; Obj 1-T1_COPD_Ast; Obj 1-T1_Asthma*

In the HES-linked sample, the patterns of common concomitant prescribing were similar to the full CPRD sample with 61.1– 64.3% of new users in the COPD diagnosis group and 46.5 – 52.4% of the Asthma diagnosis group receiving a concomitant SABD. Concomitant prescribing of LAMA (in the COPD diagnosis group) and LTRA (in the Asthma diagnosis group) were also common (excel source tables in ANNEX 1).

10.2 Results of essential analyses

10.2.1 OBJECTIVE 1: Characteristics of new users of FF/VI or other ICS/LABA FDC

10.2.1.1 Patient demographics at baseline

Due to uneven distribution of COPD and Asthma patients among the drug exposure cohorts, all demographic characteristics are presented separately for the COPD, Asthma, and Other diagnosis groups.

Mean age of new users of FF/VI or other ICS/LABA FDC in the COPD diagnosis group ranged from 68.1 to 69.4 years (Table 5). Mean age of new users was marginally higher in the COPD without asthma history diagnosis group (range 69.4 – 70.1 years) compared to the COPD with asthma history group (range 66.8 – 68.5 years) (Table 6). The mean

age of the Asthma diagnosis group varied more widely over the three exposure cohorts, ranging from 47.0 years for other ICS/LABA FDC to 53.1 for FF/VI 200/25 (Table 7). Mean age in the Other diagnosis group ranged from 58.6 to 63.8 years (Table 8).

Females comprised just over half of new users of FF/VI 100/25 (56.0%), FF/VI 200/25 (55.6%) and other ICS/LABA FDC (56.0%) in the COPD diagnosis group with a history of asthma (Table 6). The proportion of females was lower for new users in the COPD diagnosis group who did not have a history of asthma (FF/VI 100/25 45.3%; FF/VI 200/25 35.4%; other ICS/LABA FDC 46.2%). Among patients in the Asthma diagnosis group, the proportion of females was greater than in COPD (FF/VI 100/25 64.7%; FF/VI 200/25 66.5%; other ICS/LABA FDC 61.2%) (Table 7). In the Other diagnosis group, the proportion of females was similar for new users of FF/VI 100/25 (57.7%) and other ICS/LABA FDC (56.1%), but higher among new users of FF/VI 200/25 (65.1%) (Table 8).

The proportion of current smokers was highest in the COPD diagnosis group without a history of asthma (range 39.9-43.4%,Table 6), followed by COPD patients with a history of asthma (range 32.8-35.7%, Table 6), and lowest among patients in the Asthma diagnosis group (range 17.8-24.3%, Table 7). In the Other diagnosis group, the proportion of current smokers was low in new users of FF/VI 200/25 (14.3%) compared with new users of FF/VI 100/25 (36.1%) and new users of FF/VI 200/25 (23.4%, Table 8).

Mean BMI was similar among the three drug exposure cohorts, with the lowest BMI among COPD patients without a history of asthma (range 27.1 – 27.2 kg/m^2), slightly higher among COPD patients with a history of asthma (range 28.3 – 29.2 kg/m^2) and patients in the Other diagnosis group (range 29.0 – 29.8 kg/m^2), and highest among patients in the Asthma diagnosis group (range 29.5 – 31.1 kg/m^2) (Table 5, Table 6, Table 7, Table 8).

The greatest proportion of deprived patients in IMD (Index of Multiple Deprivation) quintile five was observed among new users of FF/VI 200/25 (COPD 31.9%; Asthma 21.6%, Table 5, Table 7). Of the three exposure cohorts, the lowest proportion of deprived patients (IMD quintile five) was observed among initiators of FF/VI 100/25 (COPD 25.6%; Asthma 18.4%). In the Other diagnosis group, IMD quintiles four and five were combined with the lowest proportion of deprived patients amongst new users of FF/VI 200/25 (18.6%, Table 8).

Geographically, more new users of FF/VI and other ICS/LABA FDC were registered at GP practices in London, Wales, and Scotland, with some variation across diagnosis groups and exposure cohorts (Table 5, Table 7, Table 8), possibly reflecting uneven distribution of GP practices across the UK.

Table 5 Demographic characteristics at baseline for COPD diagnosis group, by index medication, for the full CPRD sample

		Patients in COPD diagnosis group (N=16,629)[1]					
		FF/VI 100/25 N=2,205		FF/VI 200/25 N=448		Other ICS/LABA N=15,576	
		No.	(%)[2]	No.	(%)[2]	No.	(%)[2]
Age at index date	mean (SD)	69.35	10.40	68.07	11.11	68.96	11.20
Gender	female	1,105	50.11	209	46.65	7,855	50.43
Smoking status	current smoker	841	38.16	161	35.94	6,131	39.43
	ex-smoker	1,200	54.45	231	51.56	7,659	49.26
	no/never smoker	163	7.40	56	12.50	1,758	11.31
	missing[3]	*1*	*0.05*	*0*	*0.00*	*28*	*0.18*
Body Mass Index (kg/m^2)	mean (SD)	27.90	6.32	28.30	6.93	27.65	6.53
	missing[3]	*86*	*3.90*	*25*	*5.58*	*1,158*	*7.43*
Index of Multiple Deprivation quintile	Q1 (least deprived)	171	7.76	33	7.37	1,894	12.16
	Q2	244	11.07	64	14.29	2,641	16.96
	Q3	707	32.06	110	24.55	3,120	20.03
	Q4	519	23.54	98	21.88	3,588	23.04
	Q5 (most deprived)	564	25.58	143	31.92	4,333	27.82
Region (total number of practices in region contributing to CPRD)[4]	North of England (N=124)[4]	216	9.80	54	12.05	2,359	15.15
	The Midlands (N=140)[4]	73	3.31	13	2.90	1,855	11.91
	London (N=97)	456	20.68	99	22.10	2,689	17.26
	South West Central (N=117)[4]	26	1.18	15	3.35	1,371	8.80
	South East Coast (N=67)	295	13.38	48	10.71	1,513	9.71
	Northern Ireland (N=23)	142	6.44	35	7.81	506	3.25
	Scotland (N=81)	515	23.36	92	20.54	2,370	15.22
	Wales (N=69)	482	21.86	92	20.54	2,913	18.70

1. Patients can qualify for more than one qualifying index medication which is reflected in the higher number of records when summing across the exposure cohorts. 2. Unless otherwise specified. 3. Percentages were calculated separately for those with missing and without missing data. 4. The total number of practices contributing to CPRD was 718. The North of England includes: North East, North West, and Yorkshire & The Humber regions. The Midlands includes: East Midlands, West Midlands and East of England regions. The South West Central includes: South West and South Central regions. *Source Table: Obj 1-T1_COPD*

Table 6 Demographic characteristics at baseline for COPD diagnosis group, with and without a history of asthma, by index medication, for the full CPRD sample

	Patients in the COPD diagnosis group with a history of asthma (N= 7,343)[1]						Patients in the COPD diagnosis group without a history of asthma (N=9,316)[1]					
	FF/VI 100/25 N= 994		FF/VI 200/25 N= 250		Other ICS/LABA FDC N= 6,769		FF/VI 100/25 N= 1,211		FF/VI 200/25 N= 198		Other ICS/LABA FDC N= 8,807	
	No.	(%)[2]	No.	(%)[2]	No.	(%)[2]	No.	(%)[2]	No.	(%)[2]	No.	(%)[2]
Age at index date												
mean (SD)	68.48	10.71	66.78	11.71	68.38	11.70	70.07	10.08	69.70	10.09	69.41	10.78
Gender												
female	556	55.94	139	55.60	3,790	55.99	549	45.33	70	35.35	4,065	46.16
Smoking status												
current smoker	355	35.71	82	32.80	2,322	34.31	486	40.17	79	39.90	3,809	43.38
ex-smoker	530	53.32	124	49.60	3,349	49.49	670	55.37	107	54.04	4,310	49.08
no/never smoker	109	10.97	44	17.60	1,096	16.20	54	4.46	12	6.06	662	7.54
missing[3]	*0*	*0.00*	*0*	*0.00*	*2*	*0.03*	*1*	*0.08*	*0*	*0.00*	*26*	*0.30*
Body Mass Index (kg/m^2)												
mean (SD)	28.71	6.43	29.17	7.02	28.31	6.63	27.23	6.15	27.13	6.66	27.13	6.40
missing[3]	*40*	*4.02*	*8*	*3.20*	*422*	*6.23*	*46*	*3.80*	*17*	*8.59*	*736*	*8.36*
Index of Multiple Deprivation quintile												
Q1 (least deprived)	66	6.64	17	6.80	756	11.17	105	8.67	16	8.08	1,138	12.92
Q2	116	11.67	36	14.40	1,186	17.52	128	10.57	28	14.14	1,455	16.52
Q3	305	30.68	66	26.40	1,411	20.85	402	33.20	44	22.22	1,709	19.41
Q4	214	21.53	49	19.60	1,479	21.85	305	25.19	49	24.75	2,109	23.95
Q5 (most deprived)	293	29.48	82	32.80	1,937	28.62	271	22.38	61	30.81	2,396	27.21

	Patients in the COPD diagnosis group with a history of asthma (N= 7,343)[1]						Patients in the COPD diagnosis group without a history of asthma (N=9,316)[1]					
	FF/VI 100/25 N= 994		FF/VI 200/25 N= 250		Other ICS/LABA FDC N= 6,769		FF/VI 100/25 N= 1,211		FF/VI 200/25 N= 198		Other ICS/LABA FDC N= 8,807	
	No.	(%)[2]	No.	(%)[2]	No.	(%)[2]	No.	(%)[2]	No.	(%)[2]	No.	(%)[2]
Region (total number of practices in region contributing to CPRD)[4]												
North of England (N=124)[4]	107	10.76	28	11.20	998	14.74	109	9.00	29	14.65	361	361
The Midlands (N=140)[4]	42	4.23	10	4.00	801	11.83	31	2.56			361	361
London (N=97)	249	25.05	51	20.40	1,226	18.11	207	17.09	48	24.24	361	361
South West Central (N=117)[4]	6	0.60	9	3.60	589	8.70	20	1.65	6	3.03	361	361
South East Coast (N=67)	124	12.47	25	10.00	541	7.99	171	14.12	23	11.62	361	361
Northern Ireland (N=23)	54	5.43	20	8.00	150	2.22	88	7.27	15	7.58	361	361
Scotland (N=81)	171	17.20	47	18.80	970	14.33	344	28.41	45	22.73	361	361
Wales (N=69)	241	24.25	60	24.00	1,494	22.07	241	19.90	32	16.16	361	361

1. Patients can qualify for more than one qualifying index medication which is reflected in the higher number of records when summing across the exposure cohorts. 2. Unless otherwise specified. 3. Percentages were calculated separately for those with missing and without missing data. 4. The total number of practices contributing to CPRD was 718. The North of England includes: North East, North West, and Yorkshire & The Humber regions. The Midlands includes: East Midlands, West Midlands and East of England regions. The South West Central includes: South West and South Central regions. *Source Tables: Obj 1-T1_COPD_NoAst; Obj 1-T1_COPD_Ast*

Table 7 Demographic characteristics at baseline for Asthma diagnosis group, by index medication, for the full CPRD sample

		Patients in Asthma diagnosis group (N=27,051)[1]					
		FF/VI 100/25 N=1,052		FF/VI 200/25 N=502		Other ICS/LABA FDC N=27,573	
		No.	(%)[2]	No.	(%)[2]	No.	(%)[2]
Age at index date	mean (SD)	49.23	19.48	53.10	17.99	46.99	20.37
Gender	female	681	64.73	334	66.53	16,876	61.20
Smoking status	current smoker	255	24.33	89	17.76	5,461	20.50
	ex-smoker	278	26.53	145	28.94	6,480	24.32
	no/never smoker	515	49.14	267	53.29	14,701	55.18
	missing[3]	*4*	*0.38*	*1*	*0.20*	*931*	*3.38*
Body Mass Index (kg/m^2)	mean (SD)	30.05	7.01	31.08	6.85	29.51	6.84
	missing[3]	*4*	*0.38*	*1*	*0.20*	*931*	*3.38*
Index of Multiple Deprivation quintile	Q1 (least deprived)	110	10.46	54	10.76	4,976	18.05
	Q2	113	10.74	56	11.16	4,946	17.94
	Q3	368	34.98	186	37.05	5,546	20.11
	Q4	268	25.48	95	18.92	5,679	20.60
	Q5 (most deprived)	193	18.35	111	22.11	6,426	23.31
Region (total number of practices in region contributing to CPRD)[4]	North of England (N=124)[4]	113	10.74	50	9.96	2,928	10.62
	The Midlands (N=140)[4]	27	2.57	28	5.58	3,583	12.99
	London (N=97)	255	24.24	73	14.54	5,516	20.01
	South West Central (N=117)[4]	21	2.00	6	1.20	2,093	7.59
	South East Coast (N=67)	89	8.46	51	10.16	3,072	11.14
	Northern Ireland (N=23)	148	14.07	35	6.97	1,051	3.81
	Scotland (N=81)	100	9.51	68	13.55	4,384	15.90
	Wales (N=69)	299	28.42	191	38.05	4,946	17.94

1. Patients can qualify for more than one qualifying index medication which is reflected in the higher number of records when summing across the exposure cohorts. 2. Unless otherwise specified. 3. Percentages were calculated separately for those with missing and without missing data. 4. The total number of practices contributing to CPRD was 718. The North of England includes: North East, North West, and Yorkshire & The Humber regions. The Midlands includes: East Midlands, West Midlands and East of England regions. The South West Central includes: South West and South Central regions. *Source Tables: Obj 1-T1_Asthma*

Table 8 Demographic characteristics at baseline for Other diagnosis group, by index medication, for the full CPRD sample

		Patients in Other diagnosis group (N=5,250)[1]					
		FF/VI 100/25 N=123		FF/VI 200/25 N=43		Other ICS/LABA N=5,461	
		No.	(%)[2]	No.	(%)[2]	No.	(%)[2]
Age at index date	mean (SD)	63.76	17.30	63.19	17.20	58.64	19.62
Gender	female	52	42.28	15	34.88	2,324	43.89
Smoking status	current smoker	43	36.13	6	14.29	1,176	23.25
	ex-smoker	39	32.77	18	42.86	1,561	30.86
	no/never smoker	37	31.09	18	42.86	2,321	45.89
	missing[3]	4	3.25	1	2.33	237	4.48
Body Mass Index (kg/m^2)	mean (SD)	28.96	6.25	29.77	7.87	29.06	6.85
	missing[3]	43	36.13	6	14.29	1,176	23.25
Index of Multiple Deprivation quintile	Q1 and Q2 (least deprived)	25	20.33	26	60.47	2,015	38.05
	Q3	50	40.65	9	20.93	1,179	22.27
	Q4 and Q5 (most deprived)	48	39.02	8	18.60	2,101	39.68
Region (total number of practices in region contributing to CPRD)[4]	North of England (N=124)[4]	5	4.07	6	13.95	513	9.69
	The Midlands (N=140)[4]	6	4.88			684	12.92
	London (N=97)	28	22.76	5	11.63	839	15.85
	South West Central (N=117)[4]	5	4.07	5	11.63	658	12.43
	South East Coast (N=67)	13	10.57	5	11.63	883	16.68
	Northern Ireland (N=23)	19	15.45	8	18.60	419	7.91
	Scotland (N=81)	11	8.94	5	11.63	537	10.14
	Wales (N=69)	36	29.27	9	20.93	762	14.39

1. Patients can qualify for more than one qualifying index medication which is reflected in the higher number of records when summing across the exposure cohorts. 2. Unless otherwise specified. 3. Percentages were calculated separately for those with missing and without missing data. 4. The total number of practices contributing to CPRD was 718. The North of England includes: North East, North West, and Yorkshire & The Humber regions. The Midlands includes: East Midlands, West Midlands and East of England regions. The South West Central includes: South West and South Central regions. *Source Tables: Obj 1-T1_Other*

Overall, the HES-linked sample had a similar age and gender split at baseline to the full CPRD sample and showed similar patterns of current smokers. As observed for the full CPRD sample, the mean BMI in the HES-linked sample was similar across the exposure cohorts with the new users of FF/VI 200/25 in the Asthma diagnosis group having the highest mean. With the exception of practice level deprivation data (where there were fewer deprived patients initiating FF/VI in the HES-linked sample), patient demographics were similar to those observed in the full CPRD sample (excel source tables in ANNEX 1).

10.2.1.2 Clinical disease severity

10.2.1.2.1 COPD disease severity

Amongst those with COPD, the highest rates of moderate exacerbations in the year prior to index date were recorded in the new users of FF/VI 200/25 (1.53 per person year [95% CI 1.42-1.65]), followed by new users of FF/VI 100/25 (1.36 per person year [95% CI 1.31-1.41]) and new users of other ICS/LABAs (1.13 per person year [95% CI 1.12-1.15]) (Table 9). The HES-linked sample allowed us to delineate between moderate and severe exacerbations. Among this subset of patients, the moderate exacerbation rates were similar to the full CPRD sample (FF/VI 100/25: 1.37 per person year, 95% CI 1.30-1.45; FF/VI 200/25: 1.53 per person year, 95%CI 1.37-1.72; other ICS/LABA: 1.18 per person year, 95%CI 1.15-1.20). Rates of severe (i.e. hospitalised) exacerbations in the HES-linked sample were 0.16 per person year (95% CI 0.14-0.19) in new users of FF/VI 100/25, 0.16 per person year (95% CI 0.11-0.23) in new users of FF/VI 200/25 and 0.18 per person year (95% CI 0.17-0.19) in new users of other ICS/LABA FDC (excel source tables in ANNEX 1).

Airflow limitation as measured by FEV_1 percent predicted was similar among the three drug exposure cohorts (Table 9) with 7 – 8% of patients with very severe, Grade 4 (FEV_1<30%) airflow limitation. Breathlessness as measured by MRC dyspnoea score was greater in patients initiating FF/VI (100/25 or 200/25) than COPD patients initiating other ICS/LABA (Table 9).

Table 9 COPD disease severity of patients in the COPD diagnosis group in the full CPRD sample

		FF/VI 100/25 N=2,205		FF/VI 200/25 N=448		Other ICS/LABA FDC N=15,576	
		No.[1]	(%)[1]	No.[1]	(%)[1]	No.[1]	(%)[1]
Moderate COPD exacerbations (recorded in primary care only)	mean (SD)	1.36	1.53	1.53	1.64	1.13	1.40
	median (IQR)	1.00	0 - 2	1.00	0 - 2	1.00	0 - 2
	Rate per person year (95% CI)	1.36	(1.31, 1.41)	1.53	(1.42, 1.65)	1.13	(1.12, 1.15)
	0 events	847	38.41	152	33.93	6,836	43.89
	1 event	554	25.12	120	26.79	4,133	26.53
	2+ events	804	36.46	176	39.29	4,607	29.58
FEV_1 percent predicted at baseline	mean (SD)	55.59	19.47	56.09	18.87	56.79	19.15
	mild, Grade 1 (≥80%)	198	11.03	38	11.05	1,391	11.52
	moderate, Grade 2 (≥50% to <80%)	861	47.97	174	50.58	6,071	50.26
	severe, Grade 3 (≥30% to <50%)	581	32.37	108	31.40	3,750	31.05
	very severe, Grade 4 (<30%)	155	8.64	24	6.98	866	7.17
	missing[2]	*410*	*18.59*	*104*	*23.21*	*3,498*	*22.46*

		FF/VI 100/25 N=2,205		FF/VI 200/25 N=448		Other ICS/LABA FDC N=15,576	
		No.[1]	(%)[1]	No.[1]	(%)[1]	No.[1]	(%)[1]
FEV_1/FVC ratio at baseline	mean (SD)	59.01	18.32	59.42	17.61	60.85	16.00
	<70%	1,286	79.78	237	75.48	7,832	73.36
	≥70%	326	20.22	77	24.52	2,844	26.64
	missing[2]	*593*	*26.89*	*134*	*29.91*	*4,900*	*31.46*
Dyspnoea (MRC Grade)	mean (SD)	2.85	0.98	2.84	1.06	2.72	1.00
	MRC Grade 1	116	6.45	32	9.52	1,017	9.37
	MRC Grade 2	582	32.37	104	30.95	3,929	36.21
	MRC Grade 3	622	34.59	105	31.25	3,430	31.61
	MRC Grade 4	403	22.41	76	22.62	2,055	18.94
	MRC Grade 5	75	4.17	19	5.65	419	3.86
	missing[2]	*407*	*18.46*	*112*	*25.00*	*4,726*	*30.34*

1. Unless otherwise specified. 2. Percentages were calculated separately for those with missing and without missing data. *Source Table: Obj 1-T2*

10.2.1.2.2 Asthma disease severity

Amongst patients in the Asthma diagnosis group, the highest rates of OCS treated exacerbations in the year prior to index date were observed in the new users of FF/VI 200/25 (0.20 per person year [95% CI 0.17-0.25]), followed by new users of FF/VI 100/25 (0.09 per person year [95% CI 0.07-0.11]) and new users of other ICS/LABA FDC (0.08 per person year [95% CI 0.08-0.08]) (Table 10). The HES-linked sample allowed us to delineate between OCS treated and healthcare utilisation defined exacerbations. Among this subset of patients, the OCS treated exacerbation rates were similar to the full CPRD sample (FF/VI 100/25: 0.11 per person year, 95% CI 0.08-0.15; FF/VI 200/25: 0.17 per person year, 95% CI 0.12-0.25; other ICS/LABA: 0.08 per person year, 95% CI 0.08-0.09). Rates of healthcare utilisation exacerbations in the HES-linked sample were 0.01 per person year (95% CI 0.00-0.01) in new users of FF/VI 100/25, 0.01 per person year (95% CI 0.0-0.04) in new users of FF/VI 200/25 and 0.01 per person year (95% CI 0.01-0.01) in new users of other ICS/LABA FDC (excel source tables in ANNEX 1).

Table 10 Asthma exacerbations in the Asthma diagnosis group in the full CPRD sample

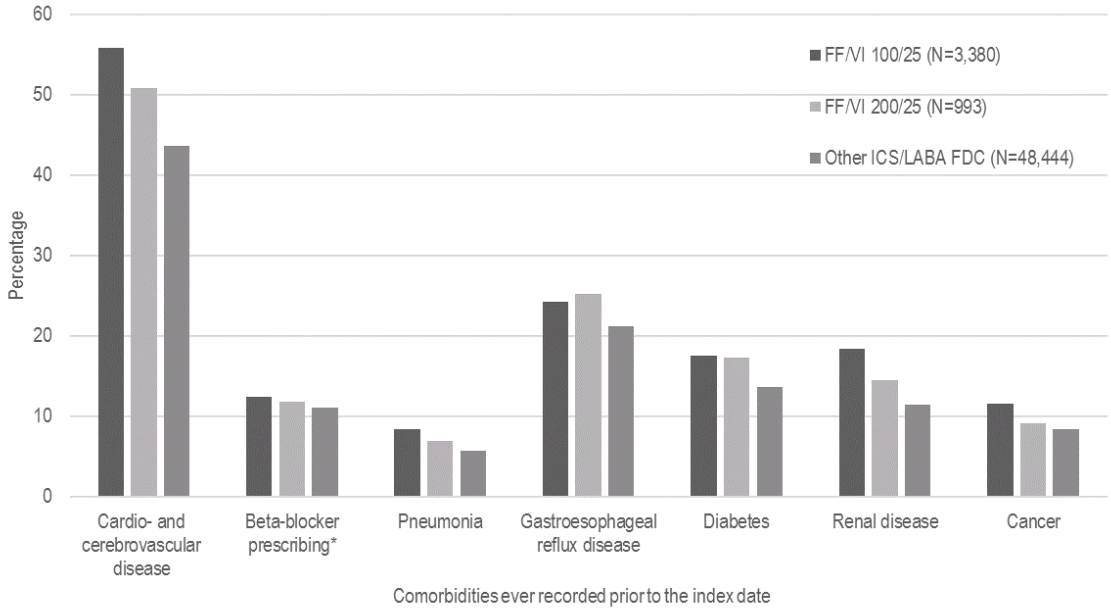
		FF/VI 100/25 N= 1,052		FF/VI 200/25 N= 502		Other ICS/LABA FDC N= 27,573	
		No.[1]	(%)[1]	No.[1]	(%)[1]	No.[1]	(%)[1]
OCS treated asthma exacerbations (recorded in primary care only)	mean (SD)	0.09	0.33	0.20	0.50	0.08	0.30
	median (IQR)	0	0-0	0	0-0	0	0-0
	Rate per person year (95% CI)	0.09	(0.07, 0.11)	0.20	(0.17, 0.25)	0.08	(0.08, 0.08)
	0 events	967	91.92	420	83.67	25,593	92.82
	1 event	76	7.22	64	12.75	1,795	6.51
	2+ events	9	0.86	18	3.59	185	0.67

1. Unless otherwise specified. *Source Table: Obj 1-T2*

10.2.1.3 Comorbidities

Figure 5 presents the frequency of comorbidities for the different index medication groups. The most common comorbidity for all groups was cardio- and cerebrovascular disease followed by gastroesophageal reflux disease. All comorbidities were more common for those with an index prescription for FF/VI vs. the other ICS/LABA FDC. The overall patterns were very similar for the HES-linked sample (excel source tables in ANNEX 1).

Figure 5 Frequency of comorbidities recorded at baseline for patients in the full CPRD sample



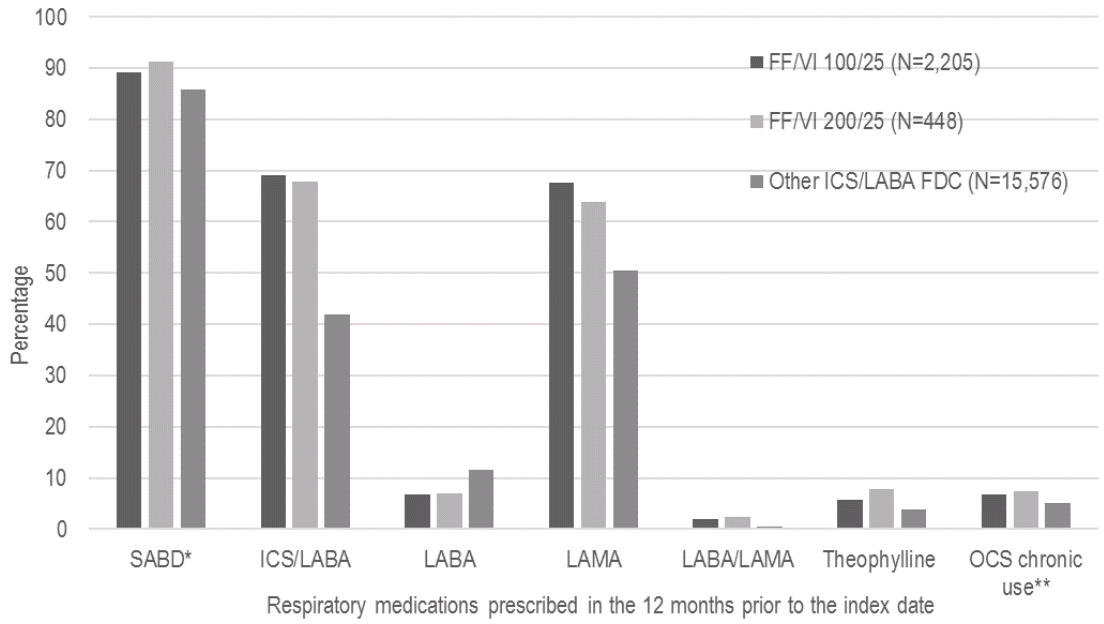
* Beta-blocker prescribing in 12 months prior to the index date. *Source Table: Obj 1-T3*

10.2.1.4 Respiratory medications in the 12 months prior to the index date

Amongst patients in the COPD diagnosis group, the most commonly prescribed respiratory medication in the 12 months prior to their index date were SABD (above 85% for FF/VI 100/25 and other ICS/LABA FDCs having at least one prescription) (Figure 6). Prior use of ICS/LABA was greater among patients initiating FF/VI (69.1% in new users of 100/25 and 67.9% in new users of 200/25) than among patients initiating another ICS/LABA FDC (42.0%). Prescribing of LABA/LAMA was also greater prior to initiation of FF/VI (FF/VI 100/25 2.0%; FF/VI 200/25 2.5%; other ICS/LABA FDC 0.4%). Few COPD patients received prescriptions for theophylline or chronic OCS in the pre-index period.

A large proportion of COPD patients had been prescribed a high-dose ICS (alone or in combination e.g. ICS/LABA) in the 12 months prior to initiating FF/VI 200/25 (37.9% in COPD patients without a history of asthma and 57.2% in COPD patients with a history of asthma). These proportions were similar in patients initiating FF/VI 100/25.

Figure 6 Frequency of medication prescribed to patients in the COPD diagnosis group within the 12 months prior to the index date, for patients in the full CPRD sample

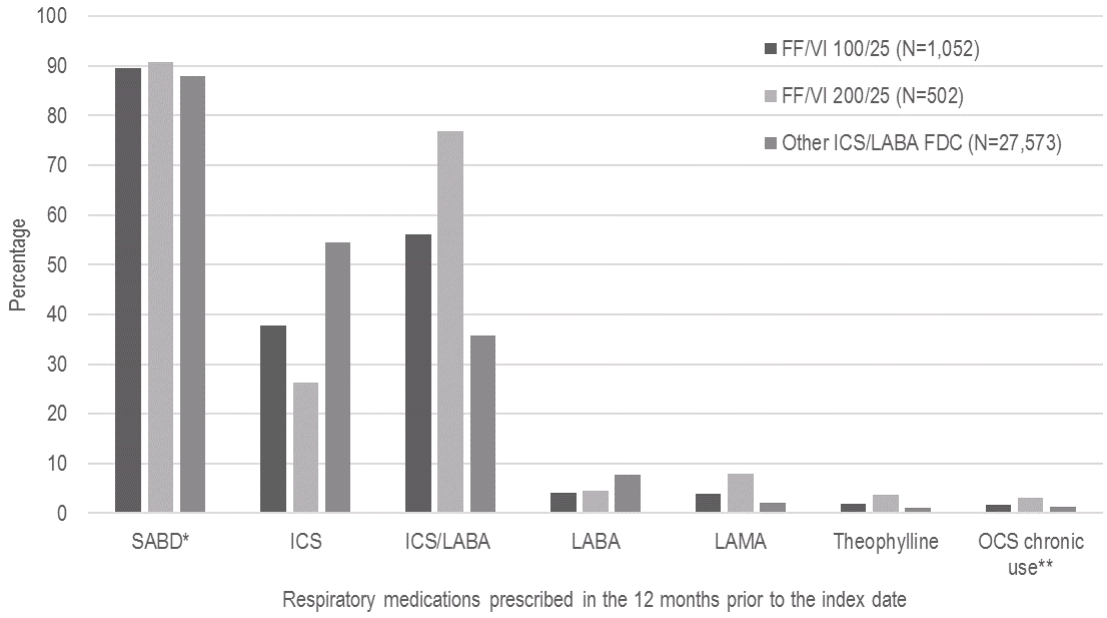


NB. Only FDC of ICS/LABA and LABA/LAMA are considered. * Includes the following COPD 'reliever' medications: SABA, SAMA, fixed combinations of SABA and cromoglycate, and fixed combinations of SABA and SAMA. ** Defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days. *Source Table: Obj 1-T4_COPD*

Patients in the Asthma diagnosis group (Figure 7) also had high levels of SABD prescribing in the 12 months prior to index date (above 85% for new users of FF/VI and other ICS/LABA FDC). Prior prescribing of ICS monotherapy was greater amongst initiators of other ICS/LABA FDC. Conversely, more asthma patients initiating FF/VI than other ICS/LABA FDC were prescribed ICS/LABA in the 12 months prior to

initiation. Few patients were prescribed other asthma maintenance therapies (LABA, LAMA, theophylline and chronic OCS) in the pre-index period.

Figure 7 Frequency of medication prescribed to patients in the Asthma diagnosis group within the 12 months prior to the index date, for patients in the full CPRD sample



NB. Only FDC of ICS/LABA are considered. * Includes the following asthma 'reliever' medications: SABA, SAMA, fixed combinations of SABA and cromoglycate, and fixed combinations of SABA and SAMA ** Defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days. *Source Table: Obj 1-T4_Asthma*

Just under half (43.7%) of new users of FF/VI 100/25 with prior prescriptions for ICS and around one fifth (22.5%) of new users of FF/VI 200/25 with prior prescriptions for ICS had received a high-dose ICS prescription (alone or in combination e.g. ICS/LABA) in the prior 12 months.

In the HES-linked sample the patterns of prior respiratory medication use were very similar, with SABD the most common in the year prior to index date with close to 90% of patients in the COPD and Asthma diagnosis groups having at least one prescription (excel source tables in ANNEX 1).

10.2.2 OBJECTIVE 2: Ascertainment of off-label prescribing

10.2.2.1 Off-label prescribing in children

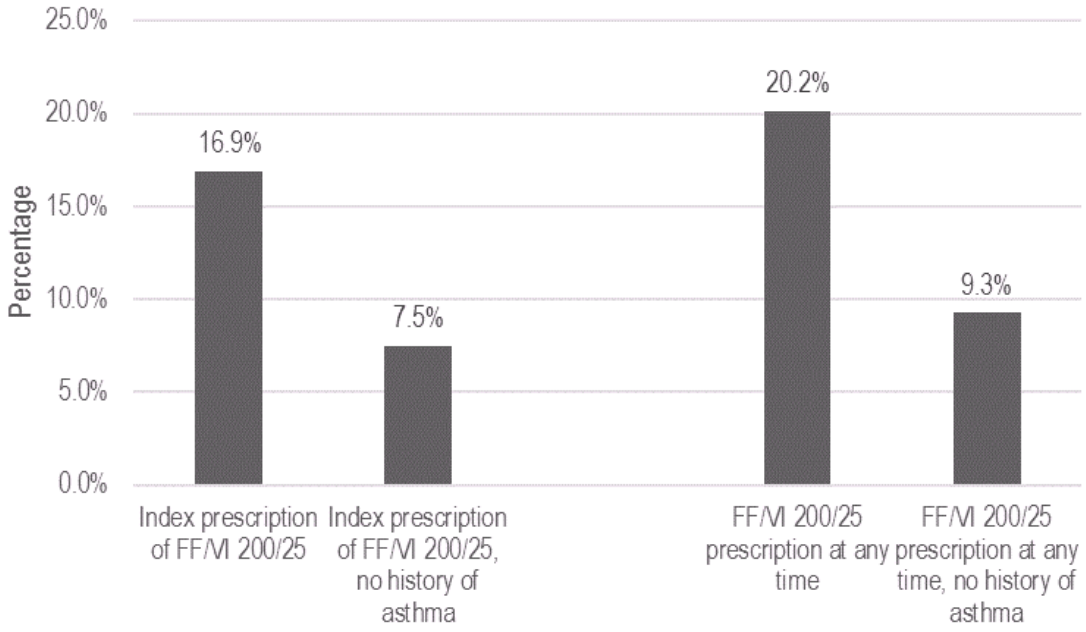
Prescribing of FF/VI (any dose) in children <12 years was very low with less than 5 patients (<0.29%) among the 1,720 initiators of FF/VI in the Asthma and Other diagnosis

groups. The results of this off-label analysis are subject to CPRD 'small cell' rules[1] (See Section 8.6.5) and thus we are unable to report the exact number and proportion of children prescribed FF/VI off-label.

10.2.2.2 Off-label prescribing in COPD

In total, 16.9% (448/2,653) of COPD patients were prescribed FF/VI 200/25 as their first or index FF/VI prescription (Figure 8). As 87 COPD patients who initiated on FF/VI 100/25 eventually escalated their dose to FF/VI 200/25 during the 12-month study period, the proportion of COPD patients with FF/VI 200/25 at any time during follow up is 20.2% (535/2,653). When considering prescriptions of FF/VI 200/25 to COPD patients with a history of asthma as not being off-label, the proportion of off-label prescribing for the first or index prescription was 7.5% (198/2,653), or 9.3% (246/2,653) when considering FF/VI 200/25 prescribing at any time during the 12-month study period.

Figure 8 Off-label prescribing of FF/VI in patients with COPD



Source Table: Obj 2-T1

Of the 535 COPD patients who received a prescription for FF/VI 200/25 at any time during the study period, a fifth (20.4%) had less than half of all their FF/VI prescriptions at the higher dose. The proportion was slightly higher (26.0%) among the 246 COPD patients without a history of asthma who were prescribed FF/VI 200/25 at any time during follow-up (excel source tables in ANNEX 1).

[1] CPRD information governance prohibits release of data which could potentially result in re-identification of patients, defined as 'small cells' of fewer than five and greater than zero.

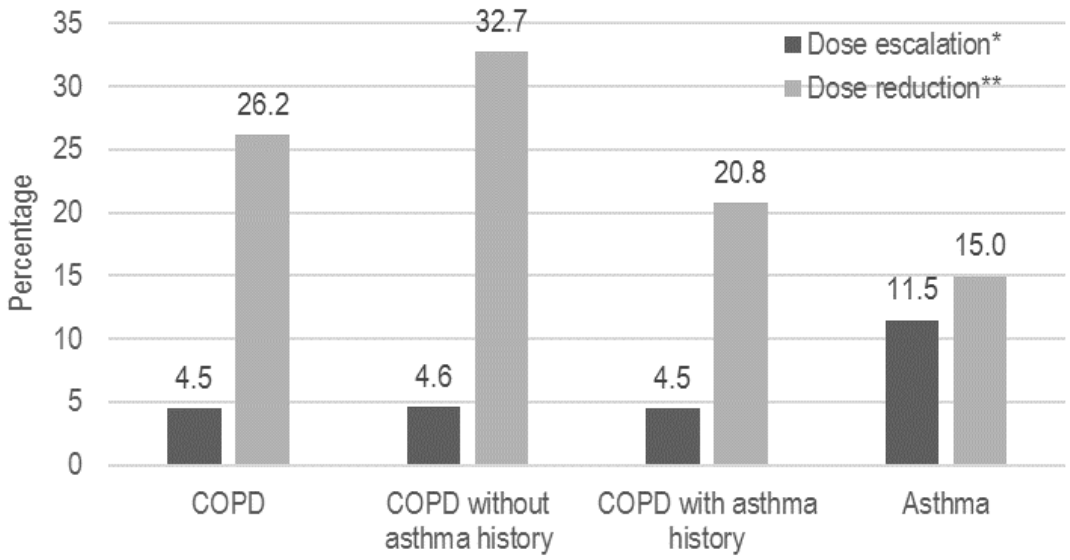
10.2.3 OBJECTIVE 3: Treatment patterns and adherence

10.2.3.1 Dose escalation/reduction of FF/VI

Overall, the majority of new users of FF/VI did not change their dose over the subsequent 12 months (COPD 93.0%; Asthma 89.7%, Other 95.8% excel source tables in ANNEX 1). However, these calculations are based on total numbers of FF/VI initiators and do not consider the numbers actually eligible for a dose change (i.e. patients with at least two prescriptions of FF/VI). Figure 9 shows the proportion of patients escalating from FF/VI 100/25 to FF/VI 200/25 (calculated using the denominator of new users of FF/VI 100/25 with at least two FF/VI prescriptions) and also shows the proportion of patients reducing from FF/VI 200/25 to FF/VI 100/25 (calculated using the denominator of new users of FF/VI 200/25 with at least two FF/VI prescriptions).

Many more patients in the COPD diagnosis group had a dose reduction (26.2%) than a dose increase (4.5%), and this was even more pronounced in the COPD diagnosis group without a history of asthma (32.8% reduced, 4.6% increased). In the Asthma diagnosis group, the proportion of patients escalating and reducing was more similar (11.5% escalated and 15.0% reduced).

Figure 9 Proportion of FF/VI new users escalating or reducing their dose during the 12 month study period, by diagnosis group



* Denominator includes all new users of FF/VI 100/25 with at least two prescriptions of FF/VI (COPD = 1,920, COPD without asthma history = 1,050, COPD with asthma history = 870, Asthma = 853)
** Denominator includes all new users of FF/VI 200/25 with at least two prescriptions of FF/VI (COPD = 378, COPD without asthma history = 171, COPD with asthma history = 207, Asthma = 414)
Source Table: ExposureCohorts-T2; Obj 3-T1

10.2.3.2 Treatment patterns during follow up

Treatment patterns were assessed among 3,312 new users of FF/VI who contributed data for the full 12 months after initiation (i.e. not censored due to death, leaving the GP practice, etc.).

Among COPD patients newly using FF/VI 100/25 or 200/25 without concomitant maintenance therapy the most common treatment pattern was to remain a continuous user in the first 12 months. Around a quarter of COPD patients with no concomitant maintenance therapy augmented with a LAMA (Table 11).

Among COPD patients taking a concomitant LAMA maintenance therapy, continuous use was also quite high with about two-thirds continuing to take both FF/VI and LAMA for the full 12 months (Table 11). Among those who discontinued the combination of FF/VI and LAMA, dropping the LAMA component was the most common pattern observed.

The majority of asthma patients with no concomitant use of a maintenance therapy were continuous users for both doses of FF/VI (FF/VI 100/25: 68.3%, FF/VI 200/25: 69.0%) (Table 11). A slightly higher proportion of FF/VI 100/25 initiators discontinued (had a break of >90 days, 18.4%) compared with FF/VI 200/25 (14.1%), while slightly more FF/VI 200/25 initiators augmented with a LAMA or a LTRA (15.4%) than FF/VI 100/25 initiators (10.8%).

Asthma patients with concomitant use of LTRA were most likely to continuously use both drugs (FF/VI 100/2: 59.7%, FF/VI 200/25: 55.4%) with around 20% discontinuing the concomitant drug only (Table 11). The numbers of asthma patients with concomitant use of LTRA following other treatment patterns were too low see any clear patterns.

Table 11 Treatment patterns of inhaled COPD and asthma maintenance therapies in the first 12 months[1] following initiation of FF/VI in COPD and Asthma diagnosis groups[2]

		FF/V1 100/25		FF/VI 200/25	
		No.	(%)	No.	(%)
COPD diagnosis group					
No concomitant maintenance therapy at initiation	All	(N=674)		(N=172)	
	Continuous user[2]	393	58.31	94	54.65
	Augmenter[3]	149	22.11	43	25.00
	Immediate switcher[4]	30	4.45	9	5.23
	Discontinuer[5]	102	15.13	26	15.12
Concomitant use of LAMA maintenance therapy at initiation	All[6]	(N=1,027)		(N=164)	
	Continuous use of both drugs[2]	686	66.80	108	65.85
	Immediate switcher to another ICS\LABA[4]	14	1.36	<5	<3.05
	Discontinuation of FF/VI only[5]	26	2.53	<5	<3.05
	Discontinuation of concomitant LAMA only[5]	218	21.23	33	20.12
	Discontinuation of both drugs at the same time[5]	83	8.08	17	10.37
COPD with a history of asthma					
No concomitant maintenance therapy at initiation	All	(N=319)		(N=107)	
	Continuous user[2]	194	60.82	54	50.47
	Augmenter[3]	69	21.63	30	28.04
	Immediate switcher[4]	14	4.39	5	4.67
	Discontinuer[5]	42	13.17	18	16.82

		FF/V1 100/25		FF/VI 200/25	
		No.	(%)	No.	(%)
Concomitant use of LAMA maintenance therapy at initiation	All	(N=453)		(N=90)	
	Continuous use of both drugs[2]	311	68.65	55	61.11
	Immediate switcher to another ICS\LABA[4]	7	1.55	<5	<5.56
	Discontinuation of FF/VI only[5]	11	2.43	<5	<5.56
	Discontinuation of concomitant LAMA only[5]	93	20.53	19	21.11
	Discontinuation of both drugs at the same time[5]	31	6.84	10	11.11
COPD without a history of asthma					
No concomitant maintenance therapy at initiation	All	(N=355)		(N=65)	
	Continuous user[2]	199	56.06	40	61.54
	Augmenter[3]	80	22.54	13	20.00
	Immediate switcher[4]	16	4.51	<5	<7.69
	Discontinuer[5]	60	16.90	8	12.31
Concomitant use of LAMA maintenance therapy at initiation	All	(N=574)		(N=74)	
	Continuous use of both drugs[2]	375	65.33	53	71.62
	Immediate switcher to another ICS\LABA[4]	7	1.22	0	0.00
	Discontinuation of FF/VI only[5]	15	2.61	0	0.00
	Discontinuation of concomitant LAMA only[5]	125	21.78	14	18.92
	Discontinuation of both drugs at the same time[5]	52	9.06	7	9.46
Asthma diagnosis group					
No concomitant maintenance therapy at initiation	All	(N=701)		(N=319)	
	Continuous user[2]	479	68.33	220	68.97
	Augmenter[3]	76	10.84	49	15.36
	Immediate switcher[4]	17	2.43	5	1.57
	Discontinuer[5]	129	18.40	45	14.11
Concomitant use of LTRA at initiation	All	(N=67)		(N=74)	
	Continuous use of both drugs[2]	40	59.70	41	55.41
	Immediate switcher to another ICS\LABA[4]	<5	<7.46	<5	<6.76
	Augmenter with LAMA[3]	7	10.45	13	17.57
	Discontinuation of FF/VI only[5]	<5	<7.46	<5	<6.76
	Discontinuation of concomitant LTRA only[5]	14	20.90	15	20.27
	Discontinuation of both drugs at the same time[5]	<5	<7.46	<5	<6.76

1. Treatment patterns only considered in patients with at least 12 months follow up. Treatment patterns could not be determined in a small number of patients who were censored between 31 and 90 days after their last FF/VI prescription hence sample size for each subgroup provided.2. No prescription for another inhaled COPD or asthma maintenance therapy and continuous prescriptions throughout 12-month study period. 3. At least 1 prescription for another inhaled COPD or asthma maintenance therapy during period ≥31 days from index date and ≥31 days before the discontinuation date of the index treatment or the end of the follow-up period following the index date. 4. at least 1 prescription for another inhaled COPD or asthma maintenance therapy 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. 5. discontinuation of the index medication (defined as a break of at least 91 days between prescriptions) or a concomitant inhaled maintenance therapy, prior to 12 months after the index date and does not meet the definitions for continuous use, immediate switching and augmentation above. *Source Table: Obj 3-T2*

10.2.3.3 Adherence measures

The MPR was assessed among 2,874 new users of FF/VI who contributed data for the full 12 months of follow up and who had 2+ prescriptions for the index FF/VI. The median MPR was 0.92 (IQR 0.63-1.05) for the COPD diagnosis group, marginally higher than the 0.82 (IQR 0.58-1.01) for patients in the Asthma diagnosis group and the 0.86 (IQR 0.60-1.00) for patients in the Other diagnosis group (Table 12). Based on an adherence threshold of ≥80%, 62.0% of COPD patients could be considered adherent to FF/VI, with 50.9% of Asthma patients and 61.1% of Other patients adherent during the 12 month study period.

The median PDC for all new users FF/VI contributing a full 12 months of follow up (N=3,312) was 0.74 (IQR 0.41-0.99) for the COPD diagnosis group and 0.66 (IQR 0.25-0.90) for patients in the Asthma diagnosis group. The PDC was lower for patients in the Other diagnosis group (median 0.25; IQR 0.08-0.74). Based on an adherence threshold of ≥80%, 46.8%, 37.7%, and 23.3% for patients in the COPD, Asthma and Other diagnosis groups respectively were adherent. For patients in all diagnosis groups, adherence based on PDC was lower than adherence based on MPR which may in part be due to the fact that only values up to 100% were allowed for the PDC (Table 12).

Table 12 Adherence to FF/VI therapy in the first 12 months following initiation[1]

		All patients initiating FF/VI with 12 months follow up (N=3,312)					
		COPD diagnosis group		Asthma diagnosis group		Other diagnosis group	
		No.[2]	(%)[2]	No.[2]	(%)[2]	No.[2]	(%)[2]
Medication Possession Ratio (MPR)	Total patients[4]	1,815	63	987	34	72	3
	mean (SD)	0.87	0.42	0.84	0.99	0.82	0.33
	Median (IQR)[6]	0.92	0.63 -1.05	0.82	0.58 - 1.01	0.86	0.60 -1.00
	Min, Max	0.09, 10.00		0.08, 30.00		0.12, 2.14	
	<80%	690	38.02	485	49.14	28	38.89
	≥80%	1,125	61.98	502	50.86	44	61.11
Proportion Days Covered (PDC)	Total patients	2,042	61.65	1,167	35.24	103	3.11
	mean (SD)	0.66	0.33	0.59	0.34	0.42	0.35
	Median (IQR)	0.74	0.41 - 0.99	0.66	0.25 - 0.90	0.25	0.08 - 0.74
	Min, Max	0.08, 1.00		0.08, 1.00		0.08, 1.00	
	<80%	1,087	53.23	727	62.30	79	76.70
	≥80%	955	46.77	440	37.70	24	23.30

1. Adherence only measured in patients with at least 12 months follow-up after initiation. 2. Unless otherwise specified. 3. The medication possession ratio was not calculated in 438 patients who only received one prescription for FF/VI. 4. 927 patients were in possession of FF/VI for greater than 365 days (hence some upper IQR and Max values are greater than 1.00). *Source Table: Obj 3-T3*

10.3 Other analyses

In a sensitivity analysis, estimates of off-label prescribing were re-calculated using a different time window for defining the COPD and Asthma diagnosis groups, including

only time prior to and up to the index date. Shortening the time period to identify diagnosis codes resulted in a slight reduction in the number of new users of FF/VI in the COPD diagnosis group (2,542 vs. 2,653) and an increase in the patients assigned to the Asthma (1,566 vs.1,554) and Other diagnosis groups (254 vs. 166).

In this sensitivity analysis, paediatric off-label prescribing was <0.27% and off-label prescribing of FF/VI 200 in patients with COPD was 16.3% at index date, or 19.5% at any time during 12 months of follow up. Excluding patients with a history of asthma from the calculations of off-label prescribing in COPD reduced the estimates to 7.3% at index date and 9.2% at any time.

10.4 Adverse events/adverse reactions

Based on the study objectives, and retrospective design of the study, it was unlikely that adverse events would have been identified during this study. Further, as the research utilised 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 was no potential for reporting of adverse events, pregnancy exposures and other incidents in this study. The following minimum criteria for reporting are missing from the data sources: an identifiable patient.

11 DISCUSSION

11.1 Interpretations of Results

In the 24-month period immediately following availability of FF/VI in the UK, only a small proportion of patients newly initiating an ICS/LABA product were prescribed FF/VI. Nearly eight out ten patients initiating FF/VI did so at the lower dose (100/25), with around two in ten patients prescribed the higher dose of (200/25).

11.1.1 Basic characteristics and clinical disease severity of new users of FF/VI

Characteristics of new users of FF/VI 100/25, FF/VI 200/25 and other ICS/LABA FDC were largely similar within the diagnosis groups in terms of demographics such as age at initiation, BMI, gender, etc. However, within the COPD diagnosis group, there was evidence of channelling of FF/VI to COPD patients with higher clinical severity, whereby new users of FF/VI, especially FF/VI 200/25 users, had greater exacerbation burden and higher dyspnoea scores compared to patients who were prescribed with other ICS/LABA FDC. Interestingly lung function among COPD patients was similar among patients initiating FF/VI 100/25, FF/VI 200/25 and other ICS/LABA FDC. Apart from exacerbation data, data on asthma disease severity were not captured in this study, making it difficult to determine whether channelling of FF/VI to people with more severe asthma is occurring in UK primary care. The other ICS/LABA FDC exposure cohort was created to provide context around the demographic and clinical characteristics of the new users of FF/VI. However, as a comparator, the other ICS/LABA FDC group is useful for

crude benchmarking only, as this group includes a range of products available in the UK, with a mix of low and high doses of ICS.

There were no obvious differences between patients in the full CPRD sample and the subset of patients eligible for linkage with HES (the 'HES-linked' sample). From this we can infer that baseline rates of moderate and severe exacerbations in the full CPRD sample are similar to those observed in the HES-linked sample.

11.1.2 Concomitant prescribing of respiratory medication at initiation of FF/VI

A large majority of COPD patients with new use of FF/VI (either dose) were receiving concomitant prescriptions for LAMA, suggesting that FF/VI is often being prescribed as a component of multiple inhaled triple therapy (MITT). MITT is recommended for the most severe COPD patients such as those in GOLD group D [GOLD 2017], and in fact, patients on FF/VI had greater exacerbation rates prior to initiation than those on other ICS/LABA FDC, suggesting that new users of FF/VI may be a severe COPD group compared to patients initiated on other LABA/ICS FDC.

The greatest concomitant LTRA use in this study was observed among new users of FF/VI 200/25 in the Asthma diagnosis group (nearly one in five), which is consistent with the GINA stepwise treatment paradigm where more severe asthma patients are treated with higher doses of ICS [GINA 2017].

11.1.3 Treatment patterns and adherence with FF/VI

The treatment pattern and adherence data for FF/VI indicate that persistent use of the drug is fairly high. Nearly half of FF/VI 100/25 initiators, and over one-third of FF/VI 200/25 users, received eight or more prescriptions of their index FF/VI during follow up.. Further, the proportion of patients with an MPR greater than 80% corroborated these treatment patterns. Adherence, as measured by the PDC appeared low considering high level of continuous use; however, PDC was capped at 100% and the analyses of treatment patterns allowed gaps of 90 days between prescriptions in continuous users, whereas MPR and PDC did not.

11.1.4 Paediatric off-label prescribing

FF/VI (any dose) is indicated for asthma patients ≥12 years of age. The lack of paediatric approval for a particular drug doesn't necessarily mean a drug is contraindicated or disapproved: it often means that insufficient data are available to grant approval status and that the risks and benefits of have not been examined in a paediatric population [Cuzzolin 2003]. The SmPC is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively.

This study demonstrates that paediatric off-label prescribing of FF/VI is rare in the UK. Less than 0.29% of new users (without COPD) were under 12 years of age at the time of their index prescription. Few studies in the published literature have specifically examined ICS/LABA prescribing in children with asthma. A review of medicines used in hospital and the community identified high levels of paediatric off-label use (11-72%,

[Cuzzolin 2003]), but this study examined all medications in children, not just ICS/LABA. In a Swedish register study, 15% of asthma medication prescriptions in children aged 0-17 were considered to be off-label [Weidinger 2014]. In a study of prescribing in Europe, off-label prescribing of salbutamol in Dutch children <18 months of age was 22.7 per 100 person years, while off-label prescribing of fixed combinations of ß2-mimetics + anticholinergics in Dutch children >6 years of age ranged from 0.5-3.5 per 100 patient years [Sen 2011]. Whilst there are no studies to directly compare off-label use of ICS/LABA in paediatric populations, we can conclude that levels of off-label prescribing of FF/VI in children under 12 years of age are low, and possibly lower than would be expected for other asthma medications not licensed for paediatric use.

11.1.5 Possible off-label prescribing of FF/VI 200/25 in COPD

Our estimates of possible off-label prescribing of FF/VI 200/25 in patients with COPD, used a validated algorithm to identify COPD diagnoses and searched each patients' entire medical history, both prior to and after initiation of FF/VI for evidence of COPD. This strategy reflects the real-world nature of CPRD data where GPs may be aware of a patient's diagnosis at the time of prescribing, but did not record the diagnosis using a code, or where there is a delay in diagnosis whilst the patient is referred to a specialist for additional spirometry.

We chose to conservatively define prescribing of FF/VI 200/25 among all patients with COPD as possibly off-label, regardless of asthma history. Approximately 1 in 6 COPD patients initiated FF/VI on the 200/25 dose, with 1 in 5 COPD patients prescribed the 200/25 dose at any time during the 12-month follow-up. However, as GPs might reasonably prescribe FF/VI 200/25 to asthma patients who may need the higher dose, and who also have a diagnosis of COPD, we therefore additionally calculated a potential lower range of off-label prescribing based on the stricter definition that removed patients with a history of asthma (approximately 50% of COPD patients). Excluding these patients reduced the off-label estimate to approximately 1 in 13 COPD patients at the time of initiation, or 1 in 11 COPD patients with an off-label prescription at any time during the 12 month follow-up.

Of note, not all COPD patients who initiated FF/VI 200/25 continued to receive prescriptions of FF/VI 200/25 for the duration of follow-up. Just over a quarter of COPD patients initiating FF/VI 200/25 (and 27.8% of those without a history of asthma) received only one FF/VI 200/25 prescription. Further, over one quarter (26.2%) of COPD patients who initiated on FF/VI 200/25 and stayed on FF/VI eventually reduced their dose, and this was much higher than the 4.5% of FF/VI 100/25 initiators that increased their dose during the 12-month study period. These data provide additional evidence that off-label prescribing of FF/VI 200/25 was not sustained in all of these COPD patients.

It is possible that GPs might have prescribed FF/VI 200/25 to more severe COPD patients who were uncontrolled on another maintenance therapy, believing that the patient may benefit from a high steroid dose. Indeed, the majority of COPD patients (67.9%) already had experience with a previous ICS/LABA before initiating FF/VI 200/25, and 37.9 % of COPD patients without a history of asthma who received FF/VI 200/25 had received a high-dose ICS prescription (alone or in combination e.g. ICS/LABA) in the 12 months

prior. The proportion of COPD patients with a history of asthma initiated on FF/VI who had previously been prescribed a high-dose ICS was 57.2%. Secondly, concomitant use of a LAMA was observed in the majority of FF/VI 200/25 COPD users (i.e. as part of a MITT therapy), which is recommended for more severe patients [GOLD 2017]. Lastly, COPD patients receiving FF/VI 200/25 experienced a greater exacerbation burden and chronic OCS use prior to initiation, again suggesting a more severe patient type. Although such use would still be considered off-label, these prescribing patterns suggest that clinicians are attempting to control severe COPD disease through pharmacologic measures.

11.2 Limitations

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:

- GSK proposed this study in the UK environment, because of the presence of robust data. The study was conducted within the CPRD, which allowed for a large and representative base sample of asthma and/or COPD primary care patient populations in the United Kingdom, with linkages to secondary care data to obtain more complete data on exacerbations [Herrett 2015].
- 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.
- Demographic and clinical characteristics of COPD patients (e.g. spirometry, dyspnoea) are routinely collected and recorded in UK primary care and thus available for research use in the CPRD. Such information is not typically available in other large linked healthcare databases.

Study limitations:

- Results apply to off-label prescribing 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, for example more severe patients may be channelled towards a new product like FF/VI relative to other ICS/LABA FDC. In this study, we did see evidence of FF/VI initiators in the COPD diagnosis group having a greater dyspnoea and exacerbation burden at baseline than new users of other ICS/LABA FDC. Characteristics of new users of FF/VI who initiate several years after approval in the UK may differ from the characteristics of new users described in this report who initiated within the first two years after UK approval. We recognise this as a limitation of the study and consequence of conducting the study in immediate period following market authorisation.

- Analysis of respiratory diagnoses and other co-morbidities include only diagnosed diseases that are recorded using coded data in EMR by the GP. Patients with COPD and asthma may have been wrongly placed into the Other diagnosis group because their medical record did not contain a coded diagnosis (i.e. the diagnosis was written in free text or in letters from specialists) or because they were in the process of receiving a diagnosis. Additionally, the COPD algorithm may include patients with a COPD diagnoses code but whose diagnosis was not confirmed with spirometry. The sensitivity analysis where only data up until the index date was used to assign patients to diagnosis group, showed that a minority of patients initiated FF/VI or other ICS/LABA FDC prior to a coded diagnosis being recorded in their primary care record.
- There is the potential to misdiagnose COPD as asthma (or vice versa), particularly in patients 40 years of age and older [Tinkelman 2006]. Some patients may indeed have both COPD and active, concurrent asthma. In our definition of "history of asthma", we will likely have included: 1) patients with current asthma (i.e. with Asthma and COPD Overlap Syndrome or ACOS, which occurs in approximately one in three COPD patients [Alshabanat 2015]), 2) patients with childhood, adolescent or early adulthood asthma who have outgrown the disease in later adulthood (i.e. do not have a current diagnosis) and 3) COPD patients initially misdiagnosed as asthma. We could not delineate between these three asthma groups in our analysis. 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.
- GPs are not required to record the indication for every prescription they issue and thus in this study we are unable to state why a GP prescribed FF/VI or other ICS/LABA FDC to their patients. The iterative algorithm used to place patients in the diagnosis groups was designed to identify patients with pure COPD (without a history of asthma), pure asthma (without COPD) and a mixed COPD with history of asthma group. These groupings allowed us to both conservatively (in all COPD patients), and more realistically (in only COPD patients without a history of asthma) estimate off-label prescribing.
- 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. As such, this study is only able to assess off-label prescribing, and cannot make strong inferences about off-label use. Where medicines have been prescribed but not dispensed, we will over estimate off-label use. Similarly, we would overestimate adherence to FF/VI, particularly using the PDC measure that does not require a second prescription (a recognised sign of compliance with the first prescription). On the other hand, information on prescriptions initiated in hospitals or secondary care are not accessible for analysis and if FF/VI or other ICS/LABA were initiated by a specialist with subsequent prescriptions issued by the GP, we may not have accurately ascertained exposure start, leading to an underestimation of FF/VI prescribing, off-label use and adherence
- We also assume that each prescribed medication provides treatment for 30 days. Whilst this might be a reasonable assumption for FF/VI prescribed in primary

care, it may be less reasonable for prescriptions of other respiratory medications. Any bias that this might introduce into ascertainment of concomitant prescribing or into the analysis of treatment patterns would be systematic in nature, impacting on all medications.

12 OTHER INFORMATION

None

13 CONCLUSIONS

This study demonstrates that use of FF/VI is rare in children under 12 years of age in the UK. As such, no risk minimisation measures or amendments to the labelling are required relating to paediatric off-label use. Some COPD patients in the UK have possibly been prescribed FF/VI 200/25 off-label (estimates range from 7.5% of COPD patients with a first prescription at the higher dose and no history of asthma to 20.2% of COPD patients with a higher dose prescription at any time, with or without an asthma history). However, potential off-label prescribing of the higher dose formulation in the UK is tightly linked to historical or concurrent asthma and, in addition, channelled to patients with more severe COPD and prior treatment with high-dose steroids. No amendments to the labelling for FF/VI 200/25 are considered necessary. While the demographic characteristics of patients newly initiating FF/VI and other ICS/LABA FDC were quite similar, there was some evidence of channelling of FF/VI to more severe COPD patients. When exploring treatment patterns, continuous use of FF/VI during the 12-month study period was high and the most common pattern observed amongst both COPD and asthma patients and at both doses of FF/VI.

14 REFERENCES

Agusti A, de Teresa L, De Backer W, et al. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. Eur Respir J. 2014; 43:763–72.

Alshabanat A, Zafari Z, Albanyan O, Dairi M, FitzGerald JM. Asthma and COPD Overlap Syndrome (ACOS): A Systematic Review and Meta Analysis. PLoS One. 2015; 10(9):e0136065.

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

Busse W, Andersen L, Frith L, Harvey C, Jacques L. An Integrated Analysis of Fluticasone Furoate/Vilanterol (FF/VI) Versus FF Safety Data Across Phase II and III Asthma Studies. Pulm Ther (2016) 2:91–114.

Calverley PM, Julie A. Anderson, M.A., Bartolome Celli, M.D., Gary T. Ferguson, M.D., Christine Jenkins, M.D. Paul W. Jones, M.D., Julie C. Yates, B.S., and Jørgen Vestbo, M.D., for the TORCH investigators* Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease N Engl J Med. 2007; 356:775-89.

Cuzzolin L, Zaccaron A, Fanos V. Unlicensed and off-label uses of drugs in paediatrics: a review of the literature. Fundam Clin Pharmacol. 2003 Feb;17(1):125-31.

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

Dransfield MT1, Feldman G2, Korenblat P3, LaForce CF4, Locantore N5, Pistolesi M6, Watkins ML5, Crim C5, Martinez FJ7. Efficacy and safety of once-daily fluticasone furoate/vilanterol (100/25 mcg) versus twice-daily fluticasone propionate/salmeterol (250/50 mcg) in COPD patients. Respir Med. 2014; 108(8):1171-9.

Ducharme FM, Ni Chroinin M, Greenstone I, Lasseson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. Cochrane Database Syst Rev 2010; 14 4):CD005533

Ferguson GT, Anzueto A, Fei R, Emmett A, Knobil K, Kalberg C. Effect of fluticasone propionate/salmeterol (250/50 mcg) or salmeterol (50 mcg) on COPD exacerbations. Respir Med. 2008; 102:1099-1108.

From the *Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma* (GINA) 2017. Available from: http://www.ginasthma.org/.

From the *Global Strategy for the Diagnosis, Management and Prevention of COPD*, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://www.goldcopd.org/.

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

Herrett E, Gallagher AM, Bhaskaran K, Forbes B, Mathur R, van Staa T, Smeeth L. Data resource profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015; 1-10.

Kardos P, Wencker M, Glaab T. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. Am J Resp Crit Care Med. 2007; 175:144-149.

Lötvall J, Bateman ED, Busse WW, O'Byrne PM, Woodcock A, Toler WT, Jacques L, Goldfrad C, Bleecker ER. Comparison of vilanterol, a novel long-acting beta2 agonist, with placebo and a salmeterol reference arm in asthma uncontrolled by inhaled corticosteroids. J Negat Results Biomed. 2014; 13(1):9.

Nissen F, Morales DR, Mullerova H, Smeeth L, Douglas IJ, Quint JK. Validation of asthma recording in the Clinical Practice Research Datalink (CPRD). BMJOpen. 2017 [InPress].

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

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

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010; 340:c332.

Sen EF, Verhamme KM, Neubert A, Hsia Y, Murray M, Felisi M, Giaquinto C, 't Jong GW, Picelli G, Baraldi E, Nicolosi A, Ceci A, Wong IC, Sturkenboom MC; TEDDY European Network of Excellence. Assessment of pediatric asthma drug use in three European countries; a TEDDY study. Eur J Pediatr. 2011; 170(1):81-92.

Sharafkhaneh, Amir, John G. Southard, Mitchell Goldman, Tom Uryniak, Ubaldo J. Martin, Effect of budesonide/formoterol pMDI on COPD exacerbations: A double-blind, randomized study. Respir Med. 2012; 106(2):257-68.

Tinkelman DG, Price DB, Nordyke RJ, Halbert RJ. Misdiagnosis of COPD and asthma in primary care patients 40 years of age and over. J Asthma. 2006; 43(1):75-80.

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

Weidinger P, Nilsson JL, Lindblad U. Medication prescribing for asthma and COPD: a register-based cross-sectional study in Swedish primary care. BMC Fam Pract. 2014 25;15:54.

Woodcock A, Bleecker ER, Lotvall J, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. Chest. 2013;144(4):1222–9.

APPENDICES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	2016N310401_01	14 September 2017	Study Protocol
2	2017N342445_00	13 September 2017	Statistical Analysis Plan
3	2017N342450_00	23 August 2017	Excel Source Tables

ANNEX 2. ADDITIONAL INFORMATION

COPD Diagnosis Codes

medcode	readterm
794	Emphysema
998	Chronic obstructive airways disease
1001	Chronic obstructive pulmonary disease
4084	Airways obstructn irreversible
5710	Chronic obstructive airways disease NOS
9520	Chronic obstructive pulmonary disease monitoring
9876	Severe chronic obstructive pulmonary disease
10802	Moderate chronic obstructive pulmonary disease
10863	Mild chronic obstructive pulmonary disease
10980	Centrilobular emphysema
11287	Chronic obstructive pulmonary disease annual review
12166	Other specified chronic obstructive airways disease
14798	Emphysematous bronchitis
18476	COPD follow-up
18621	Chronic obstructive pulmonary disease follow-up
18792	Chronic obstructive pulmonary disease monitoring admin
23492	Chronic bullous emphysema NOS
26018	Chronic obstructive pulmonary disease monitoring by nurse
26306	Chronic bullous emphysema
28755	Chronic obstructive pulmonary disease monitoring 1st letter
33450	Emphysema NOS
34202	Chronic obstructive pulmonary disease monitoring 2nd letter
34215	Chronic obstructive pulmonary disease monitoring 3rd letter
37247	Chronic obstructive pulmonary disease NOS
37371	Chronic obstructive pulmonary disease monitoring due
38074	Chronic obstructive pulmonary disease monitor phone invite
42258	Chronic obstructive pulmonary disease monitoring verb invite
42313	Health education - chronic obstructive pulmonary disease
44525	Obstructive chronic bronchitis NOS
45770	Chronic obstructive pulmonary disease disturbs sleep
45771	Chronic obstructive pulmonary disease does not disturb sleep
45777	Chronic obstructive pulmonary disease clini management plan
45998	Chronic obstructive pulmonary disease monitoring by doctor
93568	Very severe chronic obstructive pulmonary disease
108586	Chronic obstruct pulmonary disease management plan declined
109774	Telehealth chronic obstructive pulmonary disease monitoring

Asthma Diagnosis Codes

medcode	readterm
78	asthma
81	asthma monitoring
185	acute exacerbation of asthma
232	asthma attack
233	severe asthma attack
1555	bronchial asthma
2290	allergic asthma
3018	mild asthma
3366	severe asthma
3458	occasional asthma
3665	late onset asthma
4442	asthma unspecified
4606	exercise induced asthma
4892	status asthmaticus nos
5267	intrinsic asthma
5627	hay fever with asthma
5798	chronic asthmatic bronchitis
5867	exercise induced asthma
6707	extrinsic asthma with asthma attack
7058	emergency admission, asthma
7146	extrinsic (atopic) asthma
7191	asthma limiting activities
7378	asthma management plan given
7416	asthma disturbing sleep
7731	pollen asthma
8335	asthma attack nos
8355	asthma monitored
9018	number of asthma exacerbations in past year
9552	change in asthma management plan
9663	step up change in asthma management plan
10043	asthma annual review
10274	asthma medication review
10487	asthma - currently active
11370	asthma confirmed
12987	late-onset asthma
13064	asthma severity
13065	moderate asthma
13175	asthma disturbs sleep frequently
13176	asthma follow-up
14777	extrinsic asthma without status asthmaticus
15248	hay fever with asthma

medcode	readterm
16070	asthma nos
16667	asthma control step 2
16785	asthma control step 1
18223	step down change in asthma management plan
18224	asthma control step 3
18323	intrinsic asthma with asthma attack
19167	asthma monitoring by nurse
19519	asthma treatment compliance unsatisfactory
19520	asthma treatment compliance satisfactory
20860	asthma control step 5
20886	asthma control step 4
21232	allergic asthma nec
22752	occupational asthma
24479	emergency asthma admission since last appointment
24506	further asthma - drug prevent.
24884	asthma causes daytime symptoms 1 to 2 times per week
25181	asthma restricts exercise
25791	asthma clinical management plan
26501	asthma never causes daytime symptoms
26503	asthma causes daytime symptoms most days
26504	asthma never restricts exercise
26506	asthma severely restricts exercise
26861	asthma sometimes restricts exercise
27926	extrinsic asthma with status asthmaticus
29325	intrinsic asthma without status asthmaticus
30458	asthma monitoring by doctor
30815	asthma causing night waking
31167	asthma night-time symptoms
31225	asthma causes daytime symptoms 1 to 2 times per month
38143	asthma never disturbs sleep
38144	asthma limits walking up hills or stairs
38145	asthma limits walking on the flat
38146	asthma disturbs sleep weekly
39478	wood asthma
39570	asthma causes night symptoms 1 to 2 times per month
40823	brittle asthma
41017	aspirin induced asthma
41020	absent from work or school due to asthma
42824	asthma daytime symptoms
45073	intrinsic asthma nos
45782	extrinsic asthma nos
46529	attends asthma monitoring
47337	asthma accident and emergency attendance since last visit

medcode	readterm
47684	detergent asthma
58196	intrinsic asthma with status asthmaticus
73522	work aggravated asthma
93353	sequoiosis (red-cedar asthma)
93736	royal college of physicians asthma assessment
98185	asthma control test
99793	patient has a written asthma personal action plan
100107	health education - asthma self management
100397	asthma control questionnaire
100509	under care of asthma specialist nurse
100740	health education - structured asthma discussion
102170	asthma review using roy colleg of physicians three questions
102209	mini asthma quality of life questionnaire
102301	asthma trigger - seasonal
102341	asthma trigger - pollen
102395	asthma causes symptoms most nights
102400	asthma causes night time symptoms 1 to 2 times per week
102449	asthma trigger - respiratory infection
102713	asthma limits activities 1 to 2 times per month
102871	asthma trigger - exercise
102888	asthma limits activities 1 to 2 times per week
102952	asthma trigger - warm air
103318	health education - structured patient focused asthma discuss
103321	asthma trigger - animals
103612	asthma never causes night symptoms
103631	royal college physician asthma assessment 3 question score
103813	asthma trigger - cold air
103944	asthma trigger - airborne dust
103945	asthma trigger - damp
103952	asthma trigger - emotion
103955	asthma trigger - tobacco smoke
103998	asthma limits activities most days
105420	asthma self-management plan review
105674	asthma self-management plan agreed
106805	chronic asthma with fixed airflow obstruction
107167	number days absent from school due to asthma in past 6 month

1 Index

INDEX

2 Index

Excel Source Tables

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

DNG: 2017N342450_00

Study Number: 205052 / PRJ2214

Tables with H. prefix were created with the linked CPRD-HES sample, all other tables were created using the full CPRD-GOLD sample.

ExposureCohorts - T1

Descriptive statistics, overall and by index LABD cohort[1]

		All Patients (N=48,880)[2]							
		FF/VI 100		FF/VI 200		Other ICS/LABA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		3,380	6.40	993	1.88	48,444	91.72	52,817	100.00
Time to censoring in days	mean (SD)	325.09	88.45	328.37	87.29	322.94	91.30	323.18	91.05
	median (IQR)	365	365 - 365	365	365 - 365	365	365 - 365	365	365 - 365
Reason for censoring	death	159	4.70	31	3.12	1,458	3.01	1,648	3.12
	left GP practice	68	2.01	21	2.11	1,626	3.36	1,715	3.25
	last collection from GP practice	605	17.90	177	17.82	8,557	17.66	9,339	17.68
	full 365 days of follow-up	2,548	75.38	764	76.94	36,803	75.97	40,115	75.95
Total prescriptions	mean (SD)	5.47	2.83	4.82	2.96				
	median (IQR)	7	2 - 8	5	2 - 8				
	min	1		1					
	max	20		17					
	1	590	17.46	239	24.07				
	2	264	7.81	113	11.38				
	3	192	5.68	64	6.45				
	4	181	5.36	37	3.73				
	5	168	4.97	51	5.14				
	6	205	6.07	62	6.24				
	7	253	7.49	59	5.94				
	≥8	1,527	45.18	368	37.06				
Patients contributing to multiple index medication groups	gap between index medications								
	N (%)	97	2.87	26	2.62				
	mean (SD) gap in days	90.38	111.63	125.12	139.23				
	median (IQR)	38	19 - 125	80	27 - 159				
	overlap between index medications								
	N (%)	99	2.93	25	2.52				
	mean (SD) overlap in days	32.08	65.07	47.28	80.05				
	median (IQR)	16	8 - 27	23	13 - 30				

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

ExposureCohorts - T1_COPD

Descriptive statistics for COPD diagnosis group, overall and by index LABD cohort[1]

		COPD diagnosis group (N=16,629)[2]							
		FF/VI 100		FF/VI 200		Other ICS/LABA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		2,205	12.10	448	2.46	15,576	85.45	18,229	100.00
Time to censoring in days	mean (SD)	328.17	85.90	323.48	92.34	318.84	94.80	320.08	93.76
	median (IQR)	365	365 - 365	365	365 - 365	365	356 - 365	365	361 - 365
Reason for censoring	death	128	5.80	22	4.91	906	5.82	1,056	5.79
	left GP practice	34	1.54	6	1.34	387	2.48	427	2.34
	last collection from GP practice	338	15.33	83	18.53	2,779	17.84	3,200	17.55
	full 12 months of follow-up	1,705	77.32	337	75.22	11,504	73.86	13,546	74.31
Total prescriptions	mean (SD)	5.84	2.71	4.63	2.96				
	median (IQR)	8	3 - 8	5	1 - 8				
	min	1		1					
	max	20		16					
	1	303	13.74	117	26.12				
	2	149	6.76	50	11.16				
	3	120	5.44	31	6.92				
	4	106	4.81	19	4.24				
	5	102	4.63	28	6.25				
	6	124	5.62	25	5.58				
	7	178	8.07	25	5.58				
	≥8	1,123	50.93	153	34.15				
Patients contributing to multiple index medication groups	gap between index medications								
	N (%)	61	2.77	17	3.79				
	mean (SD) gap in days	81.49	100.67	137.29	136.27				
	median (IQR)	38	18 - 117	81	30 - 188				
	overlap between index medications								
	N (%)	55	2.49	9	2.01				
	mean (SD) overlap in days	35.31	71.10	71.11	116.49				
	median (IQR)	17	8 - 28	23	17 - 27				

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

ExposureCohorts - T1_COPD_NoAst

Descriptive statistics for COPD diagnosis group without a history of asthma, overall and by index LABD cohort[1]

		COPD diagnosis group without a history of Asthma (N=9,316)[2]							
		FF/VI 100		FF/VI 200		Other ICS/LABA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		1,211	11.85	198	1.94	8,807	86.21	10,216	100.00
Time to censoring in days	mean (SD)	327.19	86.65	316.91	101.00	317.17	96.20	318.36	95.26
	median (IQR)	365	365 - 365	365	350 - 365	365	348 - 365	365	354 - 365
Reason for censoring	death	76	6.28	12	6.06	581	6.60	666	6.52
	left GP practice	20	1.65			240	2.73	263	2.57
	last collection from GP practice	183	15.11	46	23.23	1,547	17.57	1,776	17.38
	full 12 months of follow-up	932	76.96	140	70.71	6,439	73.11	7,511	73.52
Total prescriptions	mean (SD)	4.73	1.92	3.78	2.19				
	median (IQR)	6	3 - 6	4	1 - 6				
	min	1		1					
	max	20		16					
	1	172	14.20	55	27.78				
	2	80	6.61	23	11.62				
	3	61	5.04	15	7.58				
	4	58	4.79	8	4.04				
	5	54	4.46	11	5.56				
	≥6	786	5.62	86	6.06				
Patients contributing to multiple index medication groups	gap between index medications								
	N (%)	29	2.39	6	3.03				
	mean (SD) gap in days	103.69	111.89	140.00	141.84				
	median (IQR)	74	20 - 126	85	69 - 159				
	overlap between index medications								
	N (%)	23	1.90	5	2.53				
	mean (SD) overlap in days	33.09	56.97	86.80	155.08				
	median (IQR)	19	9 - 30	23	16 - 23				

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

ExposureCohorts - T1_COPD_Ast

Descriptive statistics for COPD diagnosis group with a history of asthma, overall and by index LABD cohort[1]

		COPD diagnosis group with a history of Asthma (N=7,343)[2]							
		FF/VI 100		FF/VI 200		Other ICS/LABA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		994	12.40	250	3.12	6,769	84.48	8,013	100.00
Time to censoring in days	mean (SD)	329.36	85.01	328.69	84.71	321.00	92.91	322.28	91.76
	median (IQR)	365	365 - 365	365	365 - 365	365	364 - 365	365	365 - 365
Reason for censoring	death	52	5.23	16	6.40	325	4.80	390	4.87
	left GP practice	14	1.41			147	2.17	164	2.05
	last collection from GP practice	155	15.59	37	14.80	1,232	18.20	1,424	17.77
	full 12 months of follow-up	773	77.77	197	78.80	5,065	74.83	6,035	75.32
Time from asthma diagnosis to index date in days[4]	mean (SD)	3,429.70	2,065.82	3,385.64	2,311.14	3,059.07	2,114.99	3,115.24	2,119.15
	median (IQR)	3,612	1,838 - 4,562	3,395	1,645 - 4,432	3,141	1,201 - 4,314	3,211	1,285 - 4,364
Total prescriptions	mean (SD)	7.64	4.53	5.86	4.45				
	median (IQR)	8	3 - 12	5	2-10				
	min	1		0					
	max	16		14					
	1	131	13.18	62	24.80				
	2	69	6.94	27	10.80				
	3	59	5.94	16	6.40				
	4	48	4.83	11	4.40				
	5	48	4.83	17	6.80				
	≥6	639	64.29	117	46.80				
Patients contributing to multiple index medication groups	gap between index medications								
	N (%)	32	3.22	11	4.40				
	mean (SD) gap in days	61.38	86.20	135.82	140.16				
	median (IQR)	24	17.5 - 74	81	30 - 216				
	overlap between index medications								
	N (%)	32	3.22	4	1.60				
	mean (SD) overlap in days	36.91	80.60	51.50	56.51				
	median (IQR)	17	6 - 27.5	27	21.5 - 81.5				

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Time to asthma diagnosis for patients diagnosed with asthma prior to the index date

ExposureCohorts - T1_Asthma

Descriptive statistics for cohort Asthma diagnosis group, overall and by index LABD cohort[1]

		Asthma diagnosis group (N=27,051)[2]							
		FF/VI 100		FF/VI 200		Other ICS/LABA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		1,052	3.61	502	1.72	27,573	94.66	29,127	100.00
Time to censoring in days	mean (SD)	323.45	87.78	333.28	81.95	327.65	86.22	327.60	86.21
	median (IQR)	365	353 - 365	365	365 - 365	365	365 - 365	365	365 - 365
Reason for censoring	death	21	2.00	6	1.20	218	0.79	245	0.84
	left GP practice	29	2.76	13	2.59	1,042	3.78	1,084	3.72
	last collection from GP practice	231	21.96	87	17.33	4,809	17.44	5,127	17.60
	full 12 months of follow-up	771	73.29	396	78.88	21,504	77.99	22,671	77.83
Time from asthma diagnosis to index date in days[4]	N (%)	1,020	96.96	489	97.41	26,379	95.67	27,888	95.75
	mean (SD)	2,973.15	2,146.40	3,197.05	2,241.62	2,585.49	2,120.13	2,610.39	2,125.89
	median (IQR)	2,801	1109 - 4228	3,131	1287 - 4489	2,293	663 - 4034	2,331	687 - 4050
Time from index date to asthma diagnosis in days[5]	N (%)	32	3.04	13	2.59	1,194	4.33	1,239	4.25
	mean (SD)	112.88	110.63	112.69	109.29	96.11	95.49	96.72	96.02
	median (IQR)	59	28 - 214	71	27 - 189	56	25 - 145	56	26 - 147
Total prescriptions	mean (SD)	4.91	2.89	5.08	2.95				
	median (IQR)	5	2 - 8	6	2 - 8				
	min	1		1					
	max	18		17					
	1	238	22.62	108	21.51				
	2	101	9.60	55	10.96				
	3	61	5.80	31	6.18				
	4	66	6.27	14	2.79				
	5	62	5.89	22	4.38				
	6	73	6.94	37	7.37				
	7	73	6.94	31	6.18				
	≥8	378	35.93	204	40.64				
Patients contributing to multiple index medication groups	gap between index medications								
	N (%)	31	2.95	8	1.59				
	mean (SD) gap in days	102.19	125.72	99.38	160.24				
	median (IQR)	33	19 - 237	43	6 - 106				
	overlap between index medications								
	N (%)	40	3.80	15	2.99				
	mean (SD) overlap in days	29.35	59.82	34.93	51.40				
	median (IQR)	16	8.5 - 23.5	22	8 - 30				

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Time to asthma diagnosis for patients diagnosed with asthma prior to the index date

[5] Time to asthma diagnosis for patients diagnosed with asthma post index date

ExposureCohorts - T1_Other

Descriptive statistics for other diagnosis group, overall and by index LABD cohort[1]

		Other diagnosis group (N=5,250)[2]							
		FF/VI 100		FF/VI 200		Other ICS/LABA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		123	2.25	43	0.79	5,295	96.96	5,461	100.00
Time to censoring in days	mean (SD)	284.08	122.97	321.88	92.44	310.43	103.89	309.93	104.33
	median (IQR)	365	189 - 365	365	361 - 365	365	325 - 365	365	322 - 365
Reason for censoring	death	10	8.13	5	11.63	334	6.31	347	6.35
	left GP practice	5	4.07			197	3.72	204	3.74
	last collection from GP practice	36	29.27	7	16.28	969	18.30	1,012	18.53
	full 12 months of follow-up	72	58.54	31	72.09	3,795	71.67	3,898	71.38
Total prescriptions	mean (SD)	4.28	4.14	4.60	4.17				
	median (IQR)	2	1 - 6	2	1 - 8				
	min	1		1					
	max	14		14					
	1	49	39.84	14	32.56				
	2	14	11.38	8	18.60				
	≥3	60	48.78	21	48.84				
Patients contributing to multiple index medication groups	gap between index medications								
	N (%)	5	4.07	1	2.33				
	mean (SD) gap in days	125.60	157.02	124.00	[4]				
	median (IQR)	68	26 - 136	124	124 - 124				
	overlap between index medications								
	N (%)	4	3.25	1	2.33				
	mean (SD) overlap in days	15.00	11.83	18.00	[4]				
	median (IQR)	16	5 - 25	18	18 - 18				

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] No SD as only one patient

ExposureCohorts - T2

FF/VI prescriptions (any dose) among patients initiating FF/VI 100/25 or FF/VI 200/25, by diagnosis group

	COPD		COPD (**without** history of asthma)		COPD (**with** history of asthma)		Asthma (not COPD)		Other (not COPD not asthma)		All	
	N=	2,298	N=	1,221	N=	1,077	N=	1,267	N=	107	N=	3,672
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Initiated FF/VI 100 (≥2 prescriptions any dose)	1,920	83.55	1,050	86	870	80.78	853	67.32	76	71.03	2,849	77.59
Initiated FF/VI 200 (≥2 prescriptions any dose)	378	16.45	171	14	207	19.22	414	32.68	31	28.97	823	22.41

[1] This table is constructed using CPRD-GOLD

Obj 1 - T1

Demographic characteristics at baseline, by index LABD cohort[1]

		All Patients (N=48,880)[2]							
		FF/VI 100 N= 3,380		FF/VI 200 N= 993		Other ICS/LABA N= 48,444		All N= 52,817	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Age (in years) at index date	mean (SD)	62.88	16.87	60.29	16.90	55.33	20.47	55.91	20.29
	≥80 years	472	13.96	107	10.78	4,876	10.07	5,455	10.33
	65-79 years	1,382	40.89	357	35.95	13,891	28.67	15,630	29.59
	45-64 years	1,059	31.33	364	36.66	16,292	33.63	17,715	33.54
	18-44 years	395	11.69	154	15.51	10,470	21.61	11,019	20.86
	0-17 years	72	2.13	11	1.11	2,915	6.02	2,998	5.68
Gender	female	1,857	54.94	571	57.50	27,702	57.18	30,130	57.05
	male	1,523	45.06	422	42.50	20,742	42.82	22,687	42.95
Smoking status	current smoker	1,139	33.79	256	25.83	12,768	27.02	14,163	27.44
	ex-smoker	1,517	45.00	394	39.76	15,700	33.23	17,611	34.12
	no/never smoker	715	21.21	341	34.41	18,780	39.75	19,836	38.43
	missing[4]	*9*	*0.27*	*2*	*0.20*	*1,196*	*2.47*	*1,207*	*2.29*
Body Mass Index (kg/m^2)	mean (SD)	28.54	6.59	29.72	7.06	28.78	6.78	28.79	6.78
	underweight <18.5	109	3.52	28	3.11	1,077	2.73	1,214	2.80
	normal 18.5-24.9	877	28.35	205	22.75	11,067	28.06	12,149	27.97
	overweight 25.0-29.9	996	32.20	281	31.19	12,929	32.78	14,206	32.71
	obese ≥30	1,111	35.92	387	42.95	14,365	36.42	15,863	36.52
	missing[4]	*287*	*8.49*	*92*	*9.26*	*9,006*	*18.59*	*9,385*	*17.77*
Concomitant prescribing at index date	Any	2,514	74.38	685	68.98	28,370	58.56	31,569	59.77
	SABD	2,070	61.24	569	57.30	24,591	50.76	27,230	51.56
	LAMA	1,362	40.30	266	26.79	7,904	16.32	9,532	18.05
	LABA/LAMA	21	0.62	<5	<0.50	19	0.04	41	0.08
	LABA	28	0.83	8	0.81	473	0.98	509	0.96
	ICS	78	2.31	31	3.12	2,008	4.14	2,117	4.01
	Theophylline	119	3.52	41	4.13	783	1.62	943	1.79
	Roflumilast	0	0.00	0	0.00	<5	<0.01	<5	<0.01
	LTRA	177	5.24	118	11.88	2,937	6.06	3,232	6.12
Patient level area based deprivation quintile[5]	Q1 (least deprived)	189	14.03	55	14.51	5,022	20.68	5,266	20.25
	Q2	222	16.48	49	12.93	5,001	20.59	5,272	20.27
	Q3	274	20.34	82	21.64	5,038	20.75	5,394	20.74
	Q4	353	26.21	88	23.22	4,718	19.43	5,159	19.84
	Q5 (most deprived)	309	22.94	105	27.70	4,504	18.55	4,918	18.91
	missing[4]	*2,033*	*60.15*	*614*	*61.83*	*24,161*	*49.87*	*26,808*	*50.76*
Pratice level area based deprivation quintile[5]	Q1 (least deprived)	293	8.67	97	9.77	7,868	16.24	8,258	15.64
	Q2	370	10.95	136	13.70	8,604	17.76	9,110	17.25
	Q3	1,125	33.28	305	30.72	9,845	20.32	11,275	21.35
	Q4	806	23.85	195	19.64	10,458	21.59	11,459	21.70
	Q5 (most deprived)	786	23.25	260	26.18	11,669	24.09	12,715	24.07
Region (total number of practices contributing to CPRD; N= 718)[6]	North of England (N=124)[7]	334	9.88	106	10.67	5,800	11.97	6,240	11.81
	The Midlands (N=140)[8]	106	3.14	45	4.53	6,122	12.64	6,273	11.88
	London (N=97)	739	21.86	177	17.82	9,044	18.67	9,960	18.86
	South West Central (N=117)[9]	52	1.54	26	2.62	4,122	8.51	4,200	7.95
	South East Coast (N=67)	397	11.75	104	10.47	5,468	11.29	5,969	11.30
	Northern Ireland (N=23)	309	9.14	78	7.85	1,976	4.08	2,363	4.47
	Scotland (N=81)	626	18.52	165	16.62	7,291	15.05	8,082	15.30
	Wales (N=69)	817	24.17	292	29.41	8,621	17.80	9,730	18.42

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Percentages were calculated seperately for those with missing and without missing data

[5] Area based deprivation is measured using patient or practice-level Index of Multiple Deprivation (IMD) quintile in CPRD

[6] The total number of practices contributing to CPRD within the region

[7] North of England includes: North East, North West, and Yorkshire & The Humber regions

[8] The Midlands includes: East Midlands, West Midlands and East of England regions

[9] South West Central includes: South West and South Central regions

Obj 1 - T1_COPD

Demographic characteristics at baseline for COPD diagnosis group, by index LABD cohort[1]

		COPD diagnosis group (N=16,629)[2]							
		FF/VI 100 N= 2,205		FF/VI 200 N= 448		Other ICS/LABA N= 15,576		All N= 18,229	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Age (in years) at index date	mean (SD)	69.35	10.40	68.07	11.11	68.96	11.20	68.99	11.11
	≥80 years	386	17.51	68	15.18	2,825	18.14	3,279	17.99
	65-79 years	1,153	52.29	229	51.12	7,574	48.63	8,956	49.13
	45-64 years	633	28.71	143	31.92	4,874	31.29	5,650	30.99
	18-44 years	33	1.50	8	1.79	303	1.95	344	1.89
	0-17 years	0	0.00	0	0.00	0	0.00	0	0.00
Gender	female	1,105	50.11	209	46.65	7,855	50.43	9,169	50.30
	male	1,100	49.89	239	53.35	7,721	49.57	9,060	49.70
Smoking status	current smoker	841	38.16	161	35.94	6,131	39.43	7,133	39.19
	ex-smoker	1,200	54.45	231	51.56	7,659	49.26	9,090	49.95
	no/never smoker	163	7.40	56	12.50	1,758	11.31	1,977	10.86
	missing[4]	*1*	*0.05*	*0*	*0.00*	*28*	*0.18*	*29*	*0.16*
Body Mass Index (kg/m^2)	mean (SD)	27.90	6.32	28.30	6.93	27.65	6.53	27.69	6.51
	underweight <18.5	99	4.67	24	5.67	715	4.96	838	4.94
	normal 18.5-24.9	631	29.78	113	26.71	4,638	32.17	5,382	31.73
	overweight 25.0-29.9	698	32.94	141	33.33	4,570	31.70	5,409	31.89
	obese ≥30	691	32.61	145	34.28	4,495	31.18	5,331	31.43
	missing[4]	*86*	*3.90*	*25*	*5.58*	*1,158*	*7.43*	*1,269*	*6.96*
Concomitant prescribing at index date	Any	1,845	83.67	361	80.58	11,952	76.73	14,158	77.67
	SABD	1,460	66.21	284	63.39	9,845	63.21	11,589	63.57
	LAMA	1,317	59.73	232	51.79	7,068	45.38	8,617	47.27
	LABA/LAMA	21	0.95	<5	<1.11	18	0.12	40	0.22
	LABA	22	1.00	5	1.12	245	1.57	272	1.49
	ICS	33	1.50	10	2.23	378	2.43	421	2.31
	Theophylline	104	4.72	29	6.47	520	3.34	653	3.58
	Roflumilast	0	0.00	0	0.00	<5	<0.03	<5	<0.03
	LTRA	74	3.36	28	6.25	486	3.12	588	3.23
Patient level area based deprivation quintile[5]	Q1 (least deprived)	125	13.89	15	7.89	1,257	16.07	1,397	15.67
	Q2	133	14.78	23	12.11	1,430	18.28	1,586	17.79
	Q3	168	18.67	42	22.11	1,698	21.71	1,908	21.41
	Q4	244	27.11	44	23.16	1,632	20.86	1,920	21.54
	Q5 (most deprived)	230	25.56	66	34.74	1,806	23.09	2,102	23.58
	missing	*1,305*	*59.18*	*258*	*57.59*	*7,753*	*49.78*	*9,316*	*51.11*
Pratice level area based deprivation quintile[5]	Q1 (least deprived)	171	7.76	33	7.37	1,894	12.16	2,098	11.51
	Q2	244	11.07	64	14.29	2,641	16.96	2,949	16.18
	Q3	707	32.06	110	24.55	3,120	20.03	3,937	21.60
	Q4	519	23.54	98	21.88	3,588	23.04	4,205	23.07
	Q5 (most deprived)	564	25.58	143	31.92	4,333	27.82	5,040	27.65
Region (total number of practices contributing to CPRD; N= 718)[6]	North of England (N=124)[7]	216	9.80	54	12.05	2,359	15.15	2,629	14.42
	The Midlands (N=140)[8]	73	3.31	13	2.90	1,855	11.91	1,941	10.65
	London (N=97)	456	20.68	99	22.10	2,689	17.26	3,244	17.80
	South West Central (N=117)[9]	26	1.18	15	3.35	1,371	8.80	1,412	7.75
	South East Coast (N=67)	295	13.38	48	10.71	1,513	9.71	1,856	10.18
	Northern Ireland (N=23)	142	6.44	35	7.81	506	3.25	683	3.75
	Scotland (N=81)	515	23.36	92	20.54	2,370	15.22	2,977	16.33
	Wales (N=69)	482	21.86	92	20.54	2,913	18.70	3,487	19.13

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Percentages were calculated seperately for those with missing and without missing data

[5] Area based deprivation is measured using patient or practice-level Index of Multiple Deprivation (IMD) quintile in CPRD

[6] The total number of practices contributing to CPRD within the region

[7] North of England includes: North East, North West, and Yorkshire & The Humber regions

[8] The Midlands includes: East Midlands, West Midlands and East of England regions

[9] South West Central includes: South West and South Central regions

Obj 1 - T1_COPD_NoAst

Demographic characteristics at baseline for COPD diagnosis group without a history of asthma, by index LABD cohort[1]

		COPD diagnosis group without a history of asthma (N=9,316)[2]							
		FF/VI 100 N= 1,211		FF/VI 200 N= 198		Other ICS/LABA N= 8,807		All N= 10,216	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Age (in years) at index date	mean (SD)	70.07	10.08	69.70	10.09	69.41	10.78	69.50	10.69
	≥80 years	221	18.25	35	17.68	1,615	18.34	1,871	18.31
	65-79 years	637	52.60	104	52.53	4,433	50.33	5,174	50.65
	45-64 years	340	28.08	59	29.80	2,632	29.89	3,030	29.66
	18-44 years	13	1.07			127	1.44	141	1.38
	0-17 years	0	0.00	0	0.00	0	0.00	0	0.00
Gender	female	549	45.33	70	35.35	4,065	46.16	4,684	45.85
	male	662	54.67	128	64.65	4,742	53.84	5,532	54.15
Smoking status	current smoker	486	40.17	79	39.90	3,809	43.38	4,374	42.93
	ex-smoker	670	55.37	107	54.04	4,310	49.08	5,087	49.93
	no/never smoker	54	4.46	12	6.06	662	7.54	728	7.14
	missing[4]	*1*	*0.08*	*0*	*0.00*	*26*	*0.30*	*27*	*0.26*
Body Mass Index (kg/m^2)	mean (SD)	27.23	6.15	27.13	6.66	27.13	6.40	27.14	6.37
	underweight <18.5	72	6.18	14	7.73	496	6.15	582	6.18
	normal 18.5-24.9	374	32.10	56	30.94	2,761	34.21	3,191	33.89
	overweight 25.0-29.9	372	31.93	61	33.70	2,491	30.86	2,924	31.05
	obese ≥30	347	29.79	50	27.62	2,323	28.78	2,720	28.88
	missing[4]	*46*	*3.80*	*17*	*8.59*	*736*	*8.36*	*799*	*7.82*
Concomitant prescribing at index date	Any	999	82.49	155	78.28	6,615	75.11	7,769	76.05
	SABD	767	63.34	116	58.59	5,257	59.69	6,140	60.10
	LAMA	742	61.27	112	56.57	4,241	48.15	5,095	49.87
	LABA/LAMA	14	1.16	<5	<2.53	11	0.12	26	0.25
	LABA	16	1.32	<5	<2.53	127	1.44	144	1.41
	ICS	10	0.83	<5	<2.53	124	1.41	138	1.35
	Theophylline	46	3.80	<5	<2.53	182	2.07	233	2.28
	Roflumilast	0	0.00	0	0.00	0	0.00	0	0.00
	LTRA	9	0.74	<5	<2.53	55	0.62	67	0.66
Patient level area based deprivation quintile[5]	Q1 (least deprived)	67	14.96	6	6.74	719	16.02	792	15.76
	Q2	59	13.17	10	11.24	790	17.60	859	17.09
	Q3	89	19.87	20	22.47	981	21.86	1,090	21.69
	Q4	125	27.90	24	26.97	941	20.97	1,090	21.69
	Q5 (most deprived)	108	24.11	29	32.58	1,057	23.55	1,194	23.76
	missing	*763*	*63.01*	*109*	*55.05*	*4,319*	*49.04*	*5,191*	*50.81*
Pratice level area based deprivation quintile[5]	Q1 (least deprived)	105	8.67	16	8.08	1,138	12.92	1,259	12.32
	Q2	128	10.57	28	14.14	1,455	16.52	1,611	15.77
	Q3	402	33.20	44	22.22	1,709	19.41	2,155	21.09
	Q4	305	25.19	49	24.75	2,109	23.95	2,463	24.11
	Q5 (most deprived)	271	22.38	61	30.81	2,396	27.21	2,728	26.70
Region (total number of practices contributing to CPRD; N= 718)[6]	North of England (N=124)[7]	109	9.00	29	14.65	1,361	15.45	1,496	14.64
	The Midlands (N=140)[8]	31	2.56			1,054	11.97	1,088	10.65
	London (N=97)	207	17.09	48	24.24	1,463	16.61	1,718	16.82
	South West Central (N=117)[9]	20	1.65	6	3.03	782	8.88	808	7.91
	South East Coast (N=67)	171	14.12	23	11.62	972	11.04	1,166	11.41
	Northern Ireland (N=23)	88	7.27	15	7.58	356	4.04	459	4.49
	Scotland (N=81)	344	28.41	45	22.73	1,400	15.90	1,789	17.51
	Wales (N=69)	241	19.90	32	16.16	1,419	16.11	1,692	16.56

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Percentages were calculated seperately for those with missing and without missing data

[5] Area based deprivation is measured using patient or practive-level Index of Multiple Deprivation (IMD) quintile in CPRD

[6] The total number of practices contributing to CPRD within the region

[7] North of England includes: North East, North West, and Yorkshire & The Humber regions

[8] The Midlands includes: East Midlands, West Midlands and East of England regions

[9] South West Central includes: South West and South Central regions

Obj 1 - T1_COPD_Ast

Demographic characteristics at baseline for COPD diagnosis group with a history of asthma, by index LABD cohort[1]

		COPD diagnosis group with a history of asthma (N=7,343)[2]							
		FF/VI 100 N= 994		FF/VI 200 N= 250		Other ICS/LABA N= 6,769		All N= 8,013	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Age (in years) at index date	mean (SD)	68.48	10.71	66.78	11.71	68.38	11.70	68.34	11.58
	≥80 years	165	16.60	33	13.20	1,210	17.88	1,408	17.57
	65-79 years	516	51.91	125	50.00	3,141	46.40	3,782	47.20
	45-64 years	293	29.48	85	34.00	2,242	33.12	2,620	32.70
	18-44 years	20	2.01	7	2.80	176	2.60	203	2.53
	0-17 years	0	0.00	0	0.00	0	0.00	0	0.00
Gender	female	556	55.94	139	55.60	3,790	55.99	4,485	55.97
	male	438	44.06	111	44.40	2,979	44.01	3,528	44.03
Smoking status	current smoker	355	35.71	82	32.80	2,322	34.31	2,759	34.44
	ex-smoker	530	53.32	124	49.60	3,349	49.49	4,003	49.97
	no/never smoker	109	10.97	44	17.60	1,096	16.20	1,249	15.59
	missing[4]	*0*	*0.00*	*0*	*0.00*	*2*	*0.03*	*2*	*0.02*
Body Mass Index (kg/m^2)	mean (SD)	28.71	6.43	29.17	7.02	28.31	6.63	28.39	6.62
	underweight <18.5	27	2.83	10	4.13	219	3.45	256	3.39
	normal 18.5-24.9	257	26.94	57	23.55	1,877	29.57	2,191	29.05
	overweight 25.0-29.9	326	34.17	80	33.06	2,079	32.76	2,485	32.94
	obese ≥30	344	36.06	95	39.26	2,172	34.22	2,611	34.61
	missing[4]	*40*	*4.02*	*8*	*3.20*	*422*	*6.23*	*470*	*5.87*
Concomitant prescribing at index date	Any	846	85.11	206	82.40	5,337	78.84	6,389	79.73
	SABD	693	69.72	168	67.20	4,588	67.78	5,449	68.00
	LAMA	575	57.85	120	48.00	2,827	41.76	3,522	43.95
	LABA/LAMA	7	0.70	0	0.00	7	0.10	14	0.17
	LABA	6	0.60	<5	<2.00	118	1.74	128	1.60
	ICS	23	2.31	6	2.40	254	3.75	283	3.53
	Theophylline	58	5.84	24	9.60	338	4.99	420	5.24
	Roflumilast	0	0.00	0	0.00	<5	<0.07	<5	<0.06
	LTRA	65	6.54	25	10.00	431	6.37	521	6.50
Patient level area based deprivation quintile[5]	Q1 (least deprived)	58	12.83	9	8.91	538	16.13	605	15.56
	Q2	74	16.37	13	12.87	640	19.19	727	18.70
	Q3	79	17.48	22	21.78	717	21.50	818	21.04
	Q4	119	26.33	20	19.80	691	20.72	830	21.35
	Q5 (most deprived)	122	26.99	37	36.63	749	22.46	908	23.35
	missing	*542*	*54.53*	*149*	*59.60*	*3,434*	*50.73*	*4,125*	*51.48*
Pratice level area based deprivation quintile[5]	Q1 (least deprived)	66	6.64	17	6.80	756	11.17	839	10.47
	Q2	116	11.67	36	14.40	1,186	17.52	1,338	16.70
	Q3	305	30.68	66	26.40	1,411	20.85	1,782	22.24
	Q4	214	21.53	49	19.60	1,479	21.85	1,742	21.74
	Q5 (most deprived)	293	29.48	82	32.80	1,937	28.62	2,312	28.85
Region (total number of practices contributing to CPRD; N= 718)[6]	North of England (N=124)[7]	107	10.76	28	11.20	998	14.74	1,133	14.14
	The Midlands (N=140)[8]	42	4.23	10	4.00	801	11.83	853	10.65
	London (N=97)	249	25.05	51	20.40	1,226	18.11	1,526	19.04
	South West Central (N=117)[9]	6	0.60	9	3.60	589	8.70	604	7.54
	South East Coast (N=67)	124	12.47	25	10.00	541	7.99	690	8.61
	Northern Ireland (N=23)	54	5.43	20	8.00	150	2.22	224	2.80
	Scotland (N=81)	171	17.20	47	18.80	970	14.33	1,188	14.83
	Wales (N=69)	241	24.25	60	24.00	1,494	22.07	1,795	22.40

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Percentages were calculated seperately for those with missing and without missing data

[5] Area based deprivation is measured using patient or practive-level Index of Multiple Deprivation (IMD) quintile in CPRD

[6] The total number of practices contributing to CPRD within the region

[7] North of England includes: North East, North West, and Yorkshire & The Humber regions

[8] The Midlands includes: East Midlands, West Midlands and East of England regions

[9] South West Central includes: South West and South Central regions

Obj 1 - T1_Asthma

Demographic characteristics at baseline for Asthma diagnosis group and no history of COPD, by index LABD cohort[1]

		Asthma diagnosis group (N=27,051)[2]							
		FF/VI 100 N= 1,052		FF/VI 200 N= 502		Other ICS/LABA N= 27,573		All N= 29,127	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Age (in years) at index date	mean (SD)	49.23	19.48	53.10	17.99	46.99	20.37	47.18	20.31
	≥80 years	64	6.08	32	6.37	1,306	4.74	1,402	4.81
	65-79 years	187	17.78	112	22.31	4,760	17.26	5,059	17.37
	45-64 years	385	36.60	208	41.43	9,589	34.78	10,182	34.96
	18-44 years	345	32.79	139	27.69	9,193	33.34	9,677	33.22
	0-17 years	71	6.75	11	2.19	2,725	9.88	2,807	9.64
Gender	female	681	64.73	334	66.53	16,876	61.20	17,891	61.42
	male	371	35.27	168	33.47	10,697	38.80	11,236	38.58
Smoking status	current smoker	255	24.33	89	17.76	5,461	20.50	5,805	20.59
	ex-smoker	278	26.53	145	28.94	6,480	24.32	6,903	24.49
	no/never smoker	515	49.14	267	53.29	14,701	55.18	15,483	54.92
	missing[4]	*4*	*0.38*	*1*	*0.20*	*931*	*3.38*	*936*	*3.21*
Body Mass Index (kg/m^2)	mean (SD)	30.05	7.01	31.08	6.85	29.51	6.84	29.57	6.85
	underweight and normal <24.9	227	26.00	88	19.91	5,594	26.73	5,909	26.57
	overweight 25.0-29.9	268	30.70	130	29.41	7,012	33.51	7,410	33.32
	obese ≥30	378	43.30	224	50.68	8,319	39.76	8,921	40.11
	missing[4]	*179*	*17.02*	*60*	*11.95*	*6,648*	*24.11*	*6,887*	*23.64*
Concomitant prescribing at index date	Any	616	58.56	315	62.75	14,761	53.53	15,692	53.87
	SABD	564	53.61	278	55.38	13,376	48.51	14,218	48.81
	LAMA	33	3.14	31	6.18	483	1.75	547	1.88
	LABA/LAMA	0	0.00	0	0.00	0	0.00	0	0.00
	LABA	6	0.57	<5	<1.00	219	0.79	228	0.78
	ICS	41	3.90	21	4.18	1,546	5.61	1,608	5.52
	Theophylline	14	1.33	12	2.39	255	0.92	281	0.96
	Roflumilast	0	0.00	0	0.00	0	0.00	0	0.00
	LTRA	100	9.51	90	17.93	2,382	8.64	2,572	8.83
Patient level area based deprivation quintile[5]	Q1 (least deprived)	59	14.60	37	21.64	3,091	22.55	3,187	22.31
	Q2	79	19.55	22	12.87	2,937	21.42	3,038	21.27
	Q3	91	22.52	35	20.47	2,787	20.33	2,913	20.39
	Q4	101	25.00	40	23.39	2,573	18.77	2,714	19.00
	Q5 (most deprived)	74	18.32	37	21.64	2,322	16.94	2,433	17.03
	missing[4]	*648*	*61.60*	*331*	*65.94*	*13,863*	*50.28*	*14,842*	*50.96*
Pratice level area based deprivation quintile[5]	Q1 (least deprived)	110	10.46	54	10.76	4,976	18.05	5,140	17.65
	Q2	113	10.74	56	11.16	4,946	17.94	5,115	17.56
	Q3	368	34.98	186	37.05	5,546	20.11	6,100	20.94
	Q4	268	25.48	95	18.92	5,679	20.60	6,042	20.74
	Q5 (most deprived)	193	18.35	111	22.11	6,426	23.31	6,730	23.11
Region (total number of practices contributing to CPRD; N= 718)[6]	North of England (N=124)[7]	113	10.74	50	9.96	2,928	10.62	3,091	10.61
	The Midlands (N=140)[8]	27	2.57	28	5.58	3,583	12.99	3,638	12.49
	London (N=97)	255	24.24	73	14.54	5,516	20.01	5,844	20.06
	South West Central (N=117)[9]	21	2.00	6	1.20	2,093	7.59	2,120	7.28
	South East Coast (N=67)	89	8.46	51	10.16	3,072	11.14	3,212	11.03
	Northern Ireland (N=23)	148	14.07	35	6.97	1,051	3.81	1,234	4.24
	Scotland (N=81)	100	9.51	68	13.55	4,384	15.90	4,552	15.63
	Wales (N=69)	299	28.42	191	38.05	4,946	17.94	5,436	18.66

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Percentages were calculated seperately for those with missing and without missing data

[5] Area based deprivation is measured using patient or practice-level Index of Multiple Deprivation (IMD) quintile in CPRD

[6] The total number of practices contributing to CPRD within the region

[7] North of England includes: North East, North West, and Yorkshire & The Humber regions

[8] The Midlands includes: East Midlands, West Midlands and East of England regions

[9] South West Central includes: South West and South Central regions

Obj 1 - T1_Other

Demographic characteristics at baseline for Other diagnosis group, by index LABD cohort[1]

		Other diagnosis group (N=5,250)[2]							
		FF/VI 100 N= 123		FF/VI 200 N= 43		Other ICS/LABA N= 5,295		All N= 5,461	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Age (in years) at index date	mean (SD)	63.76	17.30	63.19	17.20	58.64	19.62	58.79	19.57
	≥80 years	22	17.89	7	16.28	745	14.07	774	14.17
	65-79 years	42	34.15	16	37.21	1,557	29.41	1,615	29.57
	45-64 years	41	33.33	13	30.23	1,829	34.54	1,883	34.48
	0-44 years	18	14.63	7	16.28	1,164	21.98	1,189	21.77
Gender	female	71	57.72	28	65.12	2,971	56.11	3,070	56.22
	male	52	42.28	15	34.88	2,324	43.89	2,391	43.78
Smoking status	current smoker	43	36.13	6	14.29	1,176	23.25	1,225	23.47
	ex-smoker	39	32.77	18	42.86	1,561	30.86	1,618	31.00
	no/never smoker	37	31.09	18	42.86	2,321	45.89	2,376	45.53
	missing[4]	*4*	*3.25*	*1*	*2.33*	*237*	*4.48*	*242*	*4.43*
Body Mass Index (kg/m^2)	mean (SD)	28.96	6.25	29.77	7.87	29.06	6.85	29.06	6.85
	underweight and normal <24.9	29	28.71	8	22.22	1,197	29.23	1,234	29.16
	overweight 25.0-29.9	30	29.70	10	27.78	1,347	32.89	1,387	32.77
	obese ≥30	42	41.58	18	50.00	1,551	37.88	1,611	38.07
	missing[4]	*22*	*17.89*	*7*	*16.28*	*1,200*	*22.66*	*1,229*	*22.51*
Concomitant prescribing at index date	Any	53	43.09	9	20.93	1,657	31.29	1,719	31.48
	SABD	46	37.40	7	16.28	1,370	25.87	1,423	26.06
	LAMA	12	9.76	<5	<11.63	353	6.67	368	6.74
	LABA/LAMA	0	0.00	0	0.00	<5	<0.09	<5	<0.09
	LABA	0	0.00	0	0.00	9	0.17	9	0.16
	ICS	<5	<4.07	0	0.00	84	1.59	88	1.61
	Theophylline	<5	<4.07	0	0.00	8	0.15	9	0.16
	Roflumilast	0	0.00	0	0.00	0	0.00	0	0.00
	LTRA	<5	<4.07	0	0.00	69	1.30	72	1.32
Patient level area based deprivation quintile[5]	Q1 and Q2 (least deprived)	15	34.88	7	38.89	1,308	47.56	1,330	47.31
	Q3	15	34.88	5	27.78	553	20.11	573	20.38
	Q4 and Q5 (most deprived)	13	30.23	6	33.33	889	32.33	908	32.30
	missing[4]	*80*	*65.04*	*25*	*58.14*	*2,545*	*48.06*	*2,650*	*48.53*
Pratice level area based deprivation	Q1 and Q2 (least deprived)	25	20.33	26	60.47	2,015	38.05	2,066	37.83
	Q3	50	40.65	9	20.93	1,179	22.27	1,238	22.67
	Q4 and Q5 (most deprived)	48	39.02	8	18.60	2,101	39.68	2,157	39.50
Region (total number of practices contributing to CPRD; N= 718)[6]	North of England (N=124)[7]	5	4.07	6	13.95	513	9.69	520	9.52
	The Midlands (N=140)[8]	6	4.88			684	12.92	694	12.71
	London (N=97)	28	22.76	5	11.63	839	15.85	872	15.97
	South West Central (N=117)[9]	5	4.07	5	11.63	658	12.43	668	12.23
	South East Coast (N=67)	13	10.57	5	11.63	883	16.68	901	16.50
	Northern Ireland (N=23)	19	15.45	8	18.60	419	7.91	446	8.17
	Scotland (N=81)	11	8.94	5	11.63	537	10.14	553	10.13
	Wales (N=69)	36	29.27	9	20.93	762	14.39	807	14.78

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Percentages were calculated seperately for those with missing and without missing data

[5] Area based deprivation is measured using patient or practice-level Index of Multiple Deprivation (IMD) quintile in CPRD

[6] The total number of practices contributing to CPRD within the region

[7] North of England includes: North East, North West, and Yorkshire & The Humber regions

[8] The Midlands includes: East Midlands, West Midlands and East of England regions

[9] South West Central includes: South West and South Central regions

Obj 1 - T2

COPD, Asthma and other disease burden at baseline and within year prior to index date, by index LABD cohort[1]

		All Patients (N=48,880)[2]							
		FF/VI 100 N= 3,380		FF/VI 200 N= 993		Other ICS/LABA N= 48,444		All N= 52,817	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
COPD		2,205	65.24	448	45.12	15,576	32.15	18,229	34.51
COPD with history of asthma		994	45.08	250	55.80	6,769	43.46	8,013	43.96
COPD **without** history of asthma		1,211	54.92	198	44.20	8,807	56.54	10,216	56.04
Moderate COPD exacerbations (recorded in primary care only)	mean (SD)	1.36	1.53	1.53	1.64	1.13	1.40	1.17	1.42
	median (IQR)	1.00	0 - 2	1.00	0 - 2	1.00	0 - 2	1.00	0 - 2
	Rate per person year (95% CI)	1.36	(1.31, 1.41)	1.53	(1.42, 1.65)	1.13	(1.12, 1.15)	1.17	(1.15, 1.19)
	0 events	847	38.41	152	33.93	6,836	43.89	7,835	42.98
	1 event	554	25.12	120	26.79	4,133	26.53	4,807	26.37
	2+ events	804	36.46	176	39.29	4,607	29.58	5,587	30.65
Moderate and Severe COPD exacerbations (recorded in primary and/or secondary care)	mean (SD)	*Only for CPRD-GOLD cohort of patients eligible for linkage with CPRD-HES*							
	median (IQR)								
	Rate per person year (95% CI)								
	0 events								
	1 event								
	2+ events								
FEV_1 percent predicted at baseline	mean (SD)	55.59	19.47	56.09	18.87	56.79	19.15	56.62	19.19
	mild, Grade 1 (≥80%)	198	11.03	38	11.05	1,391	11.52	1,627	22.98
	moderate, Grade 2 (≥50% to <80%)	861	47.97	174	50.58	6,071	50.26	7,106	47.71
	severe, Grade 3 (≥30% to <50%)	581	32.37	108	31.40	3,750	31.05	4,439	23.85
	very severe, Grade 4 (<30%)	155	8.64	24	6.98	866	7.17	1,045	5.47
	missing[4]	*410*	*18.59*	*104*	*23.21*	*3,498*	*22.46*	*4,012*	22.01
FEV_1/FVC ratio at baseline	mean (SD)	59.01	18.32	59.42	17.61	60.85	16.00	60.58	16.37
	<70%	1,286	79.78	237	75.48	7,832	73.36	9,355	74.23
	≥70%	326	20.22	77	24.52	2,844	26.64	3,247	25.77
	missing[4]	*593*	*26.89*	*134*	*29.91*	*4,900*	*31.46*	*5,627*	30.87
Dyspnoea (MRC Grade)	mean (SD)	2.85	0.98	2.84	1.06	2.72	1.00	2.74	1.00
	MRC Grade 1	116	6.45	32	9.52	1,017	9.37	1165	8.97
	MRC Grade 2	582	32.37	104	30.95	3,929	36.21	4,615	35.54
	MRC Grade 3	622	34.59	105	31.25	3,430	31.61	4,157	32.02
	MRC Grade 4	403	22.41	76	22.62	2,055	18.94	2,534	19.52
	MRC Grade 5	75	4.17	19	5.65	419	3.86	513	3.95
	missing[4]	*407*	*18.46*	*112*	*25.00*	*4,726*	*30.34*	*5,245*	28.77
Asthma with no history of COPD		1,052	31.12	502	50.55	27,573	56.92	29,127	55.15
Moderate Asthma exacerbations (recorded in primary care only)	mean (SD)	0.09	0.33	0.20	0.50	0.08	0.30	0.08	0.31
	median (IQR)	0.00	0 - 0	0.00	0 - 0	0.00	0 - 0	0.00	0 - 0
	Rate per person year (95% CI)	0.09	(0.07, 0.11)	0.20	(0.17, 0.25)	0.08	(0.08, 0.08)	0.05	(0.05, 0.06)
	0 events	967	91.92	420	83.67	25,593	92.82	26,980	92.63
	1 event	76	7.22	64	12.75	1,795	6.51	1,935	6.64
	2+ events	9	0.86	18	3.59	185	0.67	212	0.73
Moderate and Severe Asthma exacerbations (recorded in primary and/or secondary care)	mean (SD)	*Only for CPRD-GOLD cohort of patients eligible for linkage with CPRD-HES*							
	median (IQR)								
	Rate per person year (95% CI)								
	0 events								
	1 event								
	2+ events								
Other (not COPD or Asthma)		123	3.64	43	4.33	5,295	10.93	5,461	10.34

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Percentages were calculated seperately for those with missing and without missing data

Past history of comorbidities recorded in primary care, by index LABD cohort[1]

	All Patients (N=48,880)[2]							
	FF/VI 100 N= 3,380		FF/VI 200 N= 993		Other ICS/LABA N= 48,444		All N= 52,817	
	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Cardio- and cerebrovascular disease (ever before)	1,889	55.89	505	50.86	21,137	43.63	23,531	44.55
Beta-blocker prescribing (in year prior to index date)	422	12.49	117	11.78	5,394	11.13	5,933	11.23
Pneumonia (ever before)	284	8.40	69	6.95	2,786	5.75	3,139	5.94
Gastroesophageal reflux disease (ever before)	818	24.20	250	25.18	10,254	21.17	11,322	21.44
Diabetes (ever before)	592	17.51	172	17.32	6,620	13.67	7,384	13.98
Acute and chronic renal disease (ever before)	620	18.34	144	14.50	5,527	11.41	6,291	11.91
Cancer (ever before)	392	11.60	91	9.16	4,099	8.46	4,582	8.68

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

COPD or asthma medication use in year prior to index date, by index LABD cohort[1]

		All Patients (N=48,880)[2]											
		FF/VI 100 N= 3,380			FF/VI 200 N= 993			Other ICS/LABA N= 48,444			All N= 52,817		
		No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%)of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions
SABD[3]	1+ prescription(s)[4]	2,981	88.20	22,252	889	89.53	6,549	40,420	83.44	230,150	44,290	83.86	258,951
	4+ prescriptions[4]	2,026	59.94		589	59.32		21,966	45.34		24,581	46.54	
ICS	Any ICS	2,669	78.96	18,818	835	84.09	5,978	34,092	70.37	187,238	37,596	71.18	212,034
	ICS (in a single device)	649	19.20	2,742	204	20.54	915	19,436	40.12	78,813	20,289	38.41	82,470
	ICS/LABA (in a single device)	2,135	63.17	16,076	700	70.49	5,063	16,796	34.67	108,425	19,631	37.17	129,564
LABA	Any	2,294	67.87	17,331	740	74.52	5,385	20,286	41.88	129,234	23,320	44.15	151,950
	LABA (in a single device)	196	5.80	1,141	54	5.44	284	4,037	8.33	20,655	4,287	8.12	22,080
	ICS/LABA (in a single device)	2,135	63.17	16,076	700	70.49	5,063	16,796	34.67	108,425	19,631	37.17	129,564
LAMA	Any	1,567	46.36	12,429	338	34.04	2,378	8,733	18.03	60,889	10,638	20.14	75,696
	LAMA (in a single device)	1,545	45.71	12,315	330	33.23	2,340	8,706	17.97	60,735	10,581	20.03	75,390
	LABA/LAMA (in a single device)	46	1.36	114	16	1.61	38	67	0.14	154	129	0.24	306
Theophylline (or derivatives)		146	4.32	1,362	54	5.44	437	946	1.95	8,783	1,146	2.17	10,582
OCS	Chronic use[5]	170	5.03		50	5.04		1,257	2.59		1,477	2.80	

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Includes the following COPD and asthma 'reliever' medications: SABA, SAMA, fixed combinations of SABA and cromoglycate, and fixed combinations of SABA and SAMA

[4] Categories are not mutually exclusive

[5] Defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days

NB: Roflimulast data were investigated but counts were very low (<5) so data are not presented
NB. This analysis does not attempt to identify open combinations of LABD, SABD, or ICS in separate devices.

Obj 1 - T4_COPD

COPD or asthma medication use in year prior to index date, by index LABD cohort, in COPD diagnosis group[1]

		COPD diagnosis group (N=16,629)[2]											
		FF/VI 100 N= 2,205			FF/VI 200 N= 448			Other ICS/LABA N= 15,576			All N= 18,229		
		No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%)of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions
SABD[3]	1+ prescription(s)[4]	1,967	89.21	16,259	409	91.29	3,347	13,376	85.88	100,308	15,752	86.41	119,914
	4+ prescriptions[4]	1,464	66.39		281	62.72		8,974	57.61		10,719	58.80	
ICS	Any ICS	1,682	76.73	13,355	348	77.68	2,683	9,371	60.16	65,374	11,411	62.60	81,412
	ICS (in a single device)	220	9.98	1,076	63	14.06	268	3,316	21.29	16,253	3,599	19.74	17,597
	ICS/LABA (in a single device)	1,524	69.12	12,279	304	67.86	2,415	6,540	41.99	49,121	8,368	45.90	63,815
LABA	Any	1,647	74.69	13,330	329	73.44	2,598	8,049	51.68	59,717	10,025	54.99	75,645
	LABA (in a single device)	150	6.80	944	31	6.92	150	1,803	11.58	10,449	1,984	10.88	11,543
	ICS/LABA (in a single device)	1,524	69.12	12,279	304	67.86	2,415	6,540	41.99	49,121	8,368	45.90	63,815
LAMA	Any	1,511	68.53	12,171	289	64.51	2,110	7,888	50.64	56,611	9,688	53.15	70,892
	LAMA (in a single device)	1,492	67.66	12,064	286	63.84	2,077	7,866	50.50	56,464	9,644	52.90	70,605
	LABA/LAMA (in a single device)	43	1.95	107	11	2.46	33	62	0.40	147	116	0.64	287
Theophylline (or derivatives)		126	5.71	1,204	35	7.81	330	613	3.94	6,249	774	4.25	7,783
OCS	Chronic use[5]	151	6.85		33	7.37		785	5.04		969	5.32	

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Includes the following COPD 'reliever' medications: SABA, SAMA, fixed combinations of SABA and cromoglycate, and fixed combinations of SABA and SAMA

[4] Categories are not mutually exclusive

[5] Defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days

NB: Roflimulast data were investigated but counts were very low (<5) so data are not presented
NB. This analysis does not attempt to identify open combinations of LABD, SABD, or ICS in separate devices.

Obj 1 - T4_Asthma

COPD or asthma medication use in year prior to index date, by index LABD cohort, in Asthma diagnosis group [1]

		Asthma diagnosis group (N=27,051)[2]											
		FF/VI 100 N= 1,052			FF/VI 200 N= 502			Other ICS/LABA N= 27,573			All N= 29,127		
		No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%)of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions
SABD[3]	1+ prescription(s)[4]	941	89.45	5,692	456	90.84	3,110	24,260	87.98	121,260	25,657	88.09	130,062
	4+ prescriptions[4]	533	50.67		298	59.36		12,315	44.66		13,146	45.13	
ICS	Any ICS	927	88.12	5,268	469	93.43	3,228	23,285	84.45	117,325	24,681	84.74	125,821
	ICS (in a single device)	398	37.83	1,573	132	26.29	615	15,002	54.41	59,599	15,532	53.33	61,787
	ICS/LABA (in a single device)	590	56.08	3,695	386	76.89	2,613	9,865	35.78	57,726	10,841	37.22	64,034
LABA	Any	624	59.32	3,897	401	79.88	2,752	11,779	42.72	67,705	12,804	43.96	74,354
	LABA (in a single device)	44	4.18	195	23	4.58	134	2,159	7.83	9,974	2,226	7.64	10,303
	ICS/LABA (in a single device)	590	56.08	3,695	386	76.89	2,613	9,865	35.78	57,726	10,841	37.22	64,034
LAMA	Any	45	4.28	231	45	8.96	256	566	2.05	3,078	656	2.25	3,565
	LAMA (in a single device)	42	3.99	224	40	7.97	251	563	2.04	3,073	645	2.21	3,548
	LABA/LAMA (in a single device)	<5	<0.48	7	5	1.00	5	<5	<0.02	5	11	0.04	17
Theophylline (or derivatives)		19	1.81	157	19	3.78	107	325	1.18	2,502	363	1.25	2,766
OCS	Chronic use[5]	18	1.71		16	3.19		377	1.37		411	1.41	

[1] This table is constructed using CPRD-GOLD

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Includes the following asthma 'reliever' medications: SABA, SAMA, fixed combinations of SABA and cromoglycate, and fixed combinations of SABA and SAMA

[4] Categories are not mutually exclusive

[5] Defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days

NB: Roflimulast data were investigated but counts were very low (<5) so data are not presented
NB. This analysis does not attempt to identify open combinations of LABD, SABD, or ICS in separate devices.

Obj 1 - T5_ICS_COPD_NoAst

Highest dose of ICS containing product prescribed in year prior to index date for COPD diagnosis group in patients with no history of asthma[1]
[Primary analysis]

COPD diagnosis group with no history of asthma (N=4338)2								
Medication	FF/VI 100 N=	824	FF/VI 200 N=	128	Other ICS/LABA N=	3,728	All N=	4,680
	N	(%)	N	(%)	N	(%)	N	(%)
Valid and imputed prescriptions								
High-dose[3]	518	63.02	75	58.59	1,720	46.52	2,313	49.77
Medium-dose[4]	239	29.08	38	29.69	1,482	40.09	1,759	37.85
Low-dose[5]	65	7.91	15	11.72	491	13.28	571	12.29
Unclassifiable	0	0.00	0	0.00	*35*	0.94	*37*	*0.79*
Missing	*2*	*0.24*	*0*	*0.00*				
Valid prescriptions only								
High-dose[3]	384	60.95	54	54.00	1,338	45.43	1,776	48.33
Medium-dose[4]	185	29.37	30	30.00	1,135	38.54	1,350	36.73
Low-dose[5]	61	9.68	16	16.00	468	15.89	545	14.83
Unclassifiable	0	0.00	0	0.00	*787*	*21.14*	*1,009*	*21.58*
Missing	*194*	*23.54*	*28*	*21.88*				

[1] This table is constructed using CPRD-GOLD
[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records
[3] Patient had at least one high dose ICS or ICS combination product prescribed in the 12 months prior to index
[4] Patient had at least one medium dose and zero high dose ICS or ICS combination product prescribed in the 12 months prior to index
[5] Patient had at least one low dose and zero high or medium dose ICS or ICS combination product prescribed in the 12 months prior to index

Obj 1 - T5_ICS_COPD_Asthma

Highest dose of ICS containing product prescribed in year prior to index date for COPD diagnosis groups in patients with a history of asthma[1]
[Primary analysis]

COPD diagnosis group with a history of asthma (N=6191)2								
Medication	FF/VI 100 N=	868	FF/VI 200 N=	220	Other ICS/LABA N=	5,643	All N=	6,731
	N	(%)	N	(%)	N	(%)	N	(%)
Valid and imputed prescriptions								
High-dose[3]	533	61.41	143	65.00	2,660	47.25	3,336	49.66
Medium-dose[4]	279	32.14	63	28.64	2,328	41.35	2,670	39.74
Low-dose[5]	56	6.45	14	6.36	639	11.35	709	10.55
Unclassifiable	0	0.00	0	0.00	*16*	*0.28*	*16*	*0.24*
Missing	*0*	*0.00*	*0*	*0.00*				
Valid prescriptions only								
High-dose[3]	420	60.78	105	61.40	2,186	47.60	2,711	49.71
Medium-dose[4]	217	31.40	51	29.82	1,782	38.81	2,050	37.59
Low-dose[5]	54	7.81	15	8.77	619	13.48	688	12.61
Unclassifiable	0	0.00	0	0.00	5	0.11	5	0.09
Missing	*177*	*20.39*	*49*	*22.27*	*1,051*	*18.62*	*1,277*	*18.97*

[1] This table is constructed using CPRD-GOLD
[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records
[3] Patient had at least one high dose ICS or ICS combination product prescribed in the 12 months prior to index
[4] Patient had at least one medium dose and zero high dose ICS or ICS combination product prescribed in the 12 months prior to index
[5] Patient had at least one low dose and zero high or medium dose ICS or ICS combination product prescribed in the 12 months prior to index

Obj 1 - T5_ICS_Asthma

Highest dose of ICS containing product prescribed in year prior to index date in Asthma diagnosis group[1]
[Primary analysis]

Asthma diagnosis group (N=22,928)2								
Medication	FF/VI 100		FF/VI 200		Other ICS/LABA		All	
	N=	927	N=	469	N=	23,285	N=	24,681
	N	(%)	N	(%)	N	(%)	N	(%)
Valid and imputed prescriptions								
High-dose[3]	208	22.46	205	43.71	4,861	20.89	5,274	21.39
Medium-dose[4]	493	53.24	217	46.27	12,575	54.05	13,285	53.87
Low-dose[5]	225	24.30	47	10.02	5,824	25.03	6,096	24.72
Unclassifiable	0	0.00	0	0.00	5	0.02	5	0.02
Missing	*1*	*0.11*	*0*	*0.00*	*20*	*0.09*	*21*	*0.09*
Valid prescriptions only								
High-dose[3]	178	23.12	174	43.07	4,222	21.88	4,574	22.35
Medium-dose[4]	372	48.31	182	45.05	9,571	49.60	10,125	49.47
Low-dose[5]	220	28.57	48	11.88	5,492	28.46	5,760	28.14
Unclassifiable	0	0.00	0	0.00	10	0.05	10	0.05
Missing	*157*	*16.94*	*65*	*13.86*	*3,990*	*17.14*	*4,212*	*17.07*

[1] This table is constructed using CPRD-GOLD
[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records
[3] Patient had at least one high dose ICS or ICS combination product prescribed in the 12 months prior to index
[4] Patient had at least one medium dose and zero high dose ICS or ICS combination product prescribed in the 12 months prior to index
[5] Patient had at least one low dose and zero high or medium dose ICS or ICS combination product prescribed in the 12 months prior to index

Obj 1 - T6_ICS_COPD_NoAst

Highest dose of ICS containing product prescribed in year prior to index date for COPD diagnosis group with no history of asthma (sensitivity definition, patients diagnosed prior to index only)[1]
[Sensitivity analysis - diagnosis up to and including index date only]

COPD diagnosis group with no history of asthma (N=4186)2								
Medication	FF/VI 100 N= 807		FF/VI 200 N= 122		Other ICS/LABA N= 3,576		All N= 4,505	
	N	(%)	N	(%)	N	(%)	N	(%)
Valid and imputed prescriptions								
High-dose[3]	512	63.60	74	60.66	1,681	47.42	2,267	50.69
Medium-dose[4]	232	28.82	34	27.87	1,409	39.75	1,675	37.46
Low-dose[5]	61	7.58	14	11.48	451	12.72	526	11.76
Unclassifiable	0	0.00	0	0.00	35	0.98	37	0.82
Missing	*2*	*0.25*	*0*	*0.00*				
Valid prescriptions only								
High-dose[3]	379	61.53	54	56.84	1,301	46.25	1,734	49.21
Medium-dose[4]	179	29.06	26	27.37	1,079	38.36	1,284	36.44
Low-dose[5]	58	9.42	15	15.79	429	15.25	502	14.25
Unclassifiable	0	0.00	0	0.00	*767*	*21.48*	*985*	*21.89*
Missing	*191*	*23.67*	*27*	*22.13*				

[1] This table is constructed using CPRD-GOLD
[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records
[3] Patient had at least one high dose ICS or ICS combination product prescribed in the 12 months prior to index
[4] Patient had at least one medium dose and zero high dose ICS or ICS combination product prescribed in the 12 months prior to index
[5] Patient had at least one low dose and zero high or medium dose ICS or ICS combination product prescribed in the 12 months prior to index

Highest dose of ICS containing product prescribed in year prior to index date for COPD patients with a history of asthma (sensitivity definition, patients diagnosed prior to index only)[1]
[Sensitivity analysis - diagnosis up to and including index date only]

Cohort of Patients with COPD with a history of asthma (N=5777)2								
Medication	FF/VI 100 N=	836	FF/VI 200 N=	203	Other ICS/LABA N=	5,202	All N=	6,241
	N	(%)	N	(%)	N	(%)	N	(%)
Valid and imputed prescriptions								
High-dose[3]	535	64.00	141	69.46	2,700	52.00	3,376	54.18
Medium-dose[4]	252	30.14	50	24.63	1,970	37.94	2,272	36.46
Low-dose[5]	49	5.86	12	5.91	521	10.03	582	9.34
Unclassifiable	0	0.00	0	0.00	*11*	*0.21*	*11*	*0.18*
Missing	*0*	*0.00*	*0*	*0.00*				
Valid prescriptions only								
High-dose[3]	403	62.67	97	65.99	2,077	51.15	2,577	53.12
Medium-dose[4]	192	29.86	38	25.85	1,494	36.79	1,724	35.54
Low-dose[5]	48	7.47	12	8.16	489	12.04	549	11.32
Unclassifiable	0	0.00	0	0.00	*1,142*	*21.95*	*1,391*	*22.29*
Missing	*193*	*23.09*	*56*	*27.59*				

[1] This table is constructed using CPRD-GOLD
[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records
[3] Patient had at least one high dose ICS or ICS combination product prescribed in the 12 months prior to index
[4] Patient had at least one medium dose and zero high dose ICS or ICS combination product prescribed in the 12 months prior to index
[5] Patient had at least one low dose and zero high or medium dose ICS or ICS combination product prescribed in the 12 months prior to index

Highest dose of ICS containing product prescribed in year prior to index date for Asthma diagnosis group (sensitivity definition, patients diagnosed prior to index only)[1]
[Sensitivity analysis - diagnosis up to and including index date only]

Asthma diagnosis group (N=22,953)2								
Medication	FF/VI 100		FF/VI 200		Other ICS/LABA		All	
	N=	942	N=	481	N=	23,257	N=	24,680
	N	(%)	N	(%)	N	(%)	N	(%)
Valid and imputed prescriptions								
High-dose[3]	214	22.74	209	43.45	4,915	21.15	5,338	21.64
Medium-dose[4]	501	53.24	223	46.36	12,588	54.17	13,312	53.98
Low-dose[5]	226	24.02	49	10.19	5,732	24.66	6,007	24.36
Unclassifiable	0	0.00	0	0.00	5	0.02	5	0.02
Missing	*1*	*0.11*	*0*	*0.00*	*17*	*0.07*	*18*	*0.07*
Valid prescriptions only								
High-dose[3]	184	23.50	177	42.65	4,269	22.14	4,630	22.61
Medium-dose[4]	378	48.28	188	45.30	9,597	49.77	10,163	49.62
Low-dose[5]	221	28.22	50	12.05	5,406	28.04	5,677	27.72
Unclassifiable	0	0.00	0	0.00	10	0.05	10	0.05
Missing	*159*	*16.88*	*66*	*13.72*	*3,975*	*17.09*	*4,200*	*17.02*

[1] This table is constructed using CPRD-GOLD
[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records
[3] Patient had at least one high dose ICS or ICS combination product prescribed in the 12 months prior to index
[4] Patient had at least one medium dose and zero high dose ICS or ICS combination product prescribed in the 12 months prior to index
[5] Patient had at least one low dose and zero high or medium dose ICS or ICS combination product prescribed in the 12 months prior to index

Obj 1 - RespCodes_PreviousYear

Medcode	Readcode	Read term	Count
2581	H06z000	Chest infection NOS	849
68	H06z011	Chest infection	501
3358	H06z100	Lower resp tract infection	265
76	H05z.00	Upper respiratory infection NOS	260
2637	H05z.11	Upper respiratory tract infection NOS	240
312	H060.00	Acute bronchitis	164
2195	H34..00	Bronchiectasis	150
980	H01..00	Acute sinusitis	125
293	H06z111	Respiratory tract infection	108
6124	H062.00	Acute lower respiratory tract infection	78
138	H03..00	Acute tonsillitis	54
572	H26..00	Pneumonia due to unspecified organism	51
121	H170.11	Hay fever - pollens	51
1446	H312200	Acute exacerbation of chronic obstructive airways disease	48
2157	H27z.11	Flu like illness	42
8025	H0...00	Acute respiratory infections	41
104121	H2B..00	Community acquired pneumonia	40
243	H01..11	Sinusitis	39
6294	H051.00	Acute upper respiratory tract infection	36
5978	H060.11	Acute wheezy bronchitis	34
774	H120.00	Chronic rhinitis	33
2257	H13..00	Chronic sinusitis	26
947	H51z.00	Pleural effusion NOS	26
978	H51..00	Pleurisy	20
142	H040.00	Acute laryngitis	20
175	H17..00	Allergic rhinitis	19
103472	H563200	Pulmonary fibrosis	19
893	H02..00	Acute pharyngitis	17
7884	H3y1.00	Chron obstruct pulmonary dis wth acute exacerbation, unspec	16
3110	H1y1z12	Nasal congestion	15
8317	H58y300	Interstitial lung disease NEC	15
6421	H05z.12	Viral upper respiratory tract infection NOS	14
1257	H041.00	Acute tracheitis	14
6094	H2z..00	Pneumonia or influenza NOS	13
152	H302.00	Wheezy bronchitis	11
4686	H11..00	Nasal polyps	11
1849	H21..00	Lobar (pneumococcal) pneumonia	11
3821	H00..16	Rhinitis - acute	10
5324	H28..00	Atypical pneumonia	8
9483	H1y1z13	Sinus congestion	8
1550	H52..00	Pneumothorax	8
3683	H261.00	Basal pneumonia due to unspecified organism	7
4899	H06z200	Recurrent chest infection	7
20104	H03z.00	Acute tonsillitis NOS	7
14645	H120z00	Chronic rhinitis NOS	7
368	H00..11	Common cold	6
7074	H5yy.11	Respiratory infection NOS	6
9653	H5y1600	Bronchospasm	6
6051	H563100	Diffuse pulmonary fibrosis	6
805	H120100	Chronic catarrhal rhinitis	6
7321	H541z00	Pulmonary oedema NOS	6
148	H30..00	Bronchitis unspecified	6
21113	H0z..00	Acute respiratory infection NOS	6
9639	H260.00	Lobar pneumonia due to unspecified organism	6
2125	H03..12	Tonsillitis	5

Obj 1 - RespCodes_PreviousYear

94486	H593.00	Chronic type 2 respiratory failure	5
104264	H2C..00	Hospital acquired pneumonia	5
101204	H470.11	Aspiration pneumonia	5
886	H25..00	Bronchopneumonia due to unspecified organism	5
1001	H3...00	Chronic obstructive pulmonary disease	5
1468	H17..11	Perennial rhinitis	4
8303	H41..00	Asbestosis	4
1813	H58z.00	Lung disease NOS	4
103637	H35..11	Hypersensitivity pneumonitis	4
10086	H2...00	Pneumonia and influenza	4
20748	H5B0.00	Obstructive sleep apnoea	4
10546	H13..11	Chronic rhinosinusitis	4
1246	H00..12	Coryza - acute	3
10992	H47..11	Aspiration pneumonitis	3
1108	H18..00	Vasomotor rhinitis	3
25249	H59..00	Respiratory failure	3
1019	H061.00	Acute bronchiolitis	3
102492	H510C00	Pleural plaque	3
310	H02..13	Throat infection - pharyngitis	3
4910	H56y100	Interstitial pneumonia	3
21061	H3y0.00	Chronic obstruct pulmonary dis with acute lower resp infectn	3
3859	H57y200	Pulmonary sarcoidosis	3
5733	H....00	Respiratory system diseases	3
103753	H563.13	Idiopathic pulmonary fibrosis	3
3243	H31..00	Chronic bronchitis	3
1142	H044.00	Croup	3
100994	H410.11	Asbestos-induced pleural plaque	2
33664	H01z.00	Acute sinusitis NOS	2
15553	H120200	Chronic hypertrophic rhinitis	2
8318	H260000	Lung consolidation	2
6466	H02..12	Viral sore throat NOS	2
103559	H563300	Usual interstitial pneumonitis	2
1309	H1y1z14	Nasal infection	2
7324	H580.11	Atelectasis	2
3557	H1y0.00	Nasal turbinate hypertrophy	2
37447	H06z112	Acute lower respiratory tract infection	2
4734	H10..12	DNS - deviated nasal septum	2
1838	H170.00	Allergic rhinitis due to pollens	2
1747	H037.00	Recurrent acute tonsillitis	2
7092	H30..12	Recurrent wheezy bronchitis	2
1382	H060w00	Acute viral bronchitis unspecified	2
6014	H02..11	Sore throat NOS	2
9093	H00..15	Pyrexial cold	2
5437	H13z.00	Chronic sinusitis NOS	2
29669	H06..00	Acute bronchitis and bronchiolitis	2
1596	H1y6300	Reinke's oedema of the vocal cords	1
18130	H4y0000	Acute radiation pneumonitis	1
31447	H352100	Pigeon-fanciers' lung	1
1141	H10..00	Deviated nasal septum - acquired	1
9559	H51zz00	Pleural effusion NOS	1
2375	H50..00	Empyema	1
10342	H1y5600	Vocal cord nodule	1
18052	H5y4.00	Disorders of diaphragm	1
556	H27..00	Influenza	1
8975	H120.11	Catarrh unspecified	1
8213	H011.00	Acute frontal sinusitis	1

Obj 1 - RespCodes_PreviousYear

10863	H36..00	Mild chronic obstructive pulmonary disease	1
32727	H33z.11	Hyperreactive airways disease	1
52850	Hyu7000	[X]Pleural effusion in conditions classified elsewhere	1
1576	H231.00	Pneumonia due to mycoplasma pneumoniae	1
5047	H14z000	Chronic tonsil disease NOS	1
26125	H312300	Bronchiolitis obliterans	1
12061	H22y200	Pneumonia - Legionella	1
16134	H171.14	Hay fever - other allergen	1
17173	H135.00	Recurrent sinusitis	1
4061	H031.00	Acute follicular tonsillitis	1
896	H00..14	Nasal catarrh - acute	1
6257	H1y1600	Nasal obstruction	1
12667	H122.00	Chronic nasopharyngitis	1
10802	H37..00	Moderate chronic obstructive pulmonary disease	1
3260	H00..00	Acute nasopharyngitis	1
4868	H024.00	Acute viral pharyngitis	1
29166	H21..11	Chest infection - pneumococcal pneumonia	1
15231	H160.00	Chronic laryngitis	1
4195	H1y1.12	Nasal vestibulitis	1
24848	H585300	Adult respiratory distress syndrome	1
998	H3...11	Chronic obstructive airways disease	1
34251	H23z.00	Pneumonia due to specified organism NOS	1
29172	H5y1200	Stenosis of trachea	1
95938	H171100	Dog allergy	1
28634	H22..00	Other bacterial pneumonia	1
9389	H20..11	Chest infection - viral pneumonia	1
103785	H58y500	Respiratory bronchiolitis associated interstitial lung dis	1
19284	H01y000	Acute pansinusitis	1
46578	H321.00	Panlobular emphysema	1
19400	H26..11	Chest infection - pnemonia due to unspecified organism	1
22214	H1y7313	Subglottic stenosis	1
18081	H51yz00	Other pleural effusion	1
4229	H5C..00	Choking due to airways obstruction	1
794	H32..00	Emphysema	1
15588	H350.00	Farmers' lung	1
558	H584.00	Acute pulmonary oedema unspecified	1
8370	H580.12	Collapse of lung	1
775	H172.00	Allergic rhinitis due to unspecified allergen	1
3798	H172.11	Hay fever - unspecified allergen	1
3162	H171.15	House dust allergy	1

Obj 1 - RespCodes_ClosestIndex

Medcode	Readcode	Reqad term	Count
2581	H06z000	Chest infection NOS	844
68	H06z011	Chest infection	498
76	H05z.00	Upper respiratory infection NOS	256
3358	H06z100	Lower resp tract infection	256
2637	H05z.11	Upper respiratory tract infection NOS	238
312	H060.00	Acute bronchitis	162
2195	H34..00	Bronchiectasis	147
980	H01..00	Acute sinusitis	123
293	H06z111	Respiratory tract infection	108
6124	H062.00	Acute lower respiratory tract infection	77
138	H03..00	Acute tonsillitis	54
121	H170.11	Hay fever - pollens	51
572	H26..00	Pneumonia due to unspecified organism	47
1446	H312200	Acute exacerbation of chronic obstructive airways disease	44
2157	H27z.11	Flu like illness	42
8025	H0...00	Acute respiratory infections	40
104121	H2B..00	Community acquired pneumonia	39
243	H01..11	Sinusitis	37
6294	H051.00	Acute upper respiratory tract infection	36
5978	H060.11	Acute wheezy bronchitis	34
774	H120.00	Chronic rhinitis	32
947	H51z.00	Pleural effusion NOS	26
2257	H13..00	Chronic sinusitis	26
978	H51..00	Pleurisy	20
142	H040.00	Acute laryngitis	20
175	H17..00	Allergic rhinitis	19
103472	H563200	Pulmonary fibrosis	18
893	H02..00	Acute pharyngitis	17
8317	H58y300	Interstitial lung disease NEC	15
7884	H3y1.00	Chron obstruct pulmonary dis wth acute exacerbation, unspec	15
3110	H1y1z12	Nasal congestion	15
1257	H041.00	Acute tracheitis	14
6421	H05z.12	Viral upper respiratory tract infection NOS	14
6094	H2z..00	Pneumonia or influenza NOS	13
4686	H11..00	Nasal polyps	11
152	H302.00	Wheezy bronchitis	11
3821	H00..16	Rhinitis - acute	10
1550	H52..00	Pneumothorax	8
1849	H21..00	Lobar (pneumococcal) pneumonia	8
5324	H28..00	Atypical pneumonia	8
20104	H03z.00	Acute tonsillitis NOS	7
14645	H120z00	Chronic rhinitis NOS	7
4899	H06z200	Recurrent chest infection	7
3683	H261.00	Basal pneumonia due to unspecified organism	7
9483	H1y1z13	Sinus congestion	7
805	H120100	Chronic catarrhal rhinitis	6
7074	H5yy.11	Respiratory infection NOS	6
368	H00..11	Common cold	6
6051	H563100	Diffuse pulmonary fibrosis	6
9639	H260.00	Lobar pneumonia due to unspecified organism	6
148	H30..00	Bronchitis unspecified	6
21113	H0z..00	Acute respiratory infection NOS	6
9653	H5y1600	Bronchospasm	5
1001	H3...00	Chronic obstructive pulmonary disease	5
7321	H541z00	Pulmonary oedema NOS	5

Obj 1 - RespCodes_ClosestIndex

886	H25..00	Bronchopneumonia due to unspecified organism	5
94486	H593.00	Chronic type 2 respiratory failure	5
104264	H2C..00	Hospital acquired pneumonia	5
2125	H03..12	Tonsillitis	5
101204	H470.11	Aspiration pneumonia	5
8303	H41..00	Asbestosis	4
1468	H17..11	Perennial rhinitis	4
10546	H13..11	Chronic rhinosinusitis	4
10086	H2...00	Pneumonia and influenza	4
103637	H35..11	Hypersensitivity pneumonitis	4
20748	H5B0.00	Obstructive sleep apnoea	3
310	H02..13	Throat infection - pharyngitis	3
1142	H044.00	Croup	3
3243	H31..00	Chronic bronchitis	3
1813	H58z.00	Lung disease NOS	3
103753	H563.13	Idiopathic pulmonary fibrosis	3
1246	H00..12	Coryza - acute	3
4910	H56y100	Interstitial pneumonia	3
21061	H3y0.00	Chronic obstruct pulmonary dis with acute lower resp infectn	3
3859	H57y200	Pulmonary sarcoidosis	3
1019	H061.00	Acute bronchiolitis	3
1108	H18..00	Vasomotor rhinitis	3
102492	H510C00	Pleural plaque	3
10992	H47..11	Aspiration pneumonitis	2
7092	H30..12	Recurrent wheezy bronchitis	2
103559	H563300	Usual interstitial pneumonitis	2
15553	H120200	Chronic hypertrophic rhinitis	2
37447	H06z112	Acute lower respiratory tract infection	2
1382	H060w00	Acute viral bronchitis unspecified	2
7324	H580.11	Atelectasis	2
4734	H10..12	DNS - deviated nasal septum	2
5437	H13z.00	Chronic sinusitis NOS	2
8318	H260000	Lung consolidation	2
25249	H59..00	Respiratory failure	2
6466	H02..12	Viral sore throat NOS	2
100994	H410.11	Asbestos-induced pleural plaque	2
5733	H....00	Respiratory system diseases	2
9093	H00..15	Pyrexial cold	2
1309	H1y1z14	Nasal infection	2
1838	H170.00	Allergic rhinitis due to pollens	2
33664	H01z.00	Acute sinusitis NOS	2
29669	H06..00	Acute bronchitis and bronchiolitis	2
1747	H037.00	Recurrent acute tonsillitis	2
3557	H1y0.00	Nasal turbinate hypertrophy	2
6014	H02..11	Sore throat NOS	2
8975	H120.11	Catarrh unspecified	1
3260	H00..00	Acute nasopharyngitis	1
9559	H51zz00	Pleural effusion NOS	1
998	H3...11	Chronic obstructive airways disease	1
103785	H58y500	Respiratory bronchiolitis associated interstitial lung dis	1
28634	H22..00	Other bacterial pneumonia	1
4868	H024.00	Acute viral pharyngitis	1
4195	H1y1.12	Nasal vestibulitis	1
4061	H031.00	Acute follicular tonsillitis	1
10863	H36..00	Mild chronic obstructive pulmonary disease	1
95938	H171100	Dog allergy	1

Obj 1 - RespCodes_ClosestIndex

24848	H585300	Adult respiratory distress syndrome	1
8370	H580.12	Collapse of lung	1
9389	H20..11	Chest infection - viral pneumonia	1
1596	H1y6300	Reinke's oedema of the vocal cords	1
52850	Hyu7000	[X]Pleural effusion in conditions classified elsewhere	1
1141	H10..00	Deviated nasal septum - acquired	1
558	H584.00	Acute pulmonary oedema unspecified	1
29172	H5y1200	Stenosis of trachea	1
22214	H1y7313	Subglottic stenosis	1
10342	H1y5600	Vocal cord nodule	1
1576	H231.00	Pneumonia due to mycoplasma pneumoniae	1
46578	H321.00	Panlobular emphysema	1
3798	H172.11	Hay fever - unspecified allergen	1
12667	H122.00	Chronic nasopharyngitis	1
775	H172.00	Allergic rhinitis due to unspecified allergen	1
3162	H171.15	House dust allergy	1
29166	H21..11	Chest infection - pneumococcal pneumonia	1
556	H27..00	Influenza	1
26125	H312300	Bronchiolitis obliterans	1
5047	H14z000	Chronic tonsil disease NOS	1
8213	H011.00	Acute frontal sinusitis	1
15231	H160.00	Chronic laryngitis	1
896	H00..14	Nasal catarrh - acute	1
794	H32..00	Emphysema	1
6257	H1y1600	Nasal obstruction	1
4229	H5C..00	Choking due to airways obstruction	1
18081	H51yz00	Other pleural effusion	1
18130	H4y0000	Acute radiation pneumonitis	1
31447	H352100	Pigeon-fanciers' lung	1
32727	H33z.11	Hyperreactive airways disease	1
19400	H26..11	Chest infection - pnemonia due to unspecified organism	1
34251	H23z.00	Pneumonia due to specified organism NOS	1
12061	H22y200	Pneumonia - Legionella	1
17173	H135.00	Recurrent sinusitis	1
16134	H171.14	Hay fever - other allergen	1

Obj 2 - T1

Off-label prescribing: Recorded "indication" for patients newly initiating FF/VI[1]
[Primary analysis]

	All Patients (N=4,373)[2]					
	COPD N = 2,653 No.	COPD (**without** history of asthma) N = 1,409 No.	COPD (**with** history of asthma) N = 1,244 No.	Asthma (not COPD) N = 1,554 No.	Other (not COPD not asthma) N = 166 No.	All[2] N = 4,373 No.
FF/VI 200 (any)[3]	535	246	289	600	48	1,183
FF/VI 200 (indexed)[4]	448	198	250	502	43	993
FF/VI 100	2,205	1,211	994	1,052	123	3,380

[1] This table is constructed using CPRD-GOLD
[2] All is the total of COPD, Asthma and Other. COPD (with and without a history of asthma) are sub groups of COPD
[3] Includes patients that received a prescription for FF/VI 200 at any point during the study period
[4] Includes only patients that initiated on FF/VI 200

Obj 2 - T1_Sensitivity

Off-label prescribing: Recorded "indication" for patients newly initiating FF/VI[1]

[Sensitivity analysis - diagnosis up to and including index date only]

	All Patients (N=4,373)[2]					
	COPD N = 2,542 No.[3]	COPD (**without** history of asthma) N = 1,355 No.[3]	COPD (**with** history of asthma) N = 1,187 No.[3]	Asthma (not COPD) N = 1,566 No.[3]	Other (not COPD not asthma) N = 265 No.[3]	All N = 4,373 No.[3]
FF/VI 200 (any)[3]	496	233	263	610	77	1,183
FF/VI 200 (indexed)[4]	414	185	229	510	69	993
FF/VI 100	2,128	1,170	958	1,056	196	3,380

[1] This table is constructed using CPRD-GOLD

[2] All is the total of COPD, Asthma and Other. COPD (with and without a history of asthma) are sub groups of COPD

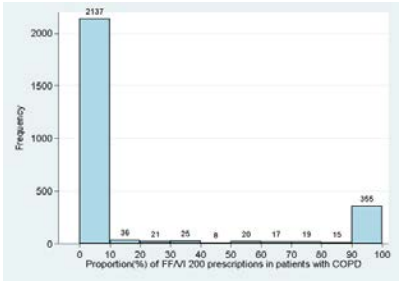
[3] Includes patients that received a prescription for FF/VI 200 at any point during the study period

[4] Includes only patients that initiated on FF/VI 200

Obj.2 - F1 - F2_COPD

Objective 2 – Off-label prescribing
[Primary analysis for CPRD data]

Figure 1: Proportion of all prescriptions for FF/VI 200 issued to patients in the COPD diagnosis group, presented using deciles and quartiles



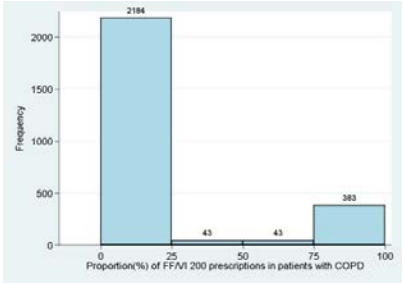
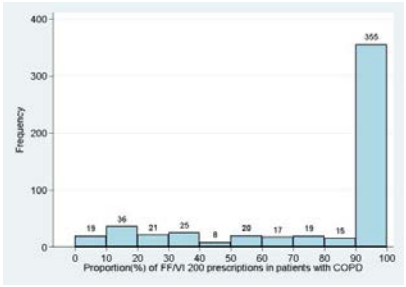
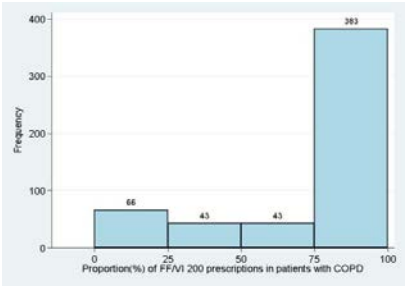


Figure 2: Proportion of all prescriptions for FF/VI 200 issued to patients in the COPD diagnosis group excluding patients with no FF/VI 200 prescriptions, presented using deciles and quartiles





Objective 2 – Off-label prescribing
[Sensitivity analysis - diagnosis up to and including index date only]

Figure 1: Proportion of all prescriptions for FF/VI 200 issued to patients in the COPD sensitivity diagnosis group, presented using deciles and quartiles

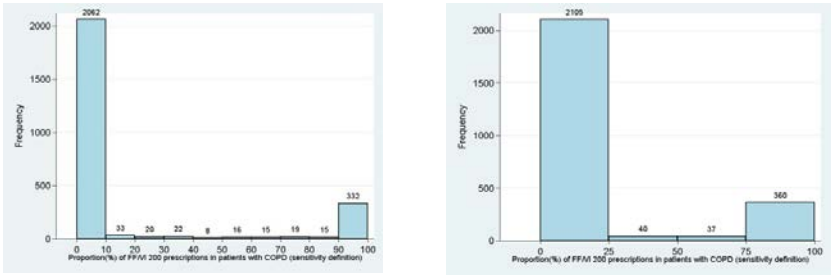
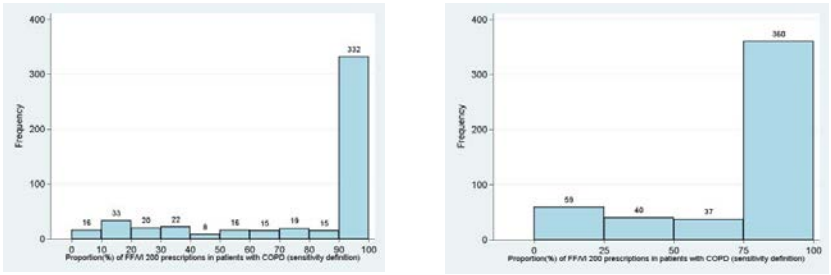


Figure 2: Proportion of all prescriptions for FF/VI 200 issued to patients in the COPD sensitivity diagnosis group excluding patients with no FF/VI 200 prescriptions, presented using deciles and quartiles



Obj.2 - F1-F2_COPD_noasthma

Objective 2 – Off-label prescribing
[Primary analysis for CPRD data]

Figure 1: Proportion of all prescriptions for FF/VI 200 issued to patients in the COPD diagnosis group without a history of asthma, presented using quartiles

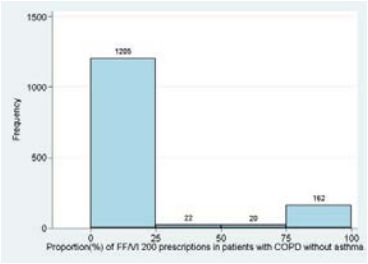
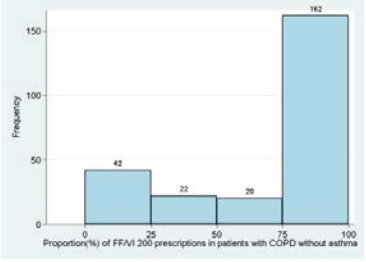


Figure 2: Proportion of all prescriptions for FF/VI 200 issued to patients in the COPD diagnosis group without a history of asthma excluding patients with no FF/VI 200 prescriptions, presented using quartiles



Obj.2 - F1-F2_COPD_asthma

Objective 2 – Off-label prescribing
[Primary analysis for CPRD data]

Figure 1: Proportion of all prescriptions for FF/VI 200 issued to patients in the COPD diagnosis group without a history of asthma, presented using quartiles

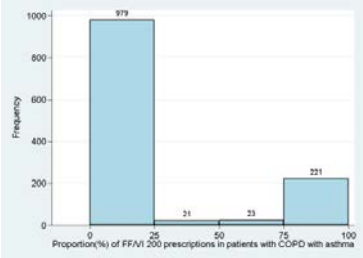
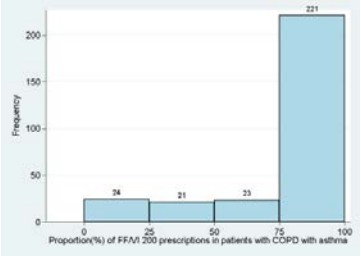


Figure 2: Proportion of all prescriptions for FF/VI 200 issued to patients in the COPD diagnosis group without a history of asthma excluding patients with no FF/VI 200 prescriptions, presented using quartiles



Obj 3 - T1

Dose escalation/reduction of inhaled COPD maintenance therapies in the first 12 months* following initiation of FF/VI in all patients[1]

[Primary analysis]

	All Patients initiating FF/VI (N=4,373)											
	COPD		COPD (**without** history of asthma)		COPD (**with** history of asthma)		Asthma (not COPD)		Other (not COPD not asthma)		All	
	N=	2,653	N=	1,409	N=	1,244	N=	1,554	N=	166	N=	4,373
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
No change (1 dose only)	355	13.38	188	13.34	167	13.42	287	18.47	59	35.54	701	16.03
No change (at least 2 doses)	2,112	79.61	1,117	79.28	995	79.98	1,107	71.24	100	60.24	3,319	75.90
Dose escalation[2]	87	NA	48	NA	39	NA	98	NA	7	NA	190	NA
Dose reduction[3]	99	NA	56	NA	43	NA	62	NA		NA	163	NA

[1] This table is constructed using CPRD-GOLD

[2] FF/VI 100 to FF/VI 200

[3] FF/VI 200 to FF/VI 100

Obj 3 - T1_12mnths

Dose escalation/reduction of inhaled COPD maintenance therapies in the first 12 months* following initiation of FF/VI in patients with 12 months follow-up[1]

[Primary analysis]

	Cohort of Patients initiating FF/VI (N=3,312)											
	COPD		COPD (**without** history of asthma)		COPD (**with** history of asthma)		Asthma (not COPD)		Other (not COPD not asthma)		All	
	N=	2,042	N=	1,072	N=	970	N=	1,167	N=	103	N=	3,312
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
No change (1 dose only)	225	11.02	122	11.38	103	10.62	180	15.42	31	30.10	436	13.16
No change (at least 2 doses)	1,669	81.73	868	80.97	801	82.58	854	73.18	65	63.11	2,588	78.14
Dose escalation[2]	71	NA	39	NA	32	NA	78	NA	7	NA	154	NA
Dose reduction[3]	77	NA	43	NA	34	NA	55	NA		NA	134	NA

[1] This table is constructed using CPRD-GOLD

[2] FF/VI 100 to FF/VI 200

[3] FF/VI 200 to FF/VI 100

Obj 3 - T2

Treatment patterns of inhaled COPD and asthma maintenance therapies in the first 12 months[1] following initiation of FF/VI in all patients[2]
[Primary analysis]

			FF/V1 100			FF/VI 200		
			No.	(%)	Mean (SD) time in days to first change	No.	(%)	Mean (SD) time in days to first change
COPD	No concomitant use of LAMA maintenance therapy at initiation	All[3]	(N=674)			(N=172)		
		Continuous user	393	58.31	n/a	94	54.65	n/a
		Augmenter	149	22.11	123.05 (88.95)	43	25.00	135.14 (99.50)
		Immediate switcher	30	4.45	92.03 (55.21)	9	5.23	108.67 (73.02)
		Discontinuer	102	15.13	102.05 (75.82)	26	15.12	99.12 (73.24)
		True discontinuer	0	0.00	n/a	0	0.00	n/a
		Discontinuer with drug hiatus	94	92.16	n/a	19-25	73.08-96.15	n/a
		Discontinuer with latent switch	8	7.84	n/a	1-5	3.85-19.23	n/a
	Concomitant use of LAMA maintenance therapy at initiation	All[4]	(N=1,027)			(N=164)		
		Continuous use of both drugs	686	66.80	n/a	108	65.85	n/a
		Immediate switcher to another ICS\LABA	14	1.36	58.50 (35.39)	<5	<3.05	52.00 ([7])
		Discontinuation of index drug only	26	2.53	122.65 (77.25)	<5	<3.05	133.50 ([7])
		Discontinuation of concomitant drug only	218	21.23	182.55 (103.38)	33	20.12	215.97 (111.72)
		Discontinuation of both drugs at the same time	83	8.08	138.70 (74.63)	17	10.37	125.65 (62.33)
Asthma	No concomitant use of LTRA maintenance therapy at initiation	All[5]	(N=701)			(N=319)		
		Continuous user	479	68.33	n/a	220	68.97	n/a
		Augmenter	76	10.84	109.57 (92.51)	49	15.36	114.55 (90.72)
		Immediate switcher	17	2.43	80.12 (51.99)	5	1.57	96.60 (52.63)
		Discontinuer	129	18.40	117.99 (77.92)	45	14.11	103.04 (71.50)
		True discontinuer	0	0.00	n/a	0	0.00	n/a
		Discontinuer with drug hiatus	124	96.12	n/a	39-44	86.67-97.78	n/a
		Discontinuer with latent switch	5	3.88	n/a	1-5	2.22-11.11	n/a
	Concomitant use of LTRA maintenance therapy at initiation	All[6]	(N=67)			(N=74)		
		Continuous use of both drugs	40	59.70	n/a	41	55.41	n/a
		Immediate switcher to another ICS\LABA	<5	<7.46	66.00 ([7])	<5	<6.76	43.00 ([7])
		Augmenter with LAMA	7	10.45	56.71 (15.50)	13	17.57	49.38 (9.48)
		Discontinuation of index drug only	<5	<7.46	231.50 ([7])	<5	<6.76	231.50 ([7])
		Discontinuation of concomitant drug only	14	20.90	161.57 (108.41)	15	20.27	195.53 (108.41)
		Discontinuation of both drugs at the same time	<5	<7.46	105.00 ([7])	<5	<6.76	102.00 ([7])

[1] Treatment patterns only considered in patients with at least 12 months follow-up after initiation.
[2] This table is constructed using CPRD-GOLD
[3] Treatment patterns not considered in 2 patients who were censored between 31 and 90 days after their last prescription as it was not possible to determine whether these patients had discontinued Relvar 100 or 200
[4] Treatment patterns not considered in 3 patients who were censored between 31 and 90 days after their last prescription as it was not possible to determine whether these patients had discontinued Relvar 100 or 200
[5] Treatment patterns not considered in 2 patients who were censored between 31 and 90 days after their last prescription as it was not possible to determine whether these patients had discontinued Relvar 100 or 200
[6] Treatment patterns not considered in 1 patient who was censored between 31 and 90 days after their last prescription as it was not possible to determine whether these patients had discontinued Relvar 100 or 200
[7] SD not reported due to small cell count

Obj 3 - T2_Sensitivity

Treatment patterns of inhaled COPD maintenance therapies in the first 12 months[1] following initiation of FF/VI in all patients[2]

			FF/V1 100			FF/VI 200		
			No.	(%)	Mean (SD) time in days to first change	No.	(%)	Mean (SD) time in days to first change
COPD without a history of asthma	No concomitant use of LAMA maintenance therapy at initiation	All[3]	(N=355)			(N=65)		
		Continuous user	199	56.06	n/a	40	61.54	n/a
		Augmenter	80	22.54	116.26 (82.21)	13	20.00	148.92 (86.91)
		Immediate switcher	16	4.51	103.81 (63.44)	<5	<7.69	110.75 ([7])
		Discontinuer	60	16.90	105.45 (80.70)	8	12.31	119.88 (97.23)
		True discontinuer	0	0.00	n/a	0	0.00	n/a
		Discontinuer with drug hiatus	55	91.67	n/a	2-7	25.00 - 87.50	n/a
		Discontinuer with latent switch	5	8.33	n/a	1-5	12.50 - 62.50	n/a
	Concomitant use of LAMA maintenance therapy at initiation	All[4]	(N=574)			(N=74)		
		Continuous use of both drugs	375	65.33	n/a	53	71.62	n/a
		Immediate switcher to another ICS\LABA	7	1.22	41.71 (16.50)	0	0.00	n/a
		Discontinuation of index drug only	15	2.61	103.93 (67.62)	0	0.00	n/a
		Discontinuation of concomitant drug only	125	21.78	180.82 (99.63)	14	18.92	207.21 (129.12)
		Discontinuation of both drugs at the same time	52	9.06	140.04 (77.48)	7	9.46	149.14 (49.49)
COPD with a history of asthma	No concomitant use of LAMA maintenance therapy at initiation	All[5]	(N=319)			(N=107)		
		Continuous user	194	60.82	n/a	54	50.47	n/a
		Augmenter	69	21.63	130.93 (96.18)	30	28.04	129.17 (105.31)
		Immediate switcher	14	4.39	78.57 (42.30)	5	4.67	107.00 (96.07)
		Discontinuer	42	13.17	97.19 (68.92)	18	16.82	89.89 (60.84)
		True discontinuer	0	0.00	n/a	0	0.00	n/a
		Discontinuer with drug hiatus	37-41	88.10 - 97.62	n/a	12-17	66.67 - 94.44	n/a
		Discontinuer with latent switch	1-5	2.38 - 11.90	n/a	1-5	5.56 - 27.78	n/a
	Concomitant use of LAMA maintenance therapy at initiation	All[6]	(N=453)			(N=90)		
		Continuous use of both drugs	311	68.65	n/a	55	61.11	n/a
		Immediate switcher to another ICS\LABA	7	1.55	75.29 (42.24)	<5	<5.56	52.00 ([7])
		Discontinuation of index drug only	11	2.43	148.18 (85.30)	<5	<5.56	133.50 ([7])
		Discontinuation of concomitant drug only	93	20.53	184.86 (108.71)	19	21.11	222.42 (100.23)
		Discontinuation of both drugs at the same time	31	6.84	136.45 (70.80)	10	11.11	109.20 (67.41)

[1] Treatment patterns only considered in patients with at least 12 months follow-up after initiation.

[2] This table is constructed using CPRD-GOLD

[3] Treatment patterns not considered in 1 patients who were censored between 31 and 90 days after their last prescription as it was not possible to determine whether these patients had discontinued Relvar 100 or 200

[4] Treatment patterns not considered in 3 patients who were censored between 31 and 90 days after their last prescription as it was not possible to determine whether these patients had discontinued Relvar 100 or 200

[5] Treatment patterns not considered in 1 patients who were censored between 31 and 90 days after their last prescription as it was not possible to determine whether these patients had discontinued Relvar 100 or 200

[6] Treatment patterns not considered in 0 patients who were censored between 31 and 90 days after their last prescription as it was not possible to determine whether these patients had discontinued Relvar 100 or 200

[7] SD not reported due to small cell count

Obj 3 - F1-F4_COPD

Treatment patterns of inhaled COPD maintenance therapies in the first 12 months[1] following initiation of FF/VI[2]
[Primary analysis]

Figure 1: Time (in days) to first treatment change in FF/VI 100 initiators with a diagnosis of COPD who were not using another maintenance therapy at initiation, by type of change
[Kaplan Meier plot]

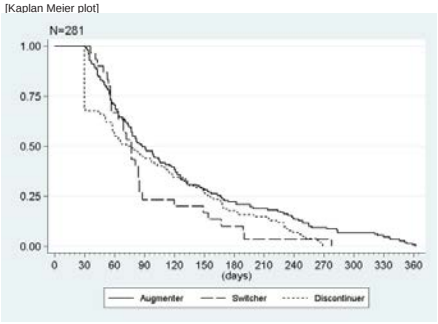


Figure 2: Time (in days) to first treatment change in FF/VI 100 initiators with a diagnosis of COPD who were using another maintenance therapy at initiation, by type of change
[Kaplan Meier plot]

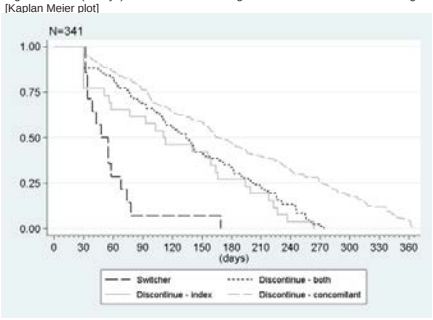


Figure 3: Time (in days) to first treatment change in FF/VI 200 initiators with a diagnosis of COPD who were not using another maintenance therapy at initiation, by type of change
[Kaplan Meier plot]

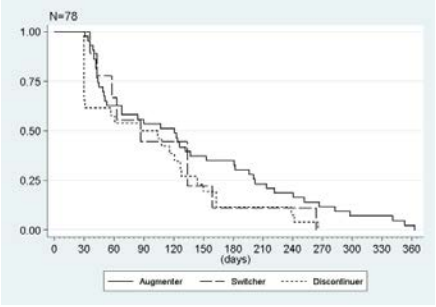
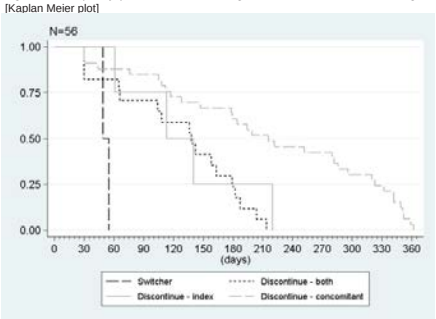


Figure 4: Time (in days) to first treatment change in FF/VI 200 initiators with a diagnosis of COPD who were using another maintenance therapy at initiation, by type of change
[Kaplan Meier plot]



[1] Treatment patterns only considered in patients with at least 12 months follow-up after initiation.
[2] These figures are constructed using CPRD-GOLD

Treatment patterns of inhaled COPD maintenance therapies in the first 12 months[1] following initiation of FF/VI[2]
[Primary analysis]

Figure 1: Time (in days) to first treatment change in FF/VI 100 initiators with a diagnosis of asthma who were not using another maintenance therapy at initiation, by type of change [Kaplan Meier plot]

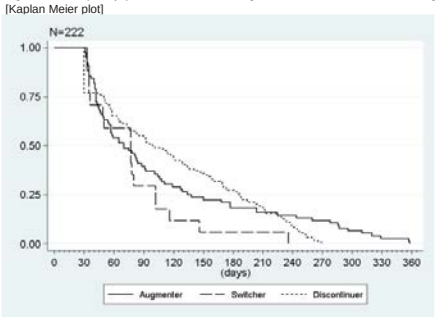


Figure 2: Time (in days) to first treatment change in FF/VI 100 initiators with a diagnosis of asthma who were using another maintenance therapy at initiation, by type of change [Kaplan Meier plot]

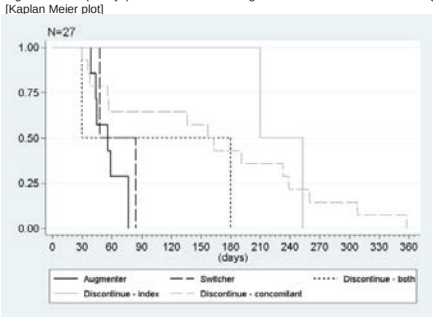


Figure 3: Time (in days) to first treatment change in FF/VI 200 initiators with a diagnosis of asthma who were not using another maintenance therapy at initiation, by type of change [Kaplan Meier plot]

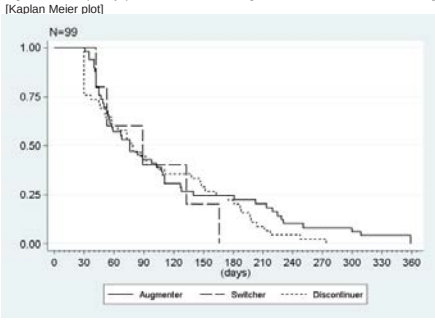
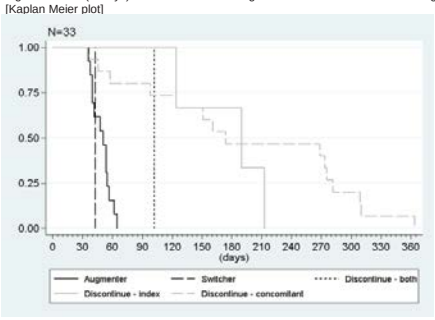


Figure 4: Time (in days) to first treatment change in FF/VI 200 initiators with a diagnosis of asthma who were using another maintenance therapy at initiation, by type of change [Kaplan Meier plot]



[1] Treatment patterns only considered in patients with at least 12 months follow-up after initiation.
[2] These figures are constructed using CPRD-GOLD

Obj 3 - T3

Adherence to FF/VI therapy in the first 12 months[1] following initiation, in all patients[2]

[Primary analysis]

		All Patients initiating FF/VI with 12 months follow up (N=3,312)[3]							
		COPD		Asthma (not COPD)		Other (not COPD not Asthma)		All	
		No.[4]	(%)[4]	No.[4]	(%)[4]	No.[4]	(%)[4]	No.[4]	(%)[4]
Medication Possession Ratio (MPR)	Total patients[5]	1,815	63	987	34	72	3	2,874	100
	mean (SD)	0.87	0.42	0.84	0.99	0.82	0.33	0.86	0.67
	Median (IQR)[6]	0.92	0.63 -1.05	0.82	0.58 - 1.01	0.86	0.60 -1.00	0.88	0.60 - 1.03
	Min	0.09		0.08		0.12		0.08	
	Max	10.00		30.00		2.14		30.00	
	<80%	690	38.02	485	49.14	28	38.89	1,203	41.86
	≥80%	1,125	61.98	502	50.86	44	61.11	1,671	58.14
Proportion Days Covered (PDC)	Total patients	2,042	61.65	1,167	35.24	103	3.11	3,312	100.00
	mean (SD)	0.66	0.33	0.59	0.34	0.42	0.35	0.63	0.34
	Median (IQR)	0.74	0.41 - 0.99	0.66	0.25 - 0.90	0.25	0.08 - 0.74	0.66	0.33 - 0.99
	Min	0.08		0.08		0.08		0.08	
	Max	1.00		1.00		1.00		1.00	
	<80%	1,087	53.23	727	62.30	79	76.70	1,893	57.16
	≥80%	955	46.77	440	37.70	24	23.30	1,419	42.84

[1] Adherence only measured in patients with at least 12 months follow-up after initiation.

[2] This table is constructed using CPRD-GOLD

[3] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[4] Unless otherwise specified

[5] The medication possession ratio was not calculated in 438 patients who only recieved one prescription for Relvar

[6] 927 patients were in possession of FF/VI for more than 365 days

H.ExposureCohorts-T1

Descriptive statistics of cohort, overall and by index LABD cohort[1]

		All Patients (N=24,221)[2]							
		FF/VI 100		FF/VI 200		Other ICS/LABA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		1,347	5.18	378	1.45	24,280	93.37	26,005	100.00
Time to censoring in days	mean (SD)	301.36	104.07	296.19	112.88	309.34	101.73	308.73	102.04
	median (IQR)	365	259 - 365	365	265 - 365	365	297 - 365	365	294 - 365
Reason for censoring	death	42	3.12	11	2.91	702	2.89	755	2.90
	left GP practice	31	2.30	7	1.85	833	3.43	871	3.35
	last collection from GP practice	423	31.40	129	34.13	5,917	24.37	6,469	24.88
	full 365 days of follow-up	851	63.18	231	61.11	16,828	69.31	17,910	68.87
Total prescriptions	mean (SD)	5.13	2.88	4.41	2.96				
	median (IQR)	6	2 - 8	4	1 - 8				
	min	1		1					
	max	19		16					
	1	274	20.34	109	28.84				
	2	114	8.46	48	12.70				
	3	96	7.13	20	5.29				
	4	78	5.79	18	4.76				
	5	73	5.42	21	5.56				
	6	86	6.38	24	6.35				
	7	85	6.31	22	5.82				
	≥8	541	40.16	116	30.69				
Patients contributing to multiple index medication groups	gap between index medications								
	N (%)	58	4.31	16	4.23				
	mean (SD) gap in days	92.14	106.67	100.56	121.52				
	median (IQR)	42	26 - 125	66	22 - 148.5				
	overlap between index medications								
	N (%)	40	2.97	11	2.91				
	mean (SD) overlap in days	26.63	54.89	41.18	56.58				
	median (IQR)	16	4.5 - 25.5	23	16 - 27				

[1] This table is constructed using CPRD-HES

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

H.ExposureCohorts-T1_COPD

Descriptive statistics for COPD diagnosis group, overall and by index LABD cohort[1]

		COPD diagnosis group (N=8,170)[2]							
		FF/VI 100		FF/VI 200		Other ICS/LABA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		900	10.10	190	2.13	7,822	87.77	8,912	100.00
Time to censoring in days	mean (SD)	311.99	97.63	293.87	116.54	306.36	103.94	306.67	103.62
	median (IQR)	365	301.5 - 365	365	228 - 365	365	284 - 365	365	285 - 365
Reason for censoring	death	30	3.33	11	5.79	408	5.22	446	5.00
	left GP practice	16	1.78			221	2.83	240	2.69
	last collection from GP practice	228	25.33	62	32.63	1,904	24.34	2,194	24.62
	full 12 months of follow-up	626	69.56	117	61.58	5,289	67.62	6,032	67.68
Total prescriptions	mean (SD)	5.55	2.81	4.42	3.00				
	median (IQR)	7	3 - 8	4	1 - 8				
	min	1		1					
	max	19		16					
	1	147	16.33	58	30.53				
	2	68	7.56	22	11.58				
	3	59	6.56	9	4.74				
	4	43	4.78	8	4.21				
	5	42	4.67	10	5.26				
	6	53	5.89	14	7.37				
	7	65	7.22	7	3.68				
	≥8	423	47.00	62	32.63				
Patients contributing to multiple index medication groups	gap between index medications								
	N (%)	40	4.44	11	5.79				
	mean (SD) gap in days	84.03	99.18	93.91	70.79				
	median (IQR)	45	21 - 116	81	30 - 159				
	overlap between index medications								
	N (%)	23	2.56	6	3.16				
	mean (SD) overlap in days	34.09	71.34	20.50	7.23				
	median (IQR)	16	3 - 40	23	16 - 26				

[1] This table is constructed using CPRD-HES

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

H.ExposureCohorts-T1_COPD_NoAst

Descriptive statistics for COPD diagnosis group without a history of asthma, overall and by index LABD cohort[1]

		COPD diagnosis group without a history of Asthma (N=4,599)[2]							
		FF/VI 100		FF/VI 200		Other ICS/LABA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		448	8.92	89	1.77	4,487	89.31	5,024	100.00
Time to censoring in days	mean (SD)	308.43	99.81	286.07	126.20	305.73	103.80	305.63	103.91
	median (IQR)	365	280 - 365	365	214 - 365	365	279 - 365	365	279 - 365
Reason for censoring	death	15	3.35			270	6.02	287	5.71
	left GP practice	9	2.01	38	42.70	141	3.14	151	3.01
	last collection from GP practice	117	26.12			1,078	24.02	1,230	24.48
	full 12 months of follow-up	307	68.53	51	57.30	2,998	66.82	3,356	66.80
Total prescriptions	mean (SD)	4.54	2.02	3.65	2.24				
	median (IQR)	6	3 - 6	4	1 - 6				
	min	1		1					
	max	19		14					
	1	77	17.19	27	30.34				
	2	31	6.92	12	13.48				
	3	29	6.47						
	4	19	4.24	12	13.48				
	5	22	4.91						
	≥6	270	60.27	38	42.70				
Patients contributing to multiple index medication groups	gap between index medications								
	N (%)	19	4.24	3	3.37				
	mean (SD) gap in days	116.00	125.06	92.33	66.01				
	median (IQR)	74	32 - 164	91	27 - 159				
	overlap between index medications								
	N (%)	8	1.79	4	4.49				
	mean (SD) overlap in days	29.00	25.98	17.50	7.14				
	median (IQR)	19	7 - 56	20	12 - 23				

[1] This table is constructed using CPRD-HEs

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

H.ExposureCohorts-T1_COPD_Ast

Descriptive statistics for COPD diagnosis gorup with a history of asthma, overall and by index LABD cohort[1]

		COPD diagnosis group with a history of Asthma (N=3,581)[2]							
		FF/VI 100		FF/VI 200		Other ICS/LABA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		452	11.63	101	2.60	3,335	85.78	3,888	100.00
Time to censoring in days	mean (SD)	315.52	95.39	300.75	107.48	307.21	104.13	308.01	103.25
	median (IQR)	365	328.5 - 365	365	265 - 365	365	289 - 365	365	292.5 - 365
Reason for censoring	death	15	3.32	8	7.92	138	4.14	159	4.09
	left GP practice	7	1.55			80	2.40	89	2.29
	last collection from GP practice	111	24.56	27	26.73	826	24.77	964	24.79
	full 12 months of follow-up	319	70.58	66	65.35	2,291	68.70	2,676	68.83
Time from asthma diagnosis to index date in days[4]	mean (SD)	3,513.99	2,170.23	3,123.44	2,351.92	3,063.75	2,168.62	3,117.64	2,177.93
	median (IQR)	3,700	1,615 - 4,908	2,738	1,143 - 4,731	2,968	1,172 - 4,518	3,053	1,216 - 4,575
Total prescriptions	mean (SD)	7.21	4.59	5.65	4.61				
	median (IQR)	7	3 - 12	5	1 - 10				
	min	1		0					
	max	16		14					
	1	70	15.49	31	30.69				
	2	37	8.19	10	9.90				
	3	30	6.64	4	3.96				
	4	24	5.31	4	3.96				
	5	20	4.42	7	6.93				
	≥6	271	59.96	45	44.55				
Patients contributing to multiple index medication groups	gap between index medications								
	N (%)	21	4.65	8	7.92				
	mean (SD) gap in days	55.10	57.06	94.50	76.89				
	median (IQR)	32	19 - 96	69	30 - 163				
	overlap between index medications								
	N (%)	15	3.32	2	1.98				
	mean (SD) overlap in days	36.80	87.39	26.50	0.71				
	median (IQR)	16	2 - 22	27	26 - 27				

[1] This table is constructed using CPRD-HES

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Time to asthma diagnosis for patients diagnosed with asthma prior to the index date

H.ExposureCohorts-T1_Asthma

Descriptive statistics for Asthma diagnosis group, overall and by index LABD cohort[1]

		Asthma diagnosis group (N=13,365)[2]							
		FF/VI 100		FF/VI 200		Other ICS/LABA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		404	2.83	170	1.19	13,708	95.98	14,282	100.00
Time to censoring in days	mean (SD)	285.95	108.42	299.62	108.00	313.29	98.30	312.35	98.82
	median (IQR)	365	213.5 - 365	365	281 - 365	365	319 - 365	365	312 - 365
Reason for censoring	death	6	1.49	5	2.94	122	0.89	130	0.91
	left GP practice	14	3.47			501	3.65	518	3.63
	last collection from GP practice	177	43.81	62	36.47	3,352	24.45	3,591	25.14
	full 12 months of follow-up	207	51.24	103	60.59	9,733	71.00	10,043	70.32
Time from asthma diagnosis to index date in days[4]	N (%)	395	97.77	165-170	>95	13,181	96.16	13,742	96.22
	mean (SD)	2,798.11	2,173.25	3,153.24	2,145.77	2,653.73	2,171.12	2,663.92	2,171.53
	median (IQR)	2,257	1,031 - 4,055	3,005	1,397 - 4,540	2,328	703 - 4,153	2,334	721 - 4,154
Time from index date to asthma diagnosis in days[5]	N (%)	9	2.23	1-5	≤5	527	3.84	540	3.78
	mean (SD)	114.89	126.40	40.25	22.32	92.50	93.11	92.50	93.42
	median (IQR)	44	28 - 217	35	24 - 57	56	25 - 130	56	25 - 128
Total prescriptions	mean (SD)	4.37	2.82	4.52	2.90				
	median (IQR)	4	1 - 8	5	1 - 8				
	min	1		1					
	max	15		15					
	1	108	26.73	43	25.29				
	2	42	10.40	23	13.53				
	3	33	8.17	10	5.88				
	4	31	7.67	9	5.29				
	5	29	7.18	11	6.47				
	6	31	7.67	10	5.88				
	7	20	4.95	14	8.24				
	≥8	110	27.23	50	29.41				
Patients contributing to multiple index medication groups	gap between index medications								
	N (%)	16	3.96	5	2.94				
	mean (SD) gap in days	97.81	105.68	115.20	206.06				
	median (IQR)	40	32 - 191	11	5 - 75				
	overlap between index medications								
	N (%)	16	3.96	4	2.35				
	mean (SD) overlap in days	17.44	12.39	78.00	87.98				
	median (IQR)	18	5 - 25.5	47	19 - 137				

[1] This table is constructed using CPRD-HES
[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records
[3] Unless otherwise specified
[4] Time to asthma diagnosis for patients diagnosed with asthma prior to the index date
[5] Time to asthma diagnosis for patients diagnosed with asthma post index date

H.ExposureCohorts-T1_Other

Descriptive statistics for Other diagnosis group, overall and by index LABD cohort[1]

		Other diagnosis gorup (N=2,707)[2]							
		FF/VI 100		FF/VI 200		Other ICS/LABA		All	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Total number of patients		43	1.53	18	0.64	2,750	97.83	2,811	100.00
Time to censoring in days	mean (SD)	223.77	139.49	288.22	124.06	298.11	110.72	296.91	111.62
	median (IQR)	239	74 - 365	365	244 - 365	365	250 - 365	365	244 - 365
Reason for censoring	death	7	16.28	7	38.89	172	6.25	179	6.37
	left GP practice					111	4.04	113	4.02
	last collection from GP practice	18	41.86			661	24.04	684	24.33
	full 12 months of follow-up	18	41.86	11	61.11	1,806	65.67	1,835	65.28
Total prescriptions	mean (SD)	3.65	3.44	3.94	4.09				
	median (IQR)	2	1 - 5	2	1 - 7				
	min	1		1					
	max	12		13					
	1 or 2	23	53.49	11	61.11				
	≥3	20	46.51	7	38.89				
Patients contributing to multiple index medication groups	gap between index medications								
	N (%)	2	4.65	0	0.00				
	mean (SD) gap in days	209.00	258.80	n\a	n\a				
	median (IQR)	209	26 - 392	n\a	n\a				
	overlap between index medications								
	N (%)	1	2.33	1	5.56				
	mean (SD) overlap in days	2.00	[4]	18.00	[4]				
	median (IQR)	2	2 - 2	18	18 - 18				

[1] This table is constructed using CPRD-HES
[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records
[3] Unless otherwise specified
[4] No SD as only one patient

H.Obj 1-T1

Demographic characteristics at baseline, by index LABD cohort[1]

		All Patients (N=24,221)[2]							
		FF/VI 100 N= 1,347		FF/VI 200 N= 378		Other ICS/LABA N= 24,280		All N= 26,005	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Age (in years) at index date	mean (SD)	62.79	17.40	61.37	17.03	55.95	20.47	56.39	20.34
	≥80 years	192	14.25	40	10.58	2,653	10.93	2,885	11.09
	65-79 years	558	41.43	150	39.68	7,078	29.15	7,786	29.94
	45-64 years	403	29.92	128	33.86	8,032	33.08	8,563	32.93
	18-44 years	151	11.21	53	14.02	5,093	20.98	5,297	20.37
	0-17 years	43	3.19	7	1.85	1,424	5.86	1,474	5.67
Gender	female	723	53.67	206	54.50	13,729	56.54	14,658	56.37
	male	624	46.33	172	45.50	10,551	43.46	11,347	43.63
Smoking status	current smoker	432	32.14	89	23.54	6,127	25.85	6,648	26.15
	ex-smoker	608	45.24	159	42.06	8,064	34.02	8,831	34.73
	no/never smoker	304	22.62	130	34.39	9,511	40.13	9,945	39.12
	missing[4]	*3*	*0.22*	*0*	*0.00*	*578*	*2.38*	*581*	*2.23*
Body Mass Index (kg/m^2)	mean (SD)	28.60	6.55	29.52	6.78	28.67	6.75	28.68	6.74
	underweight <18.5	44	3.63	11	3.24	545	2.71	600	2.77
	normal 18.5-24.9	338	27.89	78	23.01	5,827	28.93	6,243	28.78
	overweight 25.0-29.9	388	32.01	102	30.09	6,611	32.83	7,101	32.74
	obese ≥30	442	36.47	148	43.66	7,157	35.54	7,747	35.72
	missing[4]	*135*	*10.02*	*39*	*10.32*	*4,140*	*17.05*	*4,314*	*16.59*
Concomitant prescribing at index date	Any	965	71.64	254	67.20	13,726	56.53	14,945	57.47
	SABD	794	58.95	208	55.03	11,840	48.76	12,842	49.38
	LAMA	484	35.93	107	28.31	3,864	15.91	4,455	17.13
	LABA/LAMA	<5	<0.37	<5	<1.32	11	0.05	16	0.06
	LABA	14	1.04	<5	<1.32	260	1.07	278	1.07
	ICS	31	2.30	13	3.44	1,085	4.47	1,129	4.34
	Theophylline	40	2.97	12	3.17	356	1.47	408	1.57
	Roflumilast	0	0.00	0	0.00	0	0.00	0	0.00
	LTRA	68	5.05	34	8.99	1,348	5.55	1,450	5.58
Patient level area based deprivation quintile[5]	Q1 (least deprived)	189	14.03	54	14.29	5,021	20.68	5,264	20.24
	Q2	222	16.48	49	12.96	5,000	20.59	5,271	20.27
	Q3	274	20.34	82	21.69	5,037	20.75	5,393	20.74
	Q4	353	26.21	88	23.28	4,716	19.42	5,157	19.83
	Q5 (most deprived)	309	22.94	105	27.78	4,504	18.55	4,918	18.91
	missing[4]	*0*	*0.00*	*0*	*0.00*	*2*	*0.01*	*2*	*0.01*
Pratice level area based deprivation quintile[5]	Q1 (least deprived)	75	5.57	27	7.14	3,521	14.50	3,623	13.93
	Q2	168	12.47	56	14.81	5,568	22.93	5,792	22.27
	Q3	335	24.87	84	22.22	4,330	17.83	4,749	18.26
	Q4	419	31.11	82	21.69	4,556	18.76	5,057	19.45
	Q5 (most deprived)	350	25.98	129	34.13	6,305	25.97	6,784	26.09
Region (total number of practices contributing to CPRD; N= 545)[6]	North of England (N=124)[7]	303	22.49	93	24.60	5,090	20.96	5,486	21.10
	The Midlands (N=140)[8]	78	5.79	34	8.99	5,108	21.04	5,220	20.07
	London (N=97)	581	43.13	138	36.51	6,877	28.32	7,596	29.21
	South West Central (N=117)[9]	27	2.00	13	3.44	3,064	12.62	3,104	11.94
	South East Coast (N=67)	358	26.58	100	26.46	4,141	17.06	4,599	17.69

[1] This table is constructed using CPRD-HES

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Percentages were calculated seperately for those with missing and without missing data

[5] Area based deprivation is measured using patient or practive-level Index of Multiple Deprivation (IMD) quintile in CPRD

[6] The total number of practices contributing to CPRD within the region

[7] North of England includes: North East, North West, and Yorkshire & The Humber regions

[8] The Midlands includes: East Midlands, West Midlands and East of England regions

[9] South West Central includes: South West and South Central regions

H.Obj 1 T1_COPD

Demographic characteristics at baseline for COPD diagnosis group, by index LABD cohort[1]

		COPD diagnosis group (N=8,170)[2]							
		FF/VI 100 N= 900		FF/VI 200 N= 190		Other ICS/LABA N= 7,822		All N= 8,912	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Age (in years) at index date	mean (SD)	69.54	10.38	68.71	11.02	69.43	11.17	69.43	11.09
	≥80 years	164	18.22	25	13.16	1,508	19.28	1,697	19.04
	65-79 years	475	52.78	107	56.32	3,825	48.90	4,407	49.45
	45-64 years	246	27.33	58	30.53	2,339	29.90	2,639	29.61
	18-44 years	15	1.67			150	1.92	169	1.90
	0-17 years	0	0.00	0	0.00	0	0.00	0	0.00
Gender	female	429	47.67	81	42.63	3,833	49.00	4,343	48.73
	male	471	52.33	109	57.37	3,989	51.00	4,569	51.27
Smoking status	current smoker	332	36.89	65	34.21	2,943	37.69	3,340	37.54
	ex-smoker	488	54.22	103	54.21	3,901	49.96	4,492	50.48
	no/never smoker	80	8.89	22	11.58	964	12.35	1,066	11.98
	missing[4]	*0*	*0.00*	*0*	*0.00*	*14*	*0.18*	*14*	*0.16*
Body Mass Index (kg/m^2)	mean (SD)	28.11	6.29	28.53	6.48	27.55	6.41	27.62	6.41
	underweight <18.5	39	4.53	7	3.95	351	4.80	397	4.75
	normal 18.5-24.9	248	28.80	47	26.55	2,425	33.15	2,720	32.56
	overweight 25.0-29.9	280	32.52	61	34.46	2,334	31.91	2,675	32.02
	obese ≥30	294	34.15	62	35.03	2,205	30.14	2,561	30.66
	missing[4]	*39*	*4.33*	*13*	*6.84*	*507*	*6.48*	*559*	*6.27*
Concomitant prescribing at index date	Any	730	81.11	150	78.95	5,845	74.73	6,725	75.46
	SABD	579	64.33	116	61.05	4,788	61.21	5,483	61.52
	LAMA	470	52.22	91	47.89	3,413	43.63	3,974	44.59
	LABA/LAMA	<5	<0.56	<5	<2.63	11	0.14	16	0.18
	LABA	11	1.22	<5	<2.63	133	1.70	146	1.64
	ICS	15	1.67	6	3.16	214	2.74	235	2.64
	Theophylline	36	4.00	8	4.21	236	3.02	280	3.14
	Roflumilast	0	0.00	0	0.00	0	0.00	0	0.00
	LTRA	31	3.44	8	4.21	222	2.84	261	2.93
Patient level area based deprivation quintile[5]	Q1 (least deprived)	125	13.89	15	7.89	1,256	16.06	1,396	15.67
	Q2	133	14.78	23	12.11	1,430	18.28	1,586	17.80
	Q3	168	18.67	42	22.11	1,698	21.71	1,908	21.41
	Q4	244	27.11	44	23.16	1,631	20.85	1,919	21.54
	Q5 (most deprived)	230	25.56	66	34.74	1,806	23.09	2,102	23.59
	missing	*0*	*0.00*	*0*	*0.00*	*1*	*0.01*	*1*	*0.01*
Pratice level area based deprivation quintile[5]	Q1 (least deprived)	48	5.33	8	4.21	891	11.39	947	10.63
	Q2	98	10.89	18	9.47	1,645	21.03	1,761	19.76
	Q3	260	28.89	45	23.68	1,421	18.17	1,726	19.37
	Q4	243	27.00	45	23.68	1,569	20.06	1,857	20.84
	Q5 (most deprived)	251	27.89	74	38.95	2,296	29.35	2,621	29.41
Region (total number of practices contributing to CPRD; N= 545)[6]	North of England (N=124)[7]	202	22.44	45	23.68	2,063	26.37	2,310	25.92
	The Midlands (N=140)[8]	47	5.22	10	5.26	1,478	18.90	1,535	17.22
	London (N=97)	364	40.44	81	42.63	2,058	26.31	2,503	28.09
	South West Central (N=117)[9]	13	1.44	7	3.68	1,043	13.33	1,063	11.93
	South East Coast (N=67)	274	30.44	47	24.74	1,180	15.09	1,501	16.84

[1] This table is constructed using CPRD-HES

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Percentages were calculated seperately for those with missing and without missing data

[5] Area based deprivation is measured using patient or practive-level Index of Multiple Deprivation (IMD) quintile in CPRD

[6] The total number of practices contributing to CPRD within the region

[7] North of England includes: North East, North West, and Yorkshire & The Humber regions

[8] The Midlands includes: East Midlands, West Midlands and East of England regions

[9] South West Central includes: South West and South Central regions

H.Obj 1-T1_COPD_NoAst

Demographic characteristics at baseline for COPD diagnosis group without a history of asthma, by index LABD cohort[1]

		COPD diagnosis group without a history of asthma (N=4,599)[2]							
		FF/VI 100 N= 448		FF/VI 200 N= 89		Other ICS/LABA N= 4,487		All N= 5,024	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Age (in years) at index date	mean (SD)	70.16	10.07	70.27	9.55	69.81	10.84	69.85	10.75
	≥80 years	82	18.30	14	15.73	868	19.34	964	19.19
	65-79 years	237	52.90	50	56.18	2,275	50.70	2,562	51.00
	45-64 years	122	27.23	25	28.09	1,278	28.48	1,425	28.36
	18-44 years	7	1.56	0	0.00	66	1.47	73	1.45
	0-17 years	0	0.00	0	0.00	0	0.00	0	0.00
Gender	female	177	39.51	26	29.21	2,016	44.93	2,219	44.17
	male	271	60.49	63	70.79	2,471	55.07	2,805	55.83
Smoking status	current smoker	173	38.62	33	37.08	1,850	41.35	2,056	41.03
	ex-smoker	253	56.47	49	55.06	2,247	50.22	2,549	50.87
	no/never smoker	22	4.91	7	7.87	377	8.43	406	8.10
	missing[4]	*0*	*0.00*	*0*	*0.00*	*13*	*0.29*	*13*	*0.26*
Body Mass Index (kg/m^2)	mean (SD)	27.27	6.07	27.51	6.45	27.06	6.35	27.09	6.32
	underweight <18.5	27	6.28	5	6.17	254	6.12	286	6.14
	normal 18.5-24.9	134	31.16	23	28.40	1,447	34.89	1,604	34.44
	overweight 25.0-29.9	138	32.09	30	37.04	1,290	31.11	1,458	31.30
	obese ≥30	131	30.47	23	28.40	1,156	27.88	1,310	28.12
	missing[4]	*18*	*4.02*	*8*	*8.99*	*340*	*7.58*	*366*	*7.29*
Concomitant prescribing at index date	Any	352	78.57	70	78.65	3,269	72.85	3,691	73.47
	SABD	267	59.60	49	55.06	2,584	57.59	2,900	57.72
	LAMA	244	54.46	48	53.93	2,042	45.51	2,334	46.46
	LABA/LAMA	<5	<1.12	<5	<5.62	5	0.11	7	0.14
	LABA	8	1.79	<5	<5.62	68	1.52	77	1.53
	ICS	<5	<1.12	<5	<5.62	70	1.56	75	1.49
	Theophylline	16	3.57	<5	<5.62	81	1.81	98	1.95
	Roflumilast	0	0.00	0	0.00	0	0.00	0	0.00
	LTRA	6	1.34	<5	<5.62	25	0.56	33	0.66
Patient level area based deprivation quintile[5]	Q1 (least deprived)	67	14.96	6	6.74	719	16.02	792	15.76
	Q2	59	13.17	10	11.24	790	17.61	859	17.10
	Q3	89	19.87	20	22.47	981	21.86	1,090	21.70
	Q4	125	27.90	24	26.97	940	20.95	1,089	21.68
	Q5 (most deprived)	108	24.11	29	32.58	1,057	23.56	1,194	23.77
	missing	*0*	*0.00*	*0*	*0.00*	*0*	*0.00*	*0*	*0.00*
Pratice level area based deprivation quintile[5]	Q1 (least deprived)	28	6.25	12	13.48	527	11.75	559	11.13
	Q2	37	8.26			899	20.04	944	18.79
	Q3	137	30.58	23	25.84	756	16.85	916	18.23
	Q4	118	26.34	17	19.10	875	19.50	1,010	20.10
	Q5 (most deprived)	128	28.57	37	41.57	1,430	31.87	1,595	31.75
Region (total number of practices contributing to CPRD; N= 545)[6]	North of England (N=124)[7]	103	22.99	22	24.72	1,198	26.70	1,321	26.29
	The Midlands (N=140)[8]	16	3.57			839	18.70	857	17.06
	London (N=97)	157	35.04	41	46.07	1,119	24.94	1,317	26.21
	South West Central (N=117)[9]	9	2.01	26	29.21	581	12.95	593	11.80
	South East Coast (N=67)	163	36.38			750	16.71	936	18.63

[1] This table is constructed using CPRD-HES

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Percentages were calculated seperately for those with missing and without missing data

[5] Area based deprivation is measured using patient or practive-level Index of Multiple Deprivation (IMD) quintile in CPRD

[6] The total number of practices contributing to CPRD within the region

[7] North of England includes: North East, North West, and Yorkshire & The Humber regions

[8] The Midlands includes: East Midlands, West Midlands and East of England regions

[9] South West Central includes: South West and South Central regions

H.Obj 1-T1_COPD_Ast

Demographic characteristics at baseline for COPD diagnosis group with a history of asthma, by index LABD cohort[1]

		COPD diagnosis group with a history of asthma (N=3,581)[2]							
		FF/VI 100 N= 452		FF/VI 200 N= 101		Other ICS/LABA N= 3,335		All N= 3,888	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Age (in years) at index date	mean (SD)	68.92	10.64	67.33	12.05	68.92	11.59	68.88	11.50
	≥80 years	82	18.14	11	10.89	640	19.19	733	18.85
	65-79 years	238	52.65	57	56.44	1,550	46.48	1,845	47.45
	45-64 years	124	27.43	33	32.67	1,061	31.81	1,214	31.22
	18-44 years	8	1.77			84	2.52	96	2.47
	0-17 years	0	0.00	0	0.00	0	0.00	0	0.00
Gender	female	252	55.75	55	54.46	1,817	54.48	2,124	54.63
	male	200	44.25	46	45.54	1,518	45.52	1,764	45.37
Smoking status	current smoker	159	35.18	32	31.68	1,093	32.78	1,284	33.03
	ex-smoker	235	51.99	54	53.47	1,654	49.61	1,943	49.99
	no/never smoker	58	12.83	15	14.85	587	17.61	660	16.98
	missing[4]	*0*	*0.00*	*0*	*0.00*	*1*	*0.03*	*1*	*0.03*
Body Mass Index (kg/m^2)	mean (SD)	28.94	6.41	29.38	6.41	28.18	6.44	28.30	6.44
	underweight <18.5	12	2.78	26	25.74	97	3.06	111	3.00
	normal 18.5-24.9	114	26.45			978	30.87	1,116	30.20
	overweight 25.0-29.9	142	32.95	31	32.29	1,044	32.95	1,217	32.94
	obese ≥30	163	37.82	39	40.63	1,049	33.11	1,251	33.86
	missing[4]	*21*	*4.65*	*5*	*4.95*	*167*	*5.01*	*193*	*4.96*
Concomitant prescribing at index date	Any	378	83.63	80	79.21	2,576	77.24	3,034	78.03
	SABD	312	69.03	67	66.34	2,204	66.09	2,583	66.44
	LAMA	226	50.00	43	42.57	1,371	41.11	1,640	42.18
	LABA/LAMA	<5	<1.11	0	0.00	6	0.18	9	0.23
	LABA	<5	<1.11	<5	<4.95	65	1.95	69	1.77
	ICS	13	2.88	<5	<4.95	144	4.32	160	4.12
	Theophylline	20	4.42	7	6.93	155	4.65	182	4.68
	Roflumilast	0	0.00	0	0.00	0	0.00	0	0.00
	LTRA	25	5.53	6	5.94	197	5.91	228	5.86
Patient level area based deprivation quintile[5]	Q1 (least deprived)	58	12.83	9	8.91	537	16.11	604	15.54
	Q2	74	16.37	13	12.87	640	19.20	727	18.70
	Q3	79	17.48	22	21.78	717	21.51	818	21.04
	Q4	119	26.33	20	19.80	691	20.73	830	21.35
	Q5 (most deprived)	122	26.99	37	36.63	749	22.47	908	23.36
	missing	*0*	*0.00*	*0*	*0.00*	*1*	*0.03*	*1*	*0.03*
Pratice level area based deprivation quintile[5]	Q1 (least deprived)	20	4.42	14	13.86	364	10.91	388	9.98
	Q2	61	13.50			746	22.37	817	21.01
	Q3	123	27.21	22	21.78	665	19.94	810	20.83
	Q4	125	27.65	28	27.72	694	20.81	847	21.78
	Q5 (most deprived)	123	27.21	37	36.63	866	25.97	1,026	26.39
Region (total number of practices contributing to CPRD; N= 545)[6]	North of England (N=124)[7]	99	21.90	25	24.75	865	25.94	989	25.44
	The Midlands (N=140)[8]	31	6.86	8	7.92	639	19.16	678	17.44
	London (N=97)	207	45.80	40	39.60	939	28.16	1,186	30.50
	South West Central (N=117)[9]	115	25.44	28	27.72	462	13.85	470	12.09
	South East Coast (N=67)					430	12.89	565	14.53

[1] This table is constructed using CPRD-HES

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Percentages were calculated seperately for those with missing and without missing data

[5] Area based deprivation is measured using patient or practive-level Index of Multiple Deprivation (IMD) quintile in CPRD

[6] The total number of practices contributing to CPRD within the region

[7] North of England includes: North East, North West, and Yorkshire & The Humber regions

[8] The Midlands includes: East Midlands, West Midlands and East of England regions

[9] South West Central includes: South West and South Central regions

H.Obj 1-T1_Asthma

Demographic characteristics at baseline for Asthma diagnosis group a, by index LABD cohort[1]

		Asthma diagnosis group (N=13,365)[2]							
		FF/VI 100 N= 404		FF/VI 200 N= 170		Other ICS/LABA N= 13,708		All N= 14,282	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Age (in years) at index date	mean (SD)	47.39	19.95	52.51	18.60	47.50	20.46	47.55	20.43
	≥80 years	19	4.70	11	6.47	728	5.31	758	5.31
	65-79 years	65	16.09	36	21.18	2,413	17.60	2,514	17.60
	45-64 years	146	36.14	69	40.59	4,751	34.66	4,966	34.77
	18-44 years	131	32.43	47	27.65	4,478	32.67	4,656	32.60
	0-17 years	43	10.64	7	4.12	1,338	9.76	1,388	9.72
Gender	female	274	67.82	115	67.65	8,397	61.26	8,786	61.52
	male	130	32.18	55	32.35	5,311	38.74	5,496	38.48
Smoking status	current smoker	82	20.45	22	12.94	2,598	19.60	2,702	19.54
	ex-smoker	108	26.93	49	28.82	3,339	25.19	3,496	25.28
	no/never smoker	211	52.62	99	58.24	7,319	55.21	7,629	55.17
	missing[4]	*3*	*0.74*	*0*	*0.00*	*452*	*3.30*	*455*	*3.19*
Body Mass Index (kg/m^2)	mean (SD)	30.04	7.07	30.60	6.53	29.39	6.85	29.43	6.86
	underweight and normal <24.9	82	25.79	30	20.55	2,939	27.58	3,051	27.44
	overweight 25.0-29.9	99	31.13	39	26.71	3,562	33.43	3,700	33.28
	obese ≥30	137	43.08	77	52.74	4,154	38.99	4,368	39.28
	missing[4]	*86*	*21.29*	*24*	*14.12*	*3,053*	*22.27*	*3,163*	*22.15*
Concomitant prescribing at index date	Any	217	53.71	100	58.82	7,047	51.41	7,364	51.56
	SABD	198	49.01	89	52.35	6,378	46.53	6,665	46.67
	LAMA	12	2.97	14	8.24	247	1.80	273	1.91
	LABA/LAMA	0	0.00	0	0.00	0	0.00	0	0.00
	LABA	<5	<1.24	<5	<2.94	124	0.90	129	0.90
	ICS	16	3.96	7	4.12	828	6.04	851	5.96
	Theophylline	<5	<1.24	<5	<2.94	117	0.85	125	0.88
	Roflumilast	0	0.00	0	0.00	0	0.00	0	0.00
	LTRA	37	9.16	26	15.29	1,092	7.97	1,155	8.09
Patient level area based deprivation quintile[5]	Q1 (least deprived)	59	14.60	36	21.18	3,091	22.55	3,186	22.31
	Q2	79	19.55	22	12.94	2,936	21.42	3,037	21.26
	Q3	91	22.52	35	20.59	2,786	20.32	2,912	20.39
	Q4	101	25.00	40	23.53	2,573	18.77	2,714	19.00
	Q5 (most deprived)	74	18.32	37	21.76	2,322	16.94	2,433	17.04
	missing[4]	*0*	*0.00*	*0*	*0.00*	*0*	*0.00*	*0*	*0.00*
Practice level area based deprivation quintile[5]	Q1 (least deprived)	24	5.94	17	10.00	2,169	15.82	2,210	15.47
	Q2	63	15.59	28	16.47	3,205	23.38	3,296	23.08
	Q3	66	16.34	37	21.76	2,370	17.29	2,473	17.32
	Q4	166	41.09	37	21.76	2,453	17.89	2,656	18.60
	Q5 (most deprived)	85	21.04	51	30.00	3,511	25.61	3,647	25.54
Region (total number of practices contributing to CPRD; N= 545)[6]	North of England (N=124)[7]	96	23.76	46	27.06	2,567	18.73	2,709	18.97
	The Midlands (N=140)[8]	25	6.19	20	11.76	3,095	22.58	3,140	21.99
	London (N=97)	198	49.01	53	31.18	4,224	30.81	4,475	31.33
	South West Central (N=117)[9]	11	2.72	51	30.00	1,579	11.52	1,592	11.15
	South East Coast (N=67)	74	18.32			2,243	16.36	2,366	16.57

[1] This table is constructed using CPRD-HES

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Percentages were calculated seperately for those with missing and without missing data

[5] Area based deprivation is measured using patient or practive-level Index of Multiple Deprivation (IMD) quintile in CPRD

[6] The total number of practices contributing to CPRD within the region

[7] North of England includes: North East, North West, and Yorkshire & The Humber regions

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[9] South West Central includes: South West and South Central regions

H.Obj 1 T2

COPD, Asthma and other disease burden at baseline and within year prior to index date, by index LABD cohort[1]

		All Patients (N=24,221)[2]							
		FF/VI 100 N= 1,347		FF/VI 200 N= 378		Other ICS/LABA N= 24,280		All N= 26,005	
		No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
COPD		900	66.82	190	50.26	7,822	32.22	8,912	34.27
COPD with history of asthma		452	50.22	101	53.16	3,335	42.64	3,888	43.63
COPD **without** history of asthma		448	49.78	89	46.84	4,487	57.36	5,024	56.37
Moderate COPD exacerbations (recorded in primary care only)	mean (SD)	1.37	1.56	1.53	1.62	1.14	1.40	1.18	1.42
	median (IQR)	1.00	0 - 2	1.00	0 - 2	1.00	0 - 2	1.00	0 - 2
	Rate per person year (95% CI)	1.37	(1.30, 1.45)	1.53	(1.37, 1.72)	1.14	(1.12, 1.17)	1.18	(1.15, 1.20)
	0 events	347	38.56	62	32.63	3,373	43.12	3,782	42.44
	1 event	225	25.00	51	26.84	2,139	27.35	2,415	27.10
	2+ events	328	36.44	77	40.53	2,310	29.53	2,715	30.46
Severe COPD exacerbations (recorded in secondary care)	mean (SD)	0.16	0.51	0.16	0.47	0.18	0.51	0.18	0.51
	median (IQR)	0.00	0 - 0	0.00	0 - 0	0.00	0 - 0	0.00	0 - 0
	Rate per person year (95% CI)	0.16	(0.14, 0.19)	0.16	(0.11, 0.23)	0.18	(0.17, 0.19)	0.18	(0.17, 0.19)
	0 events	793	88.11	166	87.37	6,715	85.85	7,674	86.11
	1 event	83	9.22	18	9.47	871	11.14	972	10.91
	2+ events	24	2.67	6	3.16	236	3.02	266	2.98
Moderate and Severe COPD exacerbations (recorded in primary and/or secondary care)	mean (SD)	1.43	1.59	1.58	1.66	1.23	1.43	1.26	1.46
	median (IQR)	1.00	0-2	1.00	0-2	1.00	0-2	1.00	0-2
	Rate per person year (95% CI)	1.43	(1.35, 1.51)	1.58	(1.41, 1.77)	1.26	(1.21, 1.26)	1.26	(1.24, 1.28)
	0 events	334	37.11	61	32.11	3,120	39.89	3,515	39.44
	1 event	232	24.78	52	27.37	2,186	27.95	2,470	27.72
	2+ events	334	37.11	77	40.53	2,516	32.17	2,927	32.84
FEV_1 percent predicted at baseline	mean (SD)	57.70	19.44	55.20	17.92	57.17	18.95	57.18	18.98
	mild, Grade 1 (≥80%)	91	12.01	16	10.06	738	11.91	845	23.36
	moderate, Grade 2 (≥50% to <80%)	396	52.24	81	50.94	3,142	50.72	3,619	48.09
	severe, Grade 3 (≥30% to <50%)	221	29.16	51	32.08	1,909	30.82	2,181	23.64
	very severe, Grade 4 (<30%)	50	6.60	11	6.92	406	6.55	467	4.91
	missing[4]	*142*	*15.78*	*31*	*16.32*	*1,627*	*20.80*	*1,800*	20.20
FEV_1/FVC ratio at baseline	mean (SD)	60.54	18.97	60.69	20.43	61.10	16.09	61.03	16.53
	<70%	541	78.86	101	71.13	4,059	72.75	4,701	73.37
	≥70%	145	21.14	41	28.87	1,520	27.25	1,706	26.63
	missing[4]	*214*	*23.78*	*48*	*25.26*	*2,243*	*28.68*	*2,505*	28.11
Dyspnoea (MRC Grade)	mean (SD)	2.82	0.99	2.80	1.10	2.70	1.00	2.72	1.00
	MRC Grade 1	58	7.65	15	10.14	563	10.02	636	9.75
	MRC Grade 2	250	32.98	51	34.46	2,010	35.78	2,311	35.43
	MRC Grade 3	252	33.25	40	27.03	1,784	31.76	2,076	31.83
	MRC Grade 4	167	22.03	32	21.62	1,065	18.96	1,264	19.38
	MRC Grade 5	31	4.09	10	6.76	195	3.47	236	3.62
	missing[4]	*142*	*15.78*	*42*	*22.11*	*2,205*	*28.19*	*2,389*	26.81
Asthma with no history of COPD		404	29.99	170	44.97	13,708	56.46	14,282	54.92
Moderate Asthma exacerbations (recorded in primary care only)	mean (SD)	0.11	0.38	0.17	0.49	0.08	0.31	0.09	0.32
	median (IQR)	0.00	0 - 0	0.00	0 - 0	0.00	0 - 0	0.00	0 - 0
	Rate per person year (95% CI)	0.11	(0.08, 0.15)	0.17	(0.12, 0.25)	0.08	(0.08, 0.09)	0.06	(0.05, 0.06)
	0 events	368	91.09	147	86.47	12,675	92.46	13,190	92.35
	1 event	30	7.43	23	13.53	939	6.85	988	6.92
	2+ events	6	1.49			94	0.69	104	0.73
Severe Asthma exacerbations (recorded in secondary care)	mean (SD)	0.01	0.09	0.01	0.15	0.01	0.14	0.01	0.14
	median (IQR)	0.00	0 - 0	0.00	0 - 0	0.00	0 - 0	0.00	0 - 0
	Rate per person year (95% CI)	0.01	(0.00, 0.01)	0.01	(0.00, 0.04)	0.01	(0.01, 0.01)	0.01	(0.01, 0.01)
	0 events	396	98.02	161	94.71	13,173	96.10	13,730	96.13
	1 event	8	1.98	9	5.29	465	3.39	479	3.35
	2+ events					70	0.51	73	0.51
Moderate and Severe Asthma exacerbations (recorded in primary and/or secondary care)	mean (SD)	0.13	0.42	0.27	0.94	0.13	0.45	0.13	0.46
	median (IQR)	0.00	0 - 0	0.00	0 - 0	0.00	0 - 0	0.00	0 - 0
	Rate per person year (95% CI)	0.13	(0.10, 0.17)	0.27	(0.20, 0.36)	0.13	(0.12, 0.13)	0.08	(0.08, 0.09)
	0 events	362	89.60	142	83.53	12,254	89.39	12,758	89.33
	1 event	33	8.17	21	12.35	1,263	9.21	1,317	9.22
	2+ events	9	2.23	7	4.12	191	1.39	207	1.45
Other (not COPD or Asthma)		43	3.19	18	4.76	2,750	11.33	2,811	10.81

[1] This table is constructed using CPRD-HES

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

[4] Percentages were calculated seperately for those with missing and without missing data

H.Obj 1-T3

Past history of comorbidities recorded in primary care, by index LABD cohort[1]

	All Patients (N=24,221)[2]							
	FF/VI 100 N= 1,347		FF/VI 200 N= 378		Other ICS/LABA N= 24,280		All N= 26,005	
	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]	No.[3]	(%)[3]
Cardio- and cerebrovascular disease (ever before)	744	55.23	187	49.47	10,776	44.38	11,707	45.02
Beta-blocker prescribing (in year prior to index date)	169	12.55	45	11.90	2,824	11.63	3,038	11.68
Pneumonia (ever before)	107	7.94	28	7.41	1,425	5.87	1,560	6.00
Gastroesophageal reflux disease (ever before)	308	22.87	99	26.19	5,063	20.85	5,470	21.03
Diabetes (ever before)	221	16.41	59	15.61	3,395	13.98	3,675	14.13
Acute and chronic renal disease (ever before)	254	18.86	56	14.81	2,872	11.83	3,182	12.24
Cancer (ever before)	165	12.25	33	8.73	2,130	8.77	2,328	8.95

[1] This table is constructed using CPRD-HES

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Unless otherwise specified

H.Obj 1-T4

COPD or asthma medication use in year prior to index date, by index LABD cohort[1]

		All Patients (N=24,221)[2]											
		FF/VI 100 N= 1,347			FF/VI 200 N= 378			Other ICS/LABA N= 24,280			All N= 26,005		
		No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%)of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions
SABD[3]	1+ prescription(s)[4]	1,175	87.23	8,345	336	88.89	2,428	20,065	82.64	111,460	21,576	82.97	122,233
	4+ prescriptions[4]	771	57.24		215	56.88		10,663	43.92		11,649	44.80	
ICS	Any ICS	1,019	75.65	6,970	304	80.42	2,084	16,790	69.15	89,705	18,113	69.65	98,759
	ICS (in a single device)	272	20.19	1,128	82	21.69	362	10,114	41.66	40,625	10,468	40.25	42,115
	ICS/LABA (in a single device)	799	59.32	5,842	253	66.93	1,722	7,742	31.89	49,080	8,794	33.82	56,644
LABA	Any	868	64.44	6,379	273	72.22	1,886	9,582	39.46	59,808	10,723	41.23	68,073
	LABA (in a single device)	84	6.24	487	28	7.41	143	2,117	8.72	10,656	2,229	8.57	11,286
	ICS/LABA (in a single device)	799	59.32	5,842	253	66.93	1,722	7,742	31.89	49,080	8,794	33.82	56,644
LAMA	Any	590	43.80	4,759	135	35.71	1,010	4,197	17.29	29,120	4,922	18.93	34,889
	LAMA (in a single device)	581	43.13	4,709	131	34.66	989	4,187	17.24	29,048	4,899	18.84	34,746
	LABA/LAMA (in a single device)	19	1.41	50	7	1.85	21	28	0.12	72	54	0.21	143
Theophylline (or derivatives)		57	4.23	565	20	5.29	135	455	1.87	4,191	532	2.05	4,891
OCS	Chronic use[5]	68	5.05		16	4.23		649	2.67		733	2.82	

[1] This table is constructed using CPRD-HES

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Includes the following asthma 'reliever' medications: SABA, SAMA, fixed combinations of SABA and cromoglycate, and fixed combinations of SABA and SAMA

[4] Categories are not mutually exclusive

[5] Defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days

NB: Roflimulast data were investigated but counts were very low (<5) so data are not presented
NB. This analysis does not attempt to identify open combinations of LABD, SABD, or ICS in separate devices.

H.Obj 1-T4_COPD

COPD or asthma medication use in year prior to index date, by index LABD cohort, in COPD diagnosis group[1]

		COPD diagnosis group (N=8,170)[2]											
		FF/VI 100 N= 900			FF/VI 200 N= 190			Other ICS/LABA N= 7,822			All N= 8,912		
		No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%)of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions
SABD[3]	1+ prescription(s)[4]	787	87.44	6,262	175	92.11	1,411	6,646	84.97	48,950	7,608	85.37	56,623
	4+ prescriptions[4]	569	63.22		118	62.11		4,374	55.92		5,061	56.79	
ICS	Any ICS	658	73.11	5,142	143	75.26	1,092	4,534	57.96	30,879	5,335	59.86	37,113
	ICS (in a single device)	106	11.78	482	30	15.79	130	1,845	23.59	9,038	1,981	22.23	9,650
	ICS/LABA (in a single device)	582	64.67	4,660	122	64.21	962	2,941	37.60	21,841	3,645	40.90	27,463
LABA	Any	635	70.56	5,096	134	70.53	1,042	3,721	47.57	27,353	4,490	50.38	33,491
	LABA (in a single device)	62	6.89	387	15	7.89	60	917	11.72	5,444	994	11.15	5,891
	ICS/LABA (in a single device)	582	64.67	4,660	122	64.21	962	2,941	37.60	21,841	3,645	40.90	27,463
LAMA	Any	567	63.00	4,671	117	61.58	914	3,773	48.24	27,002	4,457	50.01	32,587
	LAMA (in a single device)	559	62.11	4,622	114	60.00	894	3,765	48.13	26,934	4,438	49.80	32,450
	LABA/LAMA (in a single device)	18	2.00	49	6	3.16	20	26	0.33	68	50	0.56	137
Theophylline (or derivatives)		50	5.56	522	10	5.26	93	296	3.78	3,007	356	3.99	3,622
OCS	Chronic use[5]	58	6.44		13	6.84		407	5.20		478	5.36	

[1] This table is constructed using CPRD-HES

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Includes the following asthma 'reliever' medications: SABA, SAMA, fixed combinations of SABA and cromoglycate, and fixed combinations of SABA and SAMA

[4] Categories are not mutually exclusive

[5] Defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days

NB: Roflimulast data were investigated but counts were very low (<5) so data are not presented
NB. This analysis does not attempt to identify open combinations of LABD, SABD, or ICS in separate devices.

H.Obj 1-T4_Asthma

COPD or asthma medication use in year prior to index date, by index LABD cohort, in Asthma diagnosis group[1]

		Asthma diagnosis group (N=13,365)[2]											
		FF/VI 100 N= 404			FF/VI 200 N= 170			Other ICS/LABA N= 13,708			All N= 14,282		
		No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%)of patients with prescription(s)	Total no. prescriptions	No. of patients with prescription(s)	(%) of patients with prescription(s)	Total no. prescriptions
SABD[3]	1+ prescription(s)[4]	362	89.60	1,983	153	90.00	977	12,007	87.59	58,113	12,522	87.68	61,073
	4+ prescriptions[4]	193	47.77		94	55.29		5,939	43.33		6,226	43.59	
ICS	Any ICS	350	86.63	1,790	154	90.59	962	11,487	83.80	56,400	11,991	83.96	59,152
	ICS (in a single device)	160	39.60	626	51	30.00	222	7,662	55.89	29,946	7,873	55.13	30,794
	ICS/LABA (in a single device)	212	52.48	1,164	125	73.53	740	4,602	33.57	26,454	4,939	34.58	28,358
LABA	Any	228	56.44	1,265	133	78.24	824	5,630	41.07	31,549	5,991	41.95	33,638
	LABA (in a single device)	22	5.45	100	13	7.65	83	1,164	8.49	5,091	1,199	8.40	5,274
	ICS/LABA (in a single device)	212	52.48	1,164	125	73.53	740	4,602	33.57	26,454	4,939	34.58	28,358
LAMA	Any	19	4.70	83	16	9.41	87	274	2.00	1,455	309	2.16	1,625
	LAMA (in a single device)	18	4.46	82	15	8.82	86	272	1.98	1,451	305	2.14	1,619
Theophylline (or derivatives)		6	1.49	42	10	5.88	42	155	1.13	1,179	171	1.20	1,263
OCS	Chronic use[5]	9	2.23		3	1.76		189	1.38		201	1.41	

[1] This table is constructed using CPRD-HES

[2] Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number of All records

[3] Includes the following asthma 'reliever' medications: SABA, SAMA, fixed combinations of SABA and cromoglycate, and fixed combinations of SABA and SAMA

[4] Categories are not mutually exclusive

[5] Defined as at least four prescription records with a maximum gap between two prescriptions equal to 30 days

NB: Roflimulast and LABA/LAMA data were investigated but counts were very low (<5) so data are not presented
NB. This analysis does not attempt to identify open combinations of LABD, SABD, or ICS in separate devices.

Medicines & Healthcare products Regulatory Agency

CPRD More Dimensions to Data

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

Statistical Analysis Plan

Subject: 205052: Drug Utilisation Study, Post-authorisation Safety Study, Chronic Obstructive Pulmonary Disease, asthma, Electronic Medical Records, Inhaled Corticosteroids, Long-Acting Beta-2-Agonists

Investigators: PPD [CPRD], PPD [CPRD], PPD [CPRD], PPD [GSK], PPD [GSK]

Author: PPD [CPRD]; PPD [CPRD]

Reviewers: PPD [CPRD]

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Document control sheet

Version	Summary and rationale of change(s)	Prepared by	Date	Reviewed by	Date
0.1	First draft	PPD PPD	18 Dec 2016		
0.2	Incorporate comments from SL	PPD	15 February 2017		
0.3	Update table shells and text after SSC UMEC meeting	PPD	6 June 2017		
0.4	Final update after asthma exacerbation, ICS dose coding and final review with report submission	PPD	13th September	PPD & PPD	13th September

Table of contents

Scope

This statistical analysis plan (SAP) provides a detailed description of the statistical analyses planned for the delivery of the client's (GSK's) project. Section 1 lists the objectives of the project, section 2 outlines the data sources that will be used for the analyses, and sections 3 to 5 provide details of the study period, population, and variable definitions. Section 6 gives details of the proposed statistical analysis. Finally, examples of tables for reporting the results of this study are provided in Annex 4.

1. Study details

Aims and rationale

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.

Objectives

In the initial post-approval period of 24 months from the start of FF/VI availability in the UK, we will identify patients newly prescribed either FF/VI or other ICS/LABA FDC in the CPRD GOLD UK primary care database and conduct a drug utilization review focusing on the following aims:

Objective 1) separately among new users of FF/VI, and new users of 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:

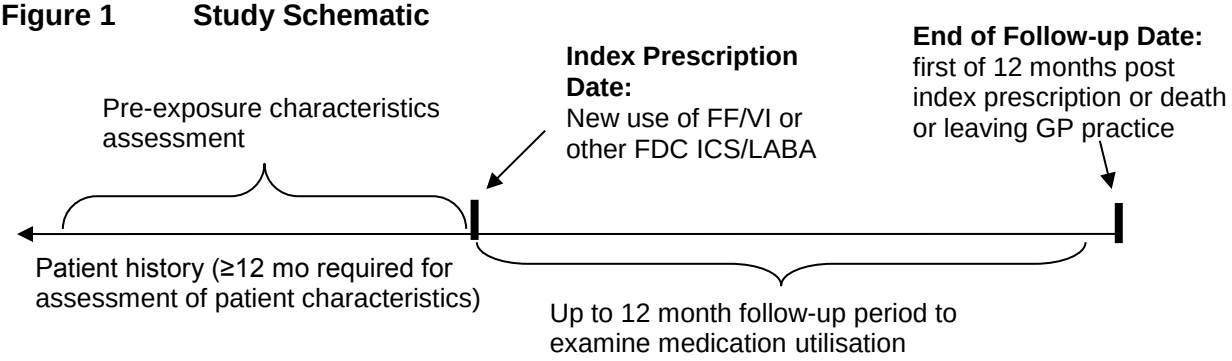
- FF/VI 200/25 formulation in patients with a COPD diagnosis (as only the FF/VI 100/25 formulation is licensed for patients with COPD), and;
- FF/VI (any dose) in children <12 years of age (as neither formulation of FF/VI is licensed for use in children <12 years of age);

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).

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 (corresponding to the period of 24 months from the start of FF/VI availability in the UK). A cross-sectional assessment of demographic and clinical characteristics of new users of FF/VI and other ICS/LABA 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. The study schematic is provided in Figure 1.

Figure 1 Study Schematic



2. Data sources

The study will primarily use data from the Clinical Practice Research Datalink primary care database (referred to hereafter as CPRD-GOLD).

CPRD-GOLD comprises the computerised medical records from general practitioners (GPs) who record information using Vision GP software. General practitioners play a key role in the UK health care system, as they are responsible for primary health care and specialist referrals. Individuals are semi-permanently affiliated to a practice, which centralises the medical information from the GPs, specialist referrals and hospitalisations. The data recorded include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes. The CPRD-GOLD database currently includes 14.3 million individuals (with acceptable quality medical records) from 1987 onwards, of which data are currently being collected on 3.1 million. The CPRD-GOLD database is an open cohort where patients can join and leave at any time. Data dictionaries for CPRD-GOLD are available in Annex 1.

For Objective 1, additional analyses will be undertaken on a subset of the CPRD-GOLD database which has been linked to Hospital Episode Statistics (HES). The linked HES data will be used to help ascertain and delineate between moderate and severe COPD and asthma exacerbations.

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. These data are collected during a patient's time primarily for administrative reasons, but the data collection 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). This study will use inpatient admissions data only from the CPRD's 'Basic' version of HES. Additional information on Basic HES is available in Annex 1.

Linkage of CPRD-GOLD data to HES is only possible for a subset of patients registered at English practices which participate in the linkage scheme. The linkage is performed by a trusted third party (NHS Digital, formerly the Health and Social Care Information Centre, HSCIC) on a quarterly basis, based on a stepwise algorithm of 8 matching-steps using a combination of NHS number, date of birth, gender, and postcode. Only records matched based on a combination of NHS number and at least one other variable will be considered as valid and successful linkages in this study (corresponding with matching-steps 1 to 5).

The following versions of CPRD-GOLD and Basic HES will be used:

Table 1: CPRD-GOLD and Basic HES versions

Data source	Version	Coverage period
CPRD-GOLD	May 2017	01/01/1987 –31/05/2017
Basic HES	Linkage set 13	01/04/1997 –28/02/2016.

3. Source populations

CPRD-GOLD source population

For the primary analysis, the source population will include all research-quality, acceptable[1] [accept=1], male [gender=1] and female [gender=2] patients in the version of CPRD-GOLD specified in section 2. Registration start and end will be defined for all patients in the source population as follows:

- Registration start [regstart] will be equal to the patient's current registration date [crd].
- Registration end [regend] will be equal to the earliest of a patient's transfer out date [todate], the patient's CPRD-GOLD derived date of death[2] [deathdate] and the practice's last collection date [lcd].

For analyses requiring linked inpatient HES data, the source population will be further restricted to patients who are eligible for linkage to HES. These are patients who:

- are registered in practices contributing to the linkage scheme;
- had a valid NHS number when their identifiers were sent to CPRD's trusted third party (NHS Digital) for linkage; and,
- have not dissented from data transfer to NHS Digital.

Patients eligible for linkage will be identified using the HES eligibility flags (hes_e) in the linkage_eligibility.txt file. Additional registration start [regstart_link] and registration end [regend_link] variables will be created for patients eligible for linkage. These new variables may or may not be the same as the [regstart] and [regend] variables defined earlier. This is because registration time for patients in this restricted source population will additionally incorporate (and censor on) the start and end dates for the CPRD-HES coverage periods. Registration start and end will be defined as follows.

- Registration Start [regstart_link] will be equal to the latest of a patient's current registration date [crd], or the start of CPRD-HES coverage.

[1] Definition provided in Annex 2.

[2] Definition provided in Annex 2.

- Registration End [regend_link] will be equal to the earliest of a patient's transfer out date [todate], CPRD-GOLD derived death date [deathdate], and the end of Basic HES coverage.

4. Study populations

Two main study populations will be identified:

- a CPRD-GOLD cohort;
- a cohort consisting of a subset of CPRD-GOLD cohort of patients eligible for linkage to HES (and patient level IMD). This will be referred to subsequently as the CPRD-HES cohort.

These cohorts will include all patients in the CPRD-GOLD source population that meet the inclusion and exclusion criteria below.

Inclusion criteria

Patients with:

- a record of a new prescription of FF/VI or other ICS/LABA FDC during the inclusion period (January 1, 2014 through December 31, 2015). This will be the index prescription.
- at least one year of practice up-to-standard (UTS)[3] recorded data prior to first (index) prescription in the inclusion period to allow characterisation of patient's status, demographics and clinical characteristics (i.e. between [regstart] and [indexdate]).

Exclusion criteria

Patients will be excluded if they:

- have a prescription for the same specific inclusion medication prior to the index prescription. Prior use of another ICS/LABA FDC product will be permitted. All available data prior to the index date will be used to ascertain new use of FF/VI and other ICS/LABA FDC.)

[3] Definition provided in Annex 2.

Table 2: Specific ICS/LABA fixed dose combination (FDC) medications eligible for inclusion

Qualifying index medication group	Generic names	Brand names	CPRD code list reference
FF/VI	fluticasone furoate + vilanterol	Relvar	pc-28
Other ICS/LABA FDC	fluticasone + salmeterol	Seretide / AirFluSal Forspiro	pc-20
	budesonide + formoterol	Symbicort/ Duoresp Spiromax	pc-7
	beclometasone + formoterol	Fostair	pc-6
	fluticasone + formoterol	Flutiform	pc-8

*See Annex 3 for full code lists

Study follow-up

All patients will be followed from their index prescription date until their censoring date [censordate] which is the earliest of the patients registration end [regend] and 365 days after the index date [indexdate]. For patients in the CPRD-HES cohort, follow-up will continue until the earliest of [regend_link] and 365 days after the index date [indexdate].

Data extraction processes

Data will be extracted as tab delimited text files using the version specified in section 2 of this SAP. Full prescribing records for all possible ICS/LABA FDC medications will be extracted initially, along with relevant registration details. These will be used to apply inclusion and exclusion criteria, after which full records will be extracted for the CPRD-GOLD cohort, including Basic HES inpatient records for the CPRD-HES cohort.

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5. Variables and definitions

Exposures

Timings will be based on the prescription event date variables in CPRD [eventdate]. All prescriptions for ICS/LABA will be given a default length of 30 days per container prescribed, irrespective of whether the prescription has a recorded value for script length.

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. A new variable [index_order] will be created to differentiate between multiple records for the same patient. Patients with multiple qualifying index medications will be considered as separate individuals in the analyses, and baseline characteristics will be derived separately at each cohort entry date.

The terms ‘baseline’ and ‘at cohort entry’ are used interchangeably in this SAP, and unless specified otherwise, refer to a patient’s medical history up to (and sometimes including) the index date.

Table 3: New users of FF/VI and other ICS/LABA fixed dose combinations

Description	Name	Type	Values	Definition and timing	CPRD source & code list number
Index order	index_order	Incrementing integer (never missing)	1 = first index event 2= second index event 3 = third index event	Chronological order of index event for patients with more than one event. All patients will have a record with index_order=1	[prodcode] and [eventdate] using therapy file and code list pc-28
Index medication group	index_cat1	categorical *(never missing)*	1 = FF/VI; 2 = Other ICS/LABA;	Category of qualifying index medication.	[prodcode] using therapy file and code lists pc28, pc6, pc7, pc8 & pc20)
Patient contributing to multiple index medication groups	index_mult	count (never missing)	≥1	Number of times a patient qualifies for separate index medication between 01 Jan 2014 and 31 Dec 2016.	derived: maximum of [index_order] for each patid
Index medication dose group	index_cat2	categorical	1 = FF/VI 100/25; 2 = FF/VI 200/25; missing if index_cat1=2	Dose category for index FF/VI prescription	[prodcode] using therapy file and code list pc28
Index medication dose group	index_cat3	categorical (never missing)	1 = FF/VI 100/25; 2 = FF/VI 200/25; 3 = Other ICS/LABA;	Category of qualifying index medication and dose category for FF/VI prescription.	[prodcode] using therapy file and code lists pc28, pc6, pc7, pc8 & pc20)
Index date	indexdate	date *(never missing)*	date	First prescription for the qualifying index medication within 1 Jan 2014 and 31 Dec 2015.	[prodcode] and [eventdate] using therapy file and code list pc28
Total prescriptions for FF/VI during follow up	any_count	integer *(never missing if index_cat1=1)*	count of prescriptions for FF/VI 100/25 and FF/VI 200/25	Between [indexdate] and [censordate] inclusive.	[prodcode] using therapy file and code list pc28
	ffvi_count_lo	integer *(never missing if index_cat1=1)*	count of prescriptions for FF/VI 100/25	Between [indexdate] and [censordate] inclusive.	[prodcode] using therapy file and code list pc28
	ffvi_count_hi	integer *(never missing if index_cat1=1)*	count of prescriptions for FF/VI 200/25	Between [indexdate] and [censordate] inclusive.	[prodcode] using therapy file and code list pc28
	ffvi_count_under	integer	count of prescriptions for	Between [indexdate] and	[prodcode], [eventdate], [yob]

Description	Name	Type	Values	Definition and timing	CPRD source & code list number
	12	*(never missing if index_cat1=1)*	FF/VI when age <12y	[censordate] inclusive.	+1800 from patient file
Age in years at index date	age_index	numerical (integer) *(never missing)*	≥0 and ≤115	year of index date [index_y] – year of birth [yob]	[yob] +1800 from patient file
	age_index2	numerical (integer) *(never missing)*	≥11 and ≤12	age in years and months (for patients aged 11-12)	
	age_index_cat	categorical *(never missing)*	0 = 0 to 5 years; 1 = 6 to 11 years; 2 = 12 to 17 years; 3 = 18 to 44 years; 4 = 45 to 64 years; 5 = 65 to 79 years; 6 = 80 to 115 years.		
Censoring date	censordate	date *(never missing)*	date	Earliest of patient transfer out date, CPRD deathdate, practice last collection date, and [index date + 365]	[todate] and [deathdate] in patient file; [lcd] in practice file; [indexdate]
Reason for censoring	censor_cat	categorical *(never missing)*	1 = death; 2 = transferred out (of GP practice); 3 = practice last collection date 4 = end of follow-up at 365 days after index date	Reason for censoring. If multiple records on one day, priority is given as follows: death, leaving practice, last collection date, end of follow-up	[todate] and [deathdate] in patient file; [lcd] in practice file; [indexdate]
Censored 31 to 90 days after last prescription for FF/VI	censor_flag	binary (not missing if index_cat=1)	0 = no; 1 = yes; . = missing	Last prescription (in patients not meeting definition of discontinuation) is between 31-90 days before censoring.	derived [censordate] variable and date associated with [prodcode] code list pc28
Date of discontinuation of the index medication	disdate	date	date; . = missing	30 days after date of last prescription before a break of ≥91 days.	[eventdate] from therapy file; and code lists pc28, pc6, pc7, pc8 & pc20
Gap (in days) between index	index_gap	count	≥0; . = missing	Number days between index date of new qualifying	derived [indexdate], [index_mult], [disdate_N] and

Description	Name	Type	Values	Definition and timing	CPRD source & code list number
medications				medication and discontinuation date for old qualifying medication, in patients who qualify for more than one medication and where last prescription date is before new index date.	[patid] variables
Overlap (in days) between index medications	index_over	count	≥0; . = missing	Number days between discontinuation date for old qualifying medication and index date for new qualifying medication, in patients who qualify for more than one medication and where the discontinuation date is on or after the new index date.	derived [indexdate], [index_mult] , [disdate_N] and [patid] variables

Table 4: Concomitant medication code lists

CPRD code list reference	Code List Name
pc-2	Beta-blockers
pc-3	Antibiotics
pc-11	ICS
pc-12	ICS/SABA
pc-14	OCS
pc-16	Roflumilast
pc-17	SABA
pc-23	Theophylline
pc-30	LAMA
pc-31	LABA
pc-32	LABA/LAMA
pc-33	ICS/LABA
pc-40	SABD
pc-44	LTRA
pc-45	ICS/LABA (excluding RELVAR)
ICS_dose	ICS, ICS/LABA, and ICS/SABA for dosage in year prior to index date
exposure_list	Combined ICS/LABA (including RELVAR)

*See Annex 3 for full code lists

Table 5: Concomitant use of other medications at index date

Description	Name	Type	Values	Definition and timing	CPRD source
Concomitant use of other specified respiratory medication at index date	sabd_con	binary *(never missing)*	0 = no; 1 = yes	Two or more prescriptions which start no later than 30 days after [indexdate], and overlap for ≥30 days with the index treatment.	[prodcode] using therapy file and code list pc-40
	lama_con	binary *(never missing)*	0 = no; 1 = yes;	Two or more prescriptions which start no later than 30 days after [indexdate], and overlap for ≥30 days with the index treatment.	[prodcode] using therapy file and code list pc-30
	theoph_con	binary *(never missing)*	0 = no; 1 = yes	Two or more prescriptions which start no later than 30 days after [indexdate], and overlap for ≥30 days with the index treatment.	[prodcode] using therapy file and code list pc-23
	rofl_con	binary *(never missing)*	0 = no; 1 = yes	Two or more prescriptions which start no later than 30 days after [indexdate], and overlap for ≥30 days with the index treatment.	[prodcode] using therapy file and code list pc-16
	ltra_con	binary *(never missing)*	0 = no; 1 = yes	Two or more prescriptions which start no later than 30 days after [indexdate], and overlap for ≥30 days with the index treatment.	[prodcode] using therapy file and code list pc-44
Concomitant use of ANY specified respiratory medication at index date	any_con	binary *(never missing)*	0 = no; 1 = yes	=0 if all variables above =0 or missing =1 if any of variables above =1	Derived: using all class specific variables above i.e. [sabd-con] to [anyics_con]

Outcomes

Objective 1: Baseline characteristics of New Users of FF/VI or Other ICS/LABA FDC

The following variables will be used to describe new users of FF/VI and new users of other ICS/LABA FDC in respect to patient demographics, co-morbidity, disease burden, and COPD or asthma medication use. Unless otherwise specified, timings will be based on the event date [eventdate] variables in CPRD.

Acute exacerbation of COPD (AECOPD)

- AECOPD were calculated only for COPD patients (regardless of their asthma history) and were identified in the 12 months prior to the index date using a validated algorithm developed by Dr. PPD from Imperial College London [Rothnie, 2016].], with further refinements implemented by GSK.

- It was not possible to delineate exacerbation type (moderate versus severe) using GP data alone. However, in the subset of patients with the HES link, severe exacerbations were also able to be defined and thus both further defined as moderate (treated with OCS and/or antibiotics) and severe (hospitalised) are presented.

- Exacerbations were described as the rate per person year, and as a count of 0, 1 and 2+ events.

Acute exacerbations of Asthma:

Asthma exacerbations were calculated only for the subgroup of patients who met the criteria for asthma. Asthma exacerbations were identified in the 12 months prior to index date.

An asthma exacerbation was defined as either:

1) asthma related accident and emergency (A&E) department visit or an asthma related hospitalisation in the HES data, or
2) any OCS use.

Exacerbations were described as the rate per person year, and as a count of 0, 1 and 2+ events

Full details of both exacerbation algorithms are included in Annex 4. These includes all code lists. Read code lists have been developed using CPRD-GOLD.

Table 6: Baseline characteristics code lists

CPRD code list reference	Code List Name
mc-1	Airways exacerbations
mc-2	Asthma
mc-3	Breathlessness
mc-4	Cancer
mc-5	Cardio- and cerebro-vascular disease
mc-7	COPD
mc-8	Cough
mc-9	Diabetes
mc-10	Dyspnoea
mc-11	Gastroesophageal reflux disease
mc-12	Lower Respiratory tract infection
mc-14	Pneumonia
mc-15	Acute or chronic renal disease
mc-16	Smoking
mc-17	Sputum
mc-50	Asthma diagnosis for exacerbations
mc-51	Asthma attack
mc-GSK	COPD annual review, OCS & antibiotic rescue packs
ICD4	Asthma diagnosis

*See Annex 3 for full code lists

Table 7: Demographic variables

Unless indicated otherwise, all the variables below will be defined using primary care data only.

Description	Name	Type	Values	Definition and timing	CPRD sources
Gender	gender	categorical *(never missing)*	1= male; 2 = female		[gender] in patient file
Smoking status at cohort entry	smoking	categorical	0 = no/never smoke; 1 = ex-smoker; 2 = (current) smoker; . = missing	Smoking status record that is most proximal to index date [indexdate] and that is on or after the start of registration (≥[regstart]) up to within 90 days of the index date (≤ [indexdate]+90). When duplicate records on the same day differ, '(current) smoker' will be chosen over 'ex-smoker', which will be chosen over 'no/never smoker'.	[medcode] and [status] from code list mc-16 code list in clinical or referral files and/or status described in additional clinical details file (entity type 4)
BMI at cohort entry in kg/m^2	bmi	numerical	≥10 and ≤70; . = missing	valid BMI (10-70 kg/m^2) record that is most proximal to index date [indexdate] and which is on or after the start of registration (≥[regstart]) up to within 90 days of the index date (≤ [indexdate]+90)	calculated from most recent valid height (1.2-2.2m) recorded after age 18 years from [data1] with [enttype]=13 in additional file and valid weight (25-450kg) from [data1] from [enttype]=14 in additional file
	bmi_cat	categorical	0 = underweight (≥10 and <18.5); 1 = normal (≥18.5 and <25); 2 = overweight (≥25 and <30); 3 = obese (≥30 and <70); . = missing		
Area based deprivation: IMD quintile	imd_prac	categorical	1 = Q1 (least deprived); 2 = Q2; 3 = Q3; 4 = Q4; 5 = Q5 (most deprived); . = missing	Based on current *practice* postcode: quintile of most recently available respective national IMD classification.	CPRD derived variables: [e2015_imd_5]; [ni2010_imd_5]; [s2012_imd_5]; [w2014_imd_5]
	imd2015_pat	categorical	1 = Q1 (least deprived); 2 = Q2; 3 = Q3; 4 = Q4; 5 = Q5 (most deprived); . = missing	Based on current *patient* postcode: quintile of English IMD 2015 score.	CPRD derived variable: [imd2015_5] Available for subset of patients registered with English practices, and eligible for postcode linkage.

Description	Name	Type	Values	Definition and timing	CPRD sources
Region	region	categorical	1 North East 2 North West 3 Yorkshire & The Humber 4 East Midlands 5 West Midlands 6 East of England 7 South West 8 South Central 9 London 10 South East Coast 11 Northern Ireland 12 Scotland 13 Wales	The Strategic Health Authority for practice postcode within England, and the country i.e. Wales, Scotland, or Northern Ireland for the rest	[region] from CPRD patient file

Table 8: Diagnosis group

Unless indicated otherwise, all the variables below will be defined using primary care data.

Description	Name	Type	Values	Definition and timing	CPRD source
Date of first COPD record (at any age)	d_copd	date	date; . = missing	date of earliest record of COPD between registration start (≥[regstart]) and the censor date (≤[censordate])	[eventdate] associated with [medcode] from code list mc-7 in clinical and referral files
	age_copd	date	integer; . = missing	age in years at earliest record of COPD up to and including censor date (≤[censordate])	derived [d_copd] variable and [yob] in patient file
Chronic obstructive pulmonary disease (COPD)	copd	binary *(never missing)*	0 = no; 1 = yes	patient is age ≥35 at time of earliest record of COPD [d_copd] between registration start (≥[regstart]) and the censor date (≤[censordate])	derived from [d_copd] and [age_copd]
	copd_sens	binary *(never missing)*	0 = no; 1 = yes	patient is age ≥35 at time of earliest record of COPD [d_copd] between registration start (≥[regstart]) and the index date (≤[indexdate])	derived from [d_copd] and [age_copd]
COPD with history of asthma	copd_asthma	binary	0 = no; 1 = yes . = missing (if [copd] = missing)	patient meets COPD definition AND has [d_asthma] ≤[indexdate]	derived from [copd], [d_asthma], [indexdate].
	copd_asthma_sens	binary	0 = no; 1 = yes . = missing (if [copd_sens] = missing)	patient meets COPD sensitivity analysis definition AND has [d_asthma] ≤ [index date]	derived from [copd_sens], [d_asthma], [indexdate].
Date of first asthma record (in patients meeting asthma definition)	d_asthma	date	date; . = missing	date of earliest record of asthma between registration start (≥[regstart]) and the censor date (≤[censordate]) in patients with asthma ([asthma=1])	[eventdate] associated with medcode from code list mc-2 variable in clinical and referral files
Asthma (not COPD)	asthma	binary *(never missing)*	0 = no; 1 = yes	not classified as COPD ([copd]=0) AND asthma diagnosis prior to censor date ([d_asthma] < [censordate])	derived: [d_asthma], [copd], [censordate]
	asthma_sens	binary	0 = no;	not classified as COPD using	derived: [d_asthma],

Description	Name	Type	Values	Definition and timing	CPRD source
		(never missing)	1 = yes	sensitivity definition ([copd_sens] =0) AND asthma diagnosis on or prior to index date ([d_asthma] ≤ [indexdate])	[copd_sens], [indexdate]
Other (not COPD, not asthma)	other	binary *(never missing)*	0 = no; 1 = yes	not classified as COPD ([copd]=0) AND not classified as asthma ([asthma]=0)	derived: [copd]; [asthma]
	other_sens	binary *(never missing)*	0 = no; 1 = yes	not classified as COPD using sensitivity definition ([copd_sens] =0) AND not classified as asthma using sensitivity definition ([asthma_sens] =0)	derived [copd_sens] variable and derived [asthma_sens] variable
Respiratory codes in other diagnosis group			*missing if [other]=0*	Other patients only: All respiratory codes in 12 months prior to index date in patients classified as other	Derived: [other]
			missing if [other]=0	Other patients only: All respiratory codes closest to index date in patients classified as other	Derived: [other]

Table 9: Disease burden variables

Unless indicated otherwise, all the variables below will be defined using primary care data.

Description	Name	Type	Values	Definition and timing	CPRD source
Number of **moderate** COPD exacerbations at baseline (as recorded in primary care)	aecopd_base	count; *missing if [copd]=0*	≥0; . = missing	Number of acute exacerbations of COPD (recorded in primary care) in year prior to (and including) the index date (within previous year (≥ [indexdate]-365)	*See Annex 4 for definition of acute exacerbation of COPD using primary care data.*
	aecopd_base_cat	categorical; *missing if [copd]=0*	0 = none; 1 = one; 2 = two or more		
Number of **severe** COPD exacerbations at baseline (as recorded in secondary care)	aecopd_base_hes	count; *missing if [copd]=0*	≥0; . = missing	Number of acute exacerbations of COPD (recorded in HES) in year prior to (and including) the index date (within previous year (≥ [indexdate]-365)	*See Annex 4 for definition of acute exacerbation of COPD using secondary care (HES) data.*
Number of **moderate or severe** COPD exacerbations at baseline (as recorded in primary and/or secondary care)	aecopd_base_hesgold	count; *missing if [copd]=0*	≥0; . = missing	Number of acute exacerbations of COPD (recorded in primary care and/or HES) in year prior to (and including) the index date (within previous year (≥ [indexdate]-365)	*See Annex 4 for definitions of acute exacerbation of COPD using primary and secondary care (HES) data.*
	aecopd_base_hesgold_cat	categorical *missing if [copd]=0*	0 = none; 1 = one; 2 = two or more; . = missing		
COPD severity at baseline	fev1	numerical; *missing if [copd]=0*	≥0 and ≤100; . = missing	Forced expiratory volume in 1 second, percent predicted, as recorded on index date [indexdate] or closest record to index date within previous 2 years (≥ [indexdate]-730) Exclude people over 95	[data2] associated with [enttype]=394 if units in percent ([data3=1] in additional file. Results in litres will be converted to % predicted based on last recorded height using the GSK CHESS algorithm provided in Annex 4.
	fev1_cat	categorical; *missing if [copd]=0*	1 = mild Grade 1 (≥80%); 2 = moderate Grade 2 (≥50% and <80%); 3 = severe Grade 3 (≥30% and <50); 4 = very severe Grade 4 (≤0 and <30); . = missing		
	fev1_imputed	categorical; missing if	0 = not imputed; 1 = imputed	flag to indicate that FEV1 % expected has been imputed	[fev1], [gender],

Description	Name	Type	Values	Definition and timing	CPRD source
		fev1 is missing		from FEV1 (in litres) plus height, age and gender	
	fev1_fvc	numerical; *missing if [copd]=0*	≥0 and ≤100; . = missing	FEV1/FVC ratio as recorded on index date [indexdate] or closest record to index date within previous 2 years (≥ [indexdate]-730	[data2] associated with [enttype]=395 if units in percent ([data3=1] in additional file
	fev1_fvc_cat	categorical; *missing if [copd]=0*	0 = ≥70%; 1 = <70%; . = missing		
Number of **moderate** asthma exacerbations at baseline (as recorded in primary care)	aeasthma_base	count; *missing if [asthma]=0*	≥0	Asthma patients only: acute exacerbations of asthma identified in primary care data in year up to and including the index date (≥ [indexdate]-365)	*See Annex 4 for definition of acute exacerbation of asthma using primary care data.*
	aeasthma_base_cat	categorical; *missing if [asthma]=0*	0 = none; 1 = one; 2 = two or more		
Number of **severe** asthma exacerbations at baseline (as recorded in secondary care)	aeasthma_base_hes	count; *missing if [asthma]=0*	≥0	Asthma patients only: acute exacerbations of asthma identified in secondary care (HES) data in year up to and including the index date (≥ [indexdate]-365)	*See Annex 4 for definition of acute exacerbation of asthma using secondary care (HES) data.*
Number of **moderate or severe** asthma exacerbations at baseline (as recorded in primary and/or secondary care)	aeasthma_base_hesgold	count; *missing if [asthma]=0*	≥0; . = missing	Asthma patients only: acute exacerbations of asthma identified in primary care or HES data in year up to and including the index date (≥ [indexdate]-365)	*See Annex 4 for definitions of acute exacerbation of asthma using primary and secondary care (HES) data.*
	aeasthma_base_hesgold_cat	categorical; *missing if [asthma]=0*	0 = none; 1 = one; 2 = two or more		

Table 10: Comorbidity variables

Unless indicated otherwise, all the variables below will be defined using primary care data only.

Description	Name	Type	Values	Definition and timing	CPRD source
Beta-blocker prescribing in year prior to index date	beta_blocker_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in the 12 months prior to and including the index date (i.e. ≥ [indexdate]-365 and ≤[indexdate])	[prodcode] in pc-2 code list in therapy file
Cardio- and cerebro-vascular disease ever before	cardio_cvd	binary *(never missing)*	0 = no; 1 = yes	Recorded at any time prior to and including the index date (i.e. [eventdate] ≤ [indexdate])	[eventdate]; [medcode] in mc-5 code list in clinical or referral files
Pneumonia disease ever before	pneumonia_base	binary *(never missing)*	0 = no; 1 = yes	Recorded at any time prior to and including the index date (i.e. [eventdate] ≤ [indexdate])	[eventdate] ;[medcode] in mc-14 code list in clinical or referral files
Gastroesophageal reflux disease ever before	gord	binary *(never missing)*	0 = no; 1 = yes	Recorded at any time prior to and including the index date (i.e. [eventdate] ≤ [indexdate])	[eventdate]; [medcode] in mc-11 code list in clinical or referral files
Diabetes ever before	diabetes	binary *(never missing)*	0 = no; 1 = yes	Recorded at any time prior to and including the index date (i.e. [eventdate] ≤ [indexdate])	[eventdate]; [medcode] in mc-9 in code list n clinical or referral files
Acute or chronic renal disease ever before	renal	binary *(never missing)*	0 = no; 1 = yes	Recorded at any time prior to and including the index date (i.e. [eventdate] ≤ [indexdate])	[eventdate]; [medcode] in mc-15 code list in clinical or referral files
Cancer (excluding non-melanoma skin cancer) ever before	cancer	binary *(never missing)*	0 = no; 1 = yes	Recorded at any time prior to and including the index date (i.e. [eventdate] ≤ [indexdate])	[eventdate]; [medcode] in mc-4 code list in clinical or referral files

Table 11: Prior use of COPD or asthma medication

Unless indicated otherwise, all the variables below will be defined using primary care data.

Description	Name	Type	Values	Definition and timing	CPRD source
Short-acting bronchodilators (SABD*), in year prior to index date	sabd_base1	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (0 ≤ [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from pc-40 code list in therapy file
	n_sabd_base	count	≥0;	Number of prescriptions issued during the 12 months prior to (and not including) index date (0 ≤ [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from pc-40 code list in therapy file
	sabd_base4	binary *(never missing)*	0 = no; 1 = yes	At least four records in the 12 months prior to (and not including) index date (0 ≤ [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from pc-40 code list in therapy file
Inhaled corticosteroids (ICS) in year prior to index date	ics_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (0 ≤ [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-11* code list in therapy file
	n_ics_base	count	≥0;	Number of prescriptions issued during the 12 months prior to (and not including) index date (0 ≤ [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-11* code list in therapy file
ICS/SABA in a single device, in year prior to index date	icssaba_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (0 ≤	[eventdate]; [prodcode] from *pc-12* code list in therapy file

Description	Name	Type	Values	Definition and timing	CPRD source
				[indexdate]-[eventdate] ≤ 365)	
	n_icssaba_base	count	≥0;	Number of prescriptions issued during the 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-12* code list in therapy file
Long-acting beta agonist (LABA) in year prior to index date	laba_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-31* code list in therapy file
	n_laba_base	count	≥0;	Number of prescriptions issued during the 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-31* code list in therapy file
ICS/LABA in a single device, in year prior to index date	icslaba_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-33* code list in therapy file
	n_icslaba_base	count	≥0;	Number of prescriptions issued during the 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-33* code list in therapy file
Long-acting anticholinergic (LAMA) in year prior to index date	lama_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (0 < [indexdate]-	[prodcode] from *pc-30* code list in therapy file

Description	Name	Type	Values	Definition and timing	CPRD source
				[eventdate] ≤ 365)	
	n_ lama_base	count	≥0;	Number of prescriptions issued during the 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-30* code list in therapy file
LABA/LAMA in a single device, in year prior to index date	labalama_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-32* code list in therapy file
	n_labalama_base	count	≥0;	Number of prescriptions issued during the 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-32* code list in therapy file
Theophylline or derivatives, in year prior to index date	theoph_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-23* code list in therapy file
	n_theoph_base	count	≥0;	Number of prescriptions issued during the 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-23* code list in therapy file
Roflumilast, in year prior to index date	roflum_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-16* code list in therapy file

Description	Name	Type	Values	Definition and timing	CPRD source
	n_roflum_base	count	≥0;	Number of prescriptions issued during the 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-16* code list in therapy file
Oral corticosteroids (OCS) chronic** use, in year prior to index date	chronic_ocs_base4	binary *(never missing)*	0 = no; 1 = yes	At least 4 prescriptions with a maximum gap between prescriptions of 30 days, in 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-14* code list in therapy file
Any ICS containing product in year prior to index date	anyics_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-11, pc-12, pc-31*, and *pc-33* code list in therapy file
	n_anyics_base	count	≥0;	Number of prescriptions issued during the 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-11, pc-12, pc-31*, and *pc-33* code list in therapy file
Any LAMA containing product in year prior to index date	anylama_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-30,* and *pc-32* code list in therapy file
	n_anylama_base	count	≥0;	Number of prescriptions issued during the 12 months prior to (and not including) index date	[eventdate]; [prodcode] from *pc-30,* and *pc-32* code list in therapy file

Description	Name	Type	Values	Definition and timing	CPRD source
				(0 < [indexdate]-[eventdate] ≤ 365)	
Any LABA containing product in year prior to index date	anylaba_base	binary *(never missing)*	0 = no; 1 = yes	At least one record in 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-30, pc-31*, and *pc-32* code list in therapy file
	n_anylaba_base	count	≥0;	Number of prescriptions issued during the 12 months prior to (and not including) index date (0 < [indexdate]-[eventdate] ≤ 365)	[eventdate]; [prodcode] from *pc-30, pc-31*, and *pc-32* code list in therapy file
Dosage of ICS and ICS/LABAs prescribed in year prior to index date (asthma and COPD with/without a history of asthma patients only)	ics_dose	categorical *(missing if [asthma]=0 AND [copd]=0)*	0 = none 1 = low 2 = medium 3 = high 4 = not classifiable . missing	All asthma & COPD medications containing ICS will be classified according to amount of ICS contained, based on defined daily dose (DDD). Only prescriptions issued during the 12 months prior to (and not including) index date will be considered	[asthma] [copd]; [eventdate]; [prodcode] from therapy files. *Dosage classification was provided by GSK and is provided in Annex 4. This will be based on GINA 2015 guidelines* (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5010591/table/Tab5/)
	ics_dose_impute	categorical *(missing if [asthma]=0 AND [copd]=0)*			
Dosageof ICS and ICS/LABAs prescribed in year prior to index date (asthma and COPD with/without a history of asthma patients only, using sensitivity analysis definitions)	ics_dose_sens	categorical *(missing if [asthma_sens]=0 AND [copd_sens]=0)*	0 = none 1 = low 2 = medium 3 = high 4 = not classifiable . missing	All asthma & COPD medications containing ICS will be classified according to amount of ICS contained, based on defined daily dose (DDD). Only prescriptions issued during the 12 months prior to (and not including) index date will be considered	[asthma_sens] [copd_sens]; [eventdate]; [prodcode] from therapy files*.* *Dosage classification was provided by GSK and is provided in Annex 4.*
	ics_dose_sens_impute				

** Includes the following "reliever" medications: SABA, SAMA, fixed combinations of SABA and cromoglycate, and fixed combinations of SABA and SAMA.*
*** At least four prescription records with a maximum gap between two prescriptions equal to 30 days.*

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 primary care 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.

Table 12: Ascertainment of off-label use

All variables in table below will be calculated ONLY for new users of FF/VI i.e. where [index_cat] = 1

Description	Name	Type	Values	Definition and timing	CPRD source
Off-label prescribing: type 1	offlabel1_index	binary	0 = no; 1 = yes . = missing (if [copd]=0)	*index* prescription of FF/VI 200/25 ([index_cat2]=2) in patient classified as COPD ([copd] = 1)	derived: [copd]; [index_cat2]
	offlabel1_index_sens	binary	0 = no; 1 = yes . = missing	index prescription of FF/VI 200/25 ([index_cat2]=2) in patient classified as COPD using sensitivity definition ([copd_sens] = 1)	derived: [copd_sens]; [index_cat2]
	offlabel1_any	binary	0 = no; 1 = yes . = missing (if [copd]=0)	*any* prescription of FF/VI 200/25 ([ffvi_count_hi]>0) in patient classified as COPD ([copd] = 1)	derived: [copd]; [ffvi_count_hi]
	offlabel1_any_sens	binary	0 = no; 1 = yes . = missing (if [copd_sens]=0)	*any* prescription of FF/VI 200/25 ([ffvi_count_hi]>0) in patient classified as COPD using sensitivity definition ([copd_sens] = 1)	derived: [copd_sens]; [ffvi_count_hi]
	off_label1_prop	numeric (range 0 to 1) missing	Range 0 to 1. missing . = missing (if [copd]=0 or [copd]=.)	proportion of all FF/VI prescriptions that are formulation 200/25, in patients classified as COPD [copd=1]	derived: [copd]; [ffvi_count_hi]; [ffvi_count_lo]
Off-label prescribing: type 2	offlabel2_index	binary *(never missing)*	0 = no; 1 = yes	index prescription of FF/VI ([index_cat1]=1) in patient aged under 12y ([age_index]<12) in the asthma [asthma] or other [other] diagnosis group.	derived: [index_cat1]; [age_index], [asthma], [other]
	off_label2_prop	numeric (range 0 to 1) missing	Range 0 to 1. missing . = missing (if [copd]=0)	proportion of all FF/VI prescriptions where patient was aged<12 at prescription date	derived: [ffvi_count_under12]; [ffvi_count_hi]; [ffvi_count_lo]
	offlabel2_sens	binary *(never missing)*	0 = no; 1 = yes	index prescription of FF/VI ([index_cat1]=1) in patient aged under 12y ([age_index]<12) in the asthma	derived: [index_cat1]; [age_index], [asthma_sens], [other_sens]

Description	Name	Type	Values	Definition and timing	CPRD source
				[asthma_sens] or other [other_sens] diagnosis group.	

Objective 3 – Treatment patterns and adherence

Treatment patterns and adherence measures will be considered only in patients with a full 12 months of follow-up after their index treatment. Treatment patterns in patients whose last prescription falls between 31 and 90 days before the end of the 12 months follow-up are deemed not classifiable with respect to discontinuation of the index medication. We will describe the first change within the 12 month period following initiation.

See notes following the table below for full definitions of treatment patterns for patients who are, or are not, receiving concomitant COPD inhalation maintenance therapy at the time of index prescriptions

Table 13: Treatment patterns and adherence

All variables in the following table should be calculated ONLY for new users of FF/VI with 365 days follow up from index prescription date i.e. where [index_cat] = 1 and [censor_cat] = 4.

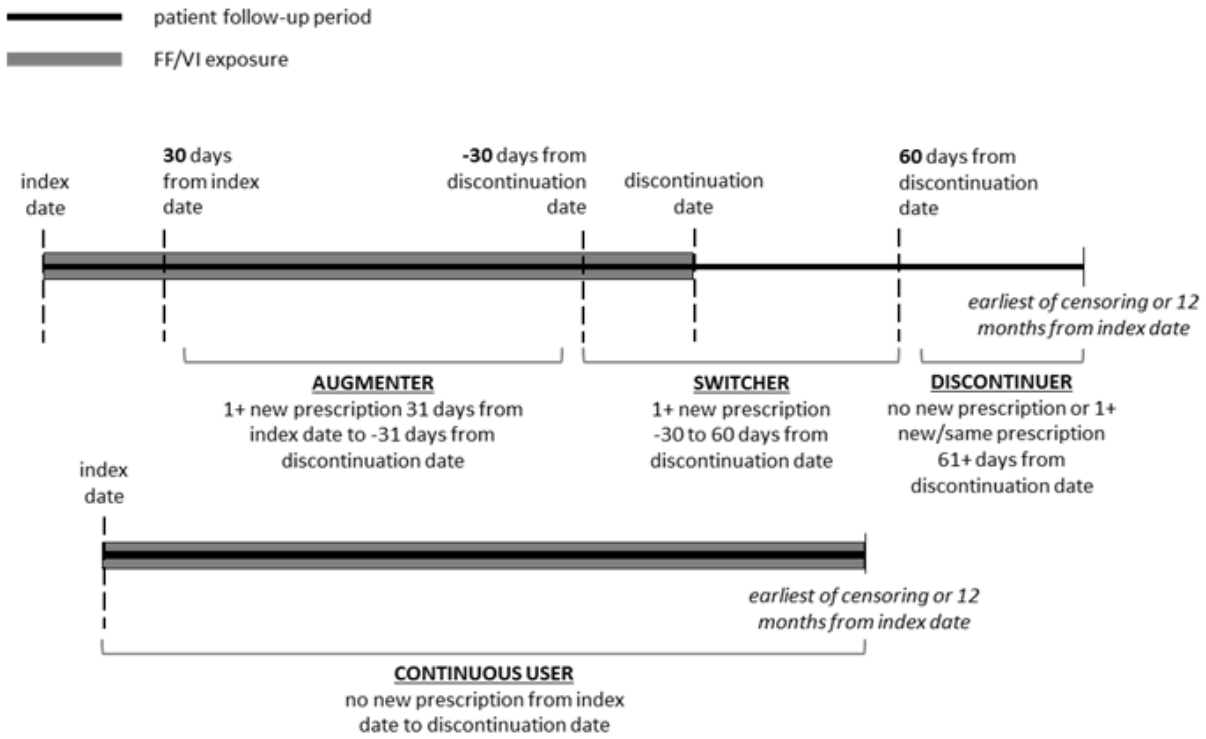
Description	Name	Type	Values	Definition and timing	CPRD source
FF/VI Dose escalation or reduction	d_dose_change	date	date; missing (if no change occurs)	Date of first occurrence of a change in formulation strength (i.e. from 100/25 to 200/25 or vice versa), within 1 year of index date	derived [index_cat2]; [eventdate] in therapy file if [prodcode] in FF/VI
	dose_change	categorical	0 = no change in dose (or only one Rx issued); 1 = dose escalation from 100/25 at index date to 200/25; 2 = dose reduction from 200/25 at index date, to 100/25	Based on first change of strength of FF/VI within 1 year of index date	derived [index_cat2]; [ffvi_count_lo]; [ffvi_count_hi]
Treatment pattern for patients *with no* concomitant therapy	nocon_pattern	categorical *(never missing in those eligible for analysis)*	0 = not classifiable 1 = continuous user; 2 = augmenter; 3 = immediate switcher; 4 = discontinuer; . = missing (if [any_con]=1)	Based on first change within 1 year of [indexdate]). *See full definitions below.*	derived [any_con] variable; [eventdate] in therapy file if [prodcode] in pc-29 [censor_flag]
	d_nocon_patter n	date	date; . = missing	Date of first change in treatment pattern within 1 year of [indexdate]	derived [any_con] variable; [eventdate] in therapy file if [prodcode] in pc-29*
	nocon_therapy_ change	categorical	0=no augmentation or switch 1 = augmentation by adding a LAMA 2= Augmentation by adding LTRA 3 = switch to ICS (with or without a SABA) 4 = switch to a LABA alone 5 = switch to another ICS/LABA (not Relvar!) 6 = switch to a LAMA alone 7 = switch to a LABA/LAMA 8 = switch to LTRA	Where first change within 1 year of [indexdate] is augmenter or immediate switcher) Only defined for people who are [noncon_pattern]=2 or 3	derived [nocon_pattern] and therapy file if [prodcode] in pc-30, pc-32, pc-12, pc-35, pc-17, pc-31, pc-33, pc-28, code lists

Description	Name	Type	Values	Definition and timing	CPRD source
Type of discontinuation for discontinuers *with no* concomitant therapy	nocon_disc	categorical	1 = true discontinuer; 2 = drug hiatus; 3 = latent switch; . = missing (if [nocon_pattern] not= 4)	Based on first change within one year of [indexdate]). *See full definitions below.*	derived [nocon_pattern]; [eventdate] in therapy file if [prodcode] in *pc-29*
Treatment pattern for patients *with* concomitant therapy	con_pattern	categorical (never missing in those eligible for analysis)	0 = not classifiable 1 = continuous use of both; 2 = augmenter (to triple); 3 = immediate switcher; 4 = discontinuation of both drugs; 5 = discontinuation of index only; 6 = discontinuation of concomitant only; . = missing	Based on first change within one year of [indexdate]). *See full definitions below.*	derived [con]; [eventdate] in therapy file if [prodcode] in pc-29
	d_con_pattern	date	date; . = missing	Date of first change in treatment pattern within one year of [indexdate]	derived [con] variable; [eventdate] in therapy file if [prodcode] in *pc-29 code list*
Medication possession ratio	mpr	proportion	≥0.0 and ≤1.0; . = missing (if <2 prescriptions for FF/VI)	Proportion of days in possession of medication between the index date and the last prescription date, for patients with ≥2 prescriptions of index medication.	*FF/VI* [prodcode] in *pc-28 code list* in therapy file
	mpr_cat	categorical	0 = non-adherent (<80%); 1 = adherent (≥80%); . = missing (if <2 prescriptions for FF/VI)	Calculated when [mpr] is non-missing	derived [mpr] variable
Proportion of days covered	pdc	proportion	≥0.08 and ≤1.0;	Proportion of days in possession of medication during the 365 days' period starting from the index date. (possession is calculated by multiplying the number of prescriptions (at any dose) in the period (minus the last	*FF/VI* [prodcode] in *pc-28 code list* in therapy file

Description	Name	Type	Values	Definition and timing	CPRD source
				prescription) by the assumed duration of 30 days)	
	pdc_cat	categorical	0 = non-adherent (<80%); 1 = adherent (≥80%); . = missing (if <2 prescriptions for FF/VI)	Calculated when [pdc] is non-missing	derived [pdc] variable

Full definitions for treatment patterns for patients *not* taking a concomitant COPD maintenance therapy

Figure 2 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, and FF/VI 200/25 and FF/VI 100/25 are considered the same for these analyses.

Continuous use: Patient DOES NOT start taking another inhaled COPD maintenance therapy, and continues to use index treatment (without a break of >91 days) through the 12 month after the index date.

Augmentation: Patient starts taking another inhaled COPD maintenance therapy (1 or more prescriptions) and the new treatment starts ≥31 days after the index date and ≥31 days before the discontinuation date for the index treatment or the end of 12 months following the index date. The augmentation date will be defined as the date of first prescription for the new COPD maintenance therapy.

Immediate Switching: Patient starts taking another inhaled COPD maintenance therapy (1 or more prescriptions) within 12 months of the index date, and the new treatment starts ≤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.

Discontinuation: Patient meets the definition of discontinuation prior to the end of 12 months after the index date and does not meet the definitions for continuous use, immediate switching and augmentation above. Discontinuers will be classified according to whether they:

- do not restart the index medication and do not start a new inhaled COPD maintenance treatment (i.e. true discontinuers)
- restart the index medication (i.e. patients taking a drug hiatus)
- start a new inhaled COPD maintenance treatment >60 days after discontinuation (i.e. latent switchers).

Full definitions for treatment patterns for patients *taking* a concomitant COPD maintenance therapy

Continuous use of both drugs: Patient continues to use both medications for 12 months from the date of index treatment until censoring.

Discontinuation of index drug (concomitant drug continues): Patient meets the definition of discontinuation for the index drug within 12 months of the index date, but continues to use the concomitant drug. The discontinuation date is therefore the date the index drug stopped.

Discontinuation of concomitant drug (index drug continues): Patient meets the definition of discontinuation for the concomitant drug within 12 months of the index date, but continues to use the index drug. The discontinuation date of the concomitant drug is therefore the date the concomitant drug stopped.

Discontinuation of both drugs: Patient meets the definition of discontinuation for both drugs (on the same day) and within 12 months from the index.

In addition, patients who augment to triple therapy (i.e. whilst still taking the index drug and the concomitant drug) will be defined as *augmenters to triple.*

Augmenter to triple: Patients who start taking another inhaled COPD maintenance therapy (1 or more prescriptions) and the new treatment starts ≥31 days after the index date and ≥31 days before the discontinuation dates for the both index treatment and the concomitant treatment, or the end of 12 months following the index date.

6. Statistical analysis

All data management and analyses will be conducted by the CPRD Observational Research Team using the standard CPRD tools (Define, Refine and Extract), as well as the latest installed version of Stata SE (currently 14.2). Full logs will be kept for audit and quality assurance (QA) purposes. Quality assurance will include a review of all logs, analysis outputs, tables/figures and text in both the interim and final reports. CPRD disclosure rules for small cell counts will be adhered to in reports intended for publication and/or dissemination outside of GSK and CPRD.

Examples of table shells and figures are available in Annex 5. Square bracket reference numbers in the text below e.g. [Obj.1 – T1] relate to table shells and figures in Annex 5.

Characteristics of the exposure cohorts

Characteristics of the exposure cohorts will be described separately for the full cohort, and the sub-cohort of patients eligible for linkage to CPRD-HES. These tables will be stratified by the diagnosis groups (asthma, COPD, COPD with/without asthma and Other)

- E1 - Descriptive statistics (mean (SD); median (range)) on duration of time until censoring and the reasons for censoring for the full cohort as well as by index medication group (FF/VI 200/25, FF/VI 100/25 and other ICS/LABA FDC) will be produced [ExposureCohorts - T1].

- E2 - For the FF/VI 200/25, and FF/VI 100/25 groups only, 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 [ExposureCohorts - T1].

- E3 - For the FF/VI 200/25, and FF/VI 100/25 groups only, the number and proportion of new users taking concomitant maintenance therapy at the index date will be calculated and the type of concomitant drug described [ExposureCohorts - T1].

- E4 - The number and proportion of patients contributing more than one index drug will 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 were the medication do overlap) will also be calculated. [ExposureCohorts – T1]

- E5 – For the cohort of patients with any history of asthma the mean (SD) and median (IQR) time in days from asthma diagnosis to index date in days will be calculated [ExposureCohorts – T1_COPD_Ast & ExposureCohorts – T1_Asthma].

OBJECTIVE 1: Baseline characteristics of new users of FF/VI or other ICS/LABA FDC

These analyses will be conducted among all patients who enter the study, and presented separately by index medication group (FF/VI 200/25, FF/VI 100/25 and other ICS/LABA FDC). Analyses will be repeated for the subgroup of patients eligible for HES linkage. Table T1 will be stratified by the diagnosis groups (asthma, COPD, COPD with/without asthma and Other) and Table T4 will be stratified by COPD and asthma.

- O1.1 – Summary statistics (count and percentage for categorical variables, mean (SD) for continuous variables) will be presented for the variables in the following categories: demographic [Obj 1 - T1]; diagnosis group (COPD with/without asthma, asthma, 'other') [Obj 1 – T2]; disease burden (COPD and asthma groups only); comorbidity [Obj 1 – T3]; respiratory medication use in previous 12 months [Obj 1 – T4].

- O1.2 - For patients in the COPD diagnosis group, the number of COPD exacerbations (moderate or moderate/severe) in the previous 12 months will be described using the mean (SD) and median (with range and interquartile range), and the proportion of patients with 0,1, or 2 or more. Exacerbations will be also be presented as rate per person-year, with 95% confidence interval [Obj 1 - T2].

- O1.3 - For patients in the asthma diagnosis group, the number of asthma exacerbations (moderate or moderate/severe) in the previous 12 months will be described using the mean (SD) and median (with range and interquartile range), and the proportion of patients with 0,1, or 2 or more. Exacerbations will be also be presented as rate per person-year, with 95% confidence interval [Obj 1 - T2].

- O1.4 - For patients in the "other" diagnosis group, we will explore respiratory diagnosis codes that were recorded in the 12 months prior to the index date as well as the respiratory diagnosis codes closest to the index date to try to understand if these patients have some other respiratory disease.

Objective 2 – Off-label prescribing

These analyses will be conducted among all patients who enter the study with an index prescription for FF/VI.

Primary analyses

- O2.1 – Proportion of all patients in the COPD diagnosis group who are prescribed FF/VI 200/25 [Obj 2 – T1], presented stratified by diagnosis group (COPD, COPD with/without asthma, Asthma, Other):

  a) at index date. Calculated as:

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

  b) at any time on or after index date. Calculated as:

$$\frac{\text{\# patients with COPD (with or without asthma) with at least one prescription of FF/VI 200/25 during follow-up}}{\text{\# patients with COPD (with or without asthma)}}$$

- O2.2 - Proportion of all prescriptions for FF/VI 200/25 issued to patients in the COPD and the COPD with/without a history of asthma diagnosis groups. Proportions will be calculated for each patient (presented as a histogram; as frequencies in categories defined by fixed cutoffs at >25%,>50%,>75%; and if possible deciles included and excluding patients with no prescriptions), and overall [Obj 2 – T1 & Obj 2 – F1, F2,F3].

- O2.3 – Proportion of all patients in the asthma and 'other diagnosis' groups who are aged under 12 at the time of their index FF/VI prescription.

- Calculated as:

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

Exploratory sensitivity analyses

- O2.5 - The primary analysis (O2.1 - O2.4) will be repeated using an alternative time period to identify COPD and asthma diagnoses using patient history only up to and including the index date. The analysis will use the following variables: [copd_sens], [copd_asthma_sens], [asthma_sens], [other_sens], [offlabel1_any_sens] and [offlabel2_sens] variables [Obj 2 – T2].

Objective 3 – Treatment patterns and adherence

These analyses will be conducted only among patients who enter the study with an index prescription for FF/VI*. Treatment patterns of inhalation therapies will be examined in the first 12 months following initiation and among patients with and without 12 months or more of follow-up. Patients who are censored between 31 and 90 days after their last prescription in the first 12 months will not be included in the analyses as it is not possible to determine whether these patients have discontinued FF/VI. Analyses will be repeated for the COPD (including history of asthma stratification), asthma, and 'other' diagnosis*

Primary analyses

- O3.1 – Among new users of FF/VI 100/25, the number (%) who only ever receive one dose, the number (%) who subsequently receive at least one prescription for FF/VI 200/25 (dose escalation); among new users of FF/VI 200/25, the number (%) who subsequently receive at least one prescription for FF/VI 100/25 (dose reduction) [Obj 3 – T1].

- O3.2 - Among eligible COPD or asthma patients who ***are not*** taking a concomitant LAMA or LTRA maintenance therapy at index date, the count and percentage of patients falling into the four main mutually exclusive treatment pattern categories (continuous users, augmenters, switchers and discontinuers; defined using [nocon_pattern] variable) will be described for FF/V1 100 and FF/VI 200 As well, the mean (SD) time (in days) from the index to the first change (among those with a change) will be reported. [Obj.3 – T2]

- O3.3 - For eligible COPD or asthma patients who ***are*** taking a concomitant LAMA or LTRA maintenance therapy at index date, the count and percentage of patients falling into the four mutually exclusive treatment pattern categories (continuous use of both drugs, immediate switcher to another ICS/LABA, discontinuation of index drug, discontinuation of concomitant drug, discontinuation of both drugs; defined with [con_pattern] variable) will be described. As well, the mean (SD) time (in days) from the index date to the first change (among those with a change) will be reported. [Obj.3 – T2]

- O3.3 - Among eligible patients with COPD that ***do not have*** concomitant use of another ***inhaled*** maintenance therapy at index date, Kaplan-Meier plots will be created to visualise time in days to first treatment change for FF/VI users by type of change. [Obj.3 – F1-F4_COPD]

- O3.5 - For eligible patients who ***are*** taking a concomitant COPD ***inhalation*** maintenance therapy at index date, Kaplan-Meier plots will be created to visualise time in days to first treatment change for FF/VI users by type of change. [Obj.3 – F1-F4_Asthma]

- O3.6 - The count and percentage of patients who are adherent to the initially prescribed therapy during follow-up will be calculated using the MPR and PDC. As well as cut offs of >=80% for the MPR and PDC, the mean (SD), min, max, median and IQR of these measures as continuous variables during follow-up will also be calculated. MPR will be calculated among patients who received at least two prescriptions during the first 12 months of follow-up; whilst the PDC will be calculated among patients who received at least one prescription in the first 12 months of follow-up. [Obj.3 – T3]

Exploratory sensitivity analyses

- The analysis of Dose escalation/reduction (O3.1) will be repeated restricted to patients with 12 months of follow up only [Obj 3 – T1_Sensitivity].

- The analysis of treatment patterns (O3.2; O3.3) will be repeated for COPD with and without a history of asthma [Obj 3 – T2_Sensitivity].

Changes and deviations from study protocol

Amendment no	Amendment	Reason
1	'Earliest recorded asthma diagnosis variable added and defined.	To better understand whether COPD patients with a history of asthma are prescribed FF/VI for COPD or asthma, we will identify the earliest recorded asthma diagnosis and calculate an average time from the index date to the first, historical asthma record.
2	Look-back period for identifying coded spirometry data relating to COPD severity (descriptor variables for Objective 1) was expanded from 12 months prior to the index date to 24 months prior to the index date.	A look-back period of 24 months for identifying records relating to COPD severity (FEV_1 % predicted, FEV_1/FVC) is more appropriate and results in less missing data than a look-back period of 12 months. This change aligns this definition with that used in internally developed GSK algorithms for spirometry data recorded in CPRD.
3	Beta-blocker variable added as a 'comorbidity'.	Data on beta-blocker prescribing will help to describe cardiovascular risk in patients newly using FF/VI or other ICS/LABA FDC.

4	Analyses of dose escalation/reduction (Objective 3) will be repeated among the all FF/VI new users eligible for dose escalation/reduction (i.e. those patients with at least two prescriptions for FF/VI during the study period), regardless of their length of follow-up.	Whilst dose escalation/reduction can be considered a treatment pattern, it is also an important variable for contextualising off-label prescribing of FF/VI in COPD. It is therefore important to explore dose escalation among all patients (eligible for dose escalation/reduction) and not just those with 12 months of follow-up.

Annex 1. Data source documentation and dictionaries

The documents and data dictionaries embedded here are the latest versions available at the time of writing (December 2015). New versions will be added when and if there are significant changes to the data source documentation and/or dictionaries.

CPRD-GOLD data dictionary (v1.9)

CPRD GOLD Full Data Specification.pdf

CPRD-IMD documentation (v2.2)

PatientLevelDeprivationMeasures_Specificati

PracticeLevelDeprivationMeasures_Specifica

CPRD-HES documentation (v1.7) and dictionary for basic HES (v1.8)

Documentation_HES_APC_set12_v1.7.pd

Data_Dictionary_HES_Basic_set12_v1.8.p

Annex 2. Glossary of terms

Acceptable patients

In CPRD, patients are labelled as ‘acceptable’ for use in research by a process that identifies and excludes patients with non-continuous follow up or patients with poor data recording that raises suspicion as to the validity of the that patients record. Patient data is checked, for the following issues:

- An empty or invalid first registration date
- An empty or invalid current registration date
- Absence of a record for a year of birth
- A first registration date prior to their birth year
- A current registration date prior to their birth year
- A transferred out reason with no transferred out date
- A transferred out date with no transferred out reason
- A transferred out date prior to their first registration date
- A transferred out date prior to their current registration date
- A current registration date prior to their first registration date
- A gender other than Female/Male/Indeterminate
- An age of greater than 115 at end of follow-up
- Recorded health care episodes in years prior to birth year
- All recorded health care episodes have empty or invalid event dates
- Registration status of temporary patients

If any of these conditions are true then the patient is labelled unacceptable, and is not recommended for use in research.

Derived date of death

The CPRD derived death date combines information from the patient registration, death administration and clinical Read codes.

Read codes

Read codes are a standard vocabulary of coded clinical terms that have been in use in the NHS since 1985. GPs use Read codes to enter medical terms into their system in the practice. Specifically, the GP software system (Vision) from which CPRD collects data uses a modified version of the unified 5-byte Read version 2. In addition to the 5-digit Read Code, the system is designed to accommodate synonyms using an additional 2 digits in codes.

Up-to-standard (UTS) date

The overall quality of data in CPRD practices is mediated by use of an 'up to standard' (UTS) date, which is deemed as the date at which data in the practice is considered to have continuous high quality data fit for use in research. This is mediated by an analysis on the total data in the practice, which is refreshed every time a new collection for a practice is processed into the database. It is based on two central concepts: assurance of continuity in data recording (gap analysis), and avoidance of use of data for which transferred out and dead patients have been removed (death recording).

Gap Analysis

To detect whether there is any meaningful gaps in the data it is necessary to look in more detail at single day gaps as well as longer gaps. A single day alone may reflect a situation where nothing was recorded that day at the practice, i.e. the practice was not open, such as on a bank holiday. A longer gamay reflect a situation where the practice did not offer a service and patients may have been treated elsewhere. If a meaningful gap is found, the earliest date after which there is no significant gap is identified.

Death Recording

It is expected that a standard number of deaths will be recorded at a practice over time. Assessment of gaps in death recording is performed taking the size of the practice into account. A safety margin is built in to account for both geographical and seasonal variation in death rates. If a meaningful gap is found, the earliest date after which there is no significant gap is identified.

The UTS date is set to the latest of these dates for each practice. The CPRD recommend that analyses are performed on data following the practice UTS date.

UTS follow-up

In CPRD, UTS follow-up begins from the latest of the patient's registration date and the practice up-to-standard date. UTS follow-up ends at the earliest of the patient's death[4], transfer out of the practice, or practice last collection date.

[4] This was defined using the CPRD algorithm for identifying dates of death,

Annex 3. Code lists

Read medical code lists

All code lists were compiled using the December 2015 version of the CPRD medical dictionary and updated between February to May 2017. With the exception of the gord and renal code lists, all Read code lists are based on those provided by Dr PPD (Imperial College London). Additionally, the pneumonia and mi code lists were cross-checked with externally published code lists (DeSantostefano 2014 and Herrett 2013). The asthma and COPD code lists were also cross-checked with code lists supplied by GSK (sent July 2015). All CPRD product code lists for COPD products were cross-checked with code lists supplied by GSK (sent April 2016) and June 2017

Product code lists for CPRD

All code lists were created using the December 2015 version of the CPRD product dictionary.

ICD-10 medical code lists for CPRD-HES

Unless otherwise indicated, these code lists were created using the latest version of the ICD-10 dictionary.

Summary of all codelists used in the study:

Combined codelists RELVAR v2.0.xlsx

Annex 4. Algorithms used for generation of variables:

Algorithm for identification of moderate and severe exacerbations of COPD

Doc 2 GSK AECOPD algorithm_updateJune

Algorithm for identification of moderate and severe exacerbations of asthma

Asthma exacerbation algorithm_Final.docx

Algorithm for calculation of COPD severity at baseline based on the CHESS study

COPDSeveritySpirometry_CPRD2017.docx

GSK Algorithm for the classification of ICS and ICS/LABAs:

GSK Algorithm for the classification of IC

Annex 5. Table shells and figures for analyses

Examples of table shells and figures are available in the embedded excel spreadsheet below. Table shells are provided for illustrative purposes and the actual contents may vary. Tables and figures are grouped into the following categories: Exposure Cohorts, Baseline, Objective 1, Objective 2, Objective 3 and labelled as being primary, secondary or exploratory sensitivity analyses. The tables will be replicated using one or more of the two cohorts: CPRD-GOLD (only), and CPRD-HES; as detailed in the embedded excel spreadsheet.

Table shells_GSK_Relvar_SAF

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
Development Phase	IV
Effective Date:	14-SEP-2017
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):	PPD

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	1.1
Date of last version of protocol	22 December 2016
EU PAS register number	EUPAS17720
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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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: PPD

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:
5th Floor,
151 Buckingham Palace Road,
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SPONSOR SIGNATORY:

PPD

PPD.n Landis PPD
Senior Director and Respiratory TA Head

14 / Sept / 2017
Date

PPD

Andrew Roddam
VP Real World Evidence & Epidemiology

14-Sept-17.
Date

SPONSOR INFORMATION PAGE

WWEpi Project Identifier: 205052 (GSK Epidemiology: PRJ2214)

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
Iron Bridge Road
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Telephone: PPD

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.

Daniel Dedman

PPD

Investigator Signature

11 September 2017

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 (100/25 and 200/25 formulations) and COPD (100/25 formulation only) patients 12 years and older, 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 (COPD-including an asthma history stratification, Asthma, Other); 2) among new users of FF/VI, describe off-label prescribing including prescription of 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 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 3) among new users of FF/VI, describe 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: July 31 2017

Study Report Approval date: September 15 2017

5. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	23-AUG-2017	9.7.1.3	Definition of asthma history stratification clarified for Objective 2, analysis of off-label prescribing of FF/VI in patients with COPD.	In Sections 4 and 9.3.3.2 we defined off-label prescribing of FF/VI 200/25 in COPD patients, including an asthma history stratification. However, due to an editorial omission, we had not clarified the meaning of this stratification in Section 9.7.1.3. Our intention (to exclude COPD patients with a history of asthma from the numerator when calculating off-label prescribing) has now been explained.
2	23-AUG-2017	9.3.2.1	'Earliest recorded asthma diagnosis variable added and defined.	To better understand whether COPD patients with a history of asthma are prescribed FF/VI for COPD or asthma, we will identify the earliest recorded asthma diagnosis and calculate an average time from the index date to the first, historical asthma record.
3	23-AUG-2017	9.3.2.1	Look-back period for identifying coded spirometry data relating to COPD severity (descriptor variables for Objective 1) was expanded from 12 months prior to the index date to 24 months prior to the index date.	A look-back period of 24 months for identifying records relating to COPD severity (FEV_1 % predicted, FEV_1/FVC) is more appropriate and results in less missing data than a look-back period of 12 months. This change aligns the definition in this protocol with that used in internally developed GSK algorithms for spirometry data recorded in CPRD.
4	23-AUG-2017	9.3.2.1	Beta-blocker variable added as a 'comorbidity'.	Data on beta-blocker prescribing will help to describe cardiovascular risk

				in patients newly using FF/VI or other ICS/LABA FDC.
5		9.3.2.3	Analyses of dose escalation/reduction (Objective 3) will be repeated among the all FF/VI new users eligible for dose escalation/reduction (i.e. those patients with at least two prescriptions for FF/VI during the study period), regardless of their length of follow-up.	Whilst dose escalation/reduction can be considered a treatment pattern, it is also an important variable for contextualising off-label prescribing of FF/VI in COPD. It is therefore important to explore dose escalation among all patients (eligible for dose escalation/reduction) and not just those with 12 months of follow-up.
6	23-AUG-2017	9.2.2.1	Asthma diagnosis group, defined using validated algorithm.	The original version of the protocol stated that the definition for the asthma diagnosis group might change based on the results of an ongoing validation study. The validation study has concluded and we will now use the validated code list and algorithm for identifying patients with asthma.
7	23-AUG-2017	9.7.1.2	Updated length of look-back period for exploring respiratory codes in the Other diagnosis group.	The vendor, who are experts in analysis of CPRD data, advised that we look for respiratory codes in the Other diagnosis group in the full year prior to and including the index date rather than codes recorded only on the index date.
8	23-AUG-2017	4; 6	Amended analysis complete and report complete milestones.	Milestone dates for analysis complete and report complete were shifted slightly after the protocol was written.
9	23-AUG-2017	4; 8; 9.3.2.2 9.7.1.3	Re-ordered text relating to off-label definitions and analysis.	For consistency within the protocol and with the final study report.

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	31 July 2017
Study Report Approval date	15 September 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, 2017]. 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 (COPD-including an asthma history stratification, Asthma, Other).

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

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

Objective 3: Among new users of FF/VI, describe treatment patterns and adherence to therapy by diagnosis group.

9. RESEARCH METHODS

9.1. Study Design

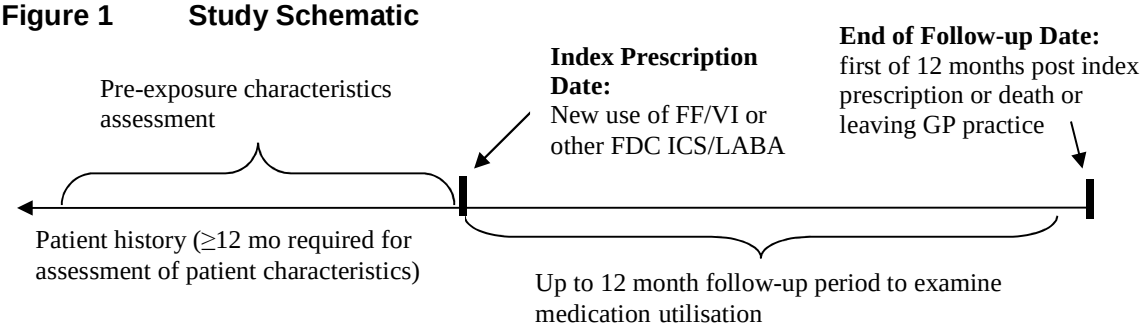
This study will take a naturalistic approach, capturing routine medical care using a retrospective longitudinal non-interventional observational design. All patients with a record of a new prescription for FF/VI or other ICS/LABA FDC during the inclusion period of January 1, 2014 through December 31, 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

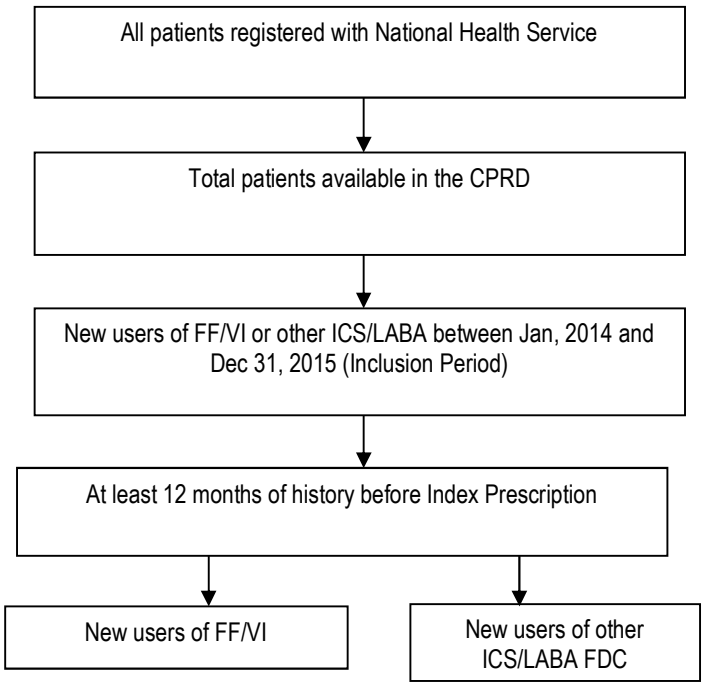


A minimum period of at least 12 months prior to index prescription date, defined as being registered with the practice for at least one year, is required to allow for a standardised period of history to describe selected patient demographics, disease burden, and previous respiratory medication use (Figure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

- ≥ 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 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. The asthma codelist will based on the results of an 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, 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 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 24 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 24 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.

In COPD patients with a history of asthma, we will also define the earliest recorded asthma diagnosis date and identify the time in days from the earliest asthma record to the index date.

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. In addition, beta-blocker prescribing in the 12 months prior to the index date will be flagged yes/no. Each comorbidity (and beta-blocker prescribing) 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) 2017 guidelines [GINA, 2017].

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 SABA/ICS*	Inhaled Corticosteroids OR Fixed Combination of Short-Acting Beta2-Agonist and Inhaled Corticosteroid
LABA	Long-Acting Beta2-Agonists
ICS/LABA*	Fixed Combination of Inhaled Corticosteroid and Long-Acting Beta2-Agonist 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 (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.
- 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.

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 (except for the analyses of dose escalation which will be repeated amongst all eligible patients, regardless of their length of follow-up). 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 [with asthma history stratification] 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.

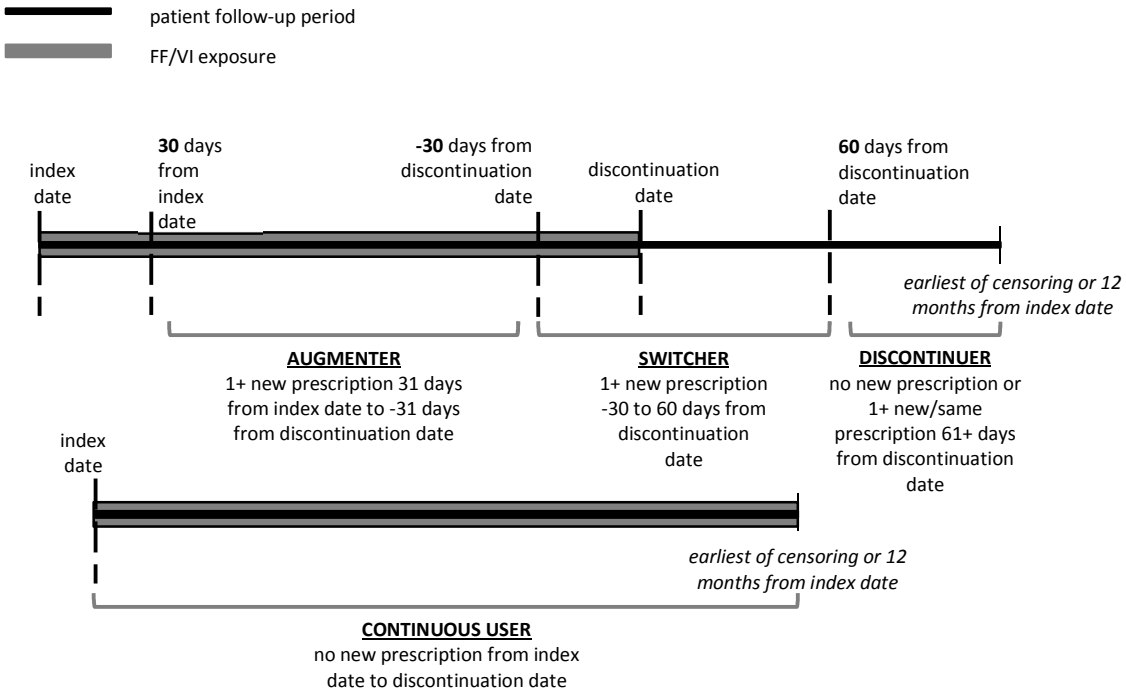
(4) Discontinuation: discontinuation of the index medication prior to 12 months after the index date and does not meet the definitions for continuous use, immediate switching and augmentation above. Patients who discontinue will be further categorised into those who restart their index therapy within 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+LTRA[2]*
	LABA alone[1]	
	LAMA alone	
	LAMA/LABA	
	LTRA alone[2]	

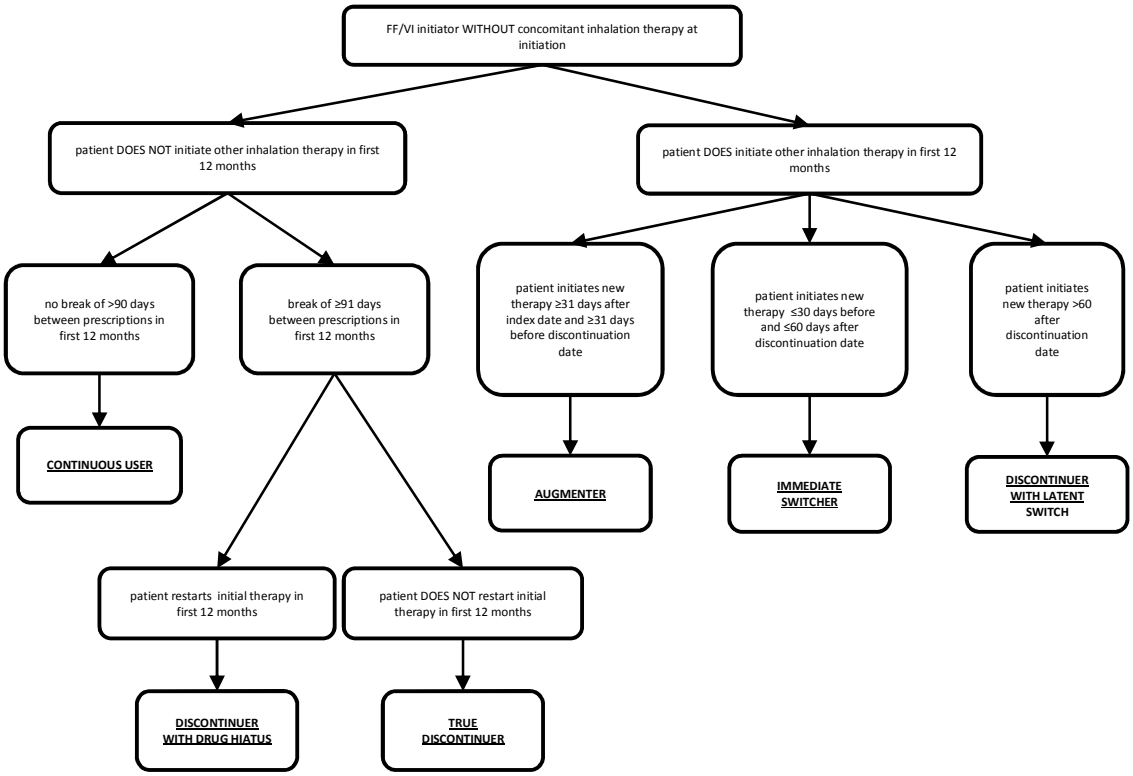
1. *ICS/LABA other than FF/VI (fixed dose)*
2. *For patients with an asthma diagnosis and no history of COPD*

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 (patients with concomitant inhaled maintenance therapy for COPD or asthma)**: 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.

Adherence measures:

- **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 in the year prior to 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 (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:

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

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:

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

The above calculations will be repeated with an asthma history stratification whereby COPD patients with a history of asthma who are prescribed FF/VI 200/25 will not be considered off-label and will therefore be removed from the numerator.

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

Agusti A, de Teresa L, De Backer W, et al. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. Eur Respir J. 2014; 43:763–72.

Ashworth M, Latinovic R, Charlton J, Cox K, Rowlands G, Gulliford M. Why has antibiotic prescribing for respiratory illness declined in primary care? A longitudinal study using the General Practice Research Database. J Public Health (Oxf). 2004; 26(3):268-74.

Bateman ED, O'Byrne PM, Busse WW, Lötvall J, Bleecker ER, Andersen L, Jacques L, Frith L, Lim J, Woodcock A. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. Thorax. 2014; 69(4):312-9.

Calverley PM, Julie A. Anderson, M.A., Bartolome Celli, M.D., Gary T. Ferguson, M.D., Christine Jenkins, M.D. Paul W. Jones, M.D., Julie C. Yates, B.S., and Jørgen Vestbo, M.D., for the TORCH investigators* Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease N Engl J Med. 2007; 356:775-89.

Coloma PM, Valkhoff VE, Mazzaglia G, Nielsson MS, Pedersen L, Molokhia M et al. Identification of acute myocardial infarction from electronic healthcare records using different disease coding systems: a validation study in three European countries. BMJ Open. 2013; 3:e002862.

DiSantostefano RL, Davis KJ. Prescription patterns in asthma patients initiating salmeterol in UK general practice: a retrospective cohort study using the General Practice Research Database (GPRD). Drug Saf. 2011; 34(6):511-20.

Dransfield M, Bourbeau J, Jones PW, Hanania NA , Mahler DA, Vestbo J, Wachtel A, Martinez FJ, Barnhart F, Sanford L, Lettis S, Crim C, Calverley P. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. Lancet Resp Med. 2013; 1(3):210-23.

Dransfield MT1, Feldman G2, Korenblat P3, LaForce CF4, Locantore N5, Pistolesi M6, Watkins ML5, Crim C5, Martinez FJ7. Efficacy and safety of once-daily fluticasone furoate/vilanterol (100/25 mcg) versus twice-daily fluticasone propionate/salmeterol (250/50 mcg) in COPD patients. Respir Med. 2014; 108(8):1171-9.

Ducharme FM, Ni Chroinin M, Greenstone I, Lasseson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. Cochrane Database Syst Rev 2010; 14 4):CD005533

From the *Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma* (GINA) 2017. Available from: http://www.ginasthma.org/.

From the *Global Strategy for the Diagnosis, Management and Prevention of COPD*, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016. Available from: http://www.goldcopd.org/.

Ferguson GT, Anzueto A, Fei R, Emmett A, Knobil K, Kalberg C. Effect of fluticasone propionate/salmeterol (250/50 mcg) or salmeterol (50 mcg) on COPD exacerbations. Respir Med. 2008; 102:1099-1108.

Kardos P, Wencker M, Glaab T. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. Am J Resp Crit Care Med. 2007; 175:144-149.

Lötvall J, Bateman ED, Busse WW, O'Byrne PM, Woodcock A, Toler WT, Jacques L, Goldfrad C, Bleecker ER. Comparison of vilanterol, a novel long-acting beta2 agonist, with placebo and a salmeterol reference arm in asthma uncontrolled by inhaled corticosteroids. J Negat Results Biomed. 2014; 13(1):9.

Quint JK, Mullerova H, DiSantostefano RL, Forbes H, Eaton S, Hurst JR et al. Validation of Chronic Obstructive Pulmonary Disease (COPD) recording in the Clinical Practice Research Datalink (CPRD_GOLD). BMJ Open 2014; 4:e005540.

Rothnie K, Mullerova H, Hurst JR, Smeeth L, Davis K, Thomas SL, Quint JK. Validation of the Recording of Acute Exacerbations of COPD in UK Primary Care Electronic Healthcare Records. Plos One. 2016; 11(3):e0151357.
Sharafkhaneh, Amir, John G. Southard, Mitchell Goldman, Tom Uryniak, Ubaldo J. Martin, Effect of budesonide/formoterol pMDI on COPD exacerbations: A double-blind, randomized study. Respir Med. 2012; 106(2):257-68.

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010; 340:c332.

Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest.* 2005; 128:2099-107.

van Staa TP, Cooper C, Leufkens HG, Lammers JW, Suissa S. The use of inhaled corticosteroids in the United Kingdom and the Netherlands. Respir Med. 2003; 97(5):578-85.

Tinkelman DG, Price DB, Nordyke RJ, Halbert RJ. Misdiagnosis of COPD and asthma in primary care patients 40 years of age and over. J Asthma. 2006; 43(1):75-80.