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ORIGINAL RESEARCH ARTICLE

Comparative Safety Profile of the Fixed-Dose Combination Corticosteroid and Long-acting β_2-Agonist Fluticasone Propionate/Formoterol Fumarate: A 36-Month Longitudinal Cohort Study in UK Primary Care

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Abstract

Objective The inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) fluticasone propionate/formoterol fumarate (FP/FORM; *Flutiform*®) has been available as fixed-dose combination (FDC) therapy for asthma patients aged ≥ 12 years in the UK since 2012. This post-authorisation safety study examined adverse outcomes and prescribing practices for FP/FORM and other FDC ICS/LABA therapies in a real-life clinical setting over 36 months.

Methods Historical, longitudinal cohort database study using UK primary care data from the Clinical Practice Research Datalink (CPRD) database, for patients initiated on or switched to an FDC ICS/LABA (ENCePP study number: EUPAS12330). The main cohort was adults aged ≥ 18 years with asthma. The primary outcome was incidence of new adverse outcomes after initiation of ICS/LABA; hazard ratios (HRs) and 95% confidence intervals were estimated for FP/FORM versus other FDC ICS/LABAs using Cox regression models.

Results A total of 241,007 patients with an FDC ICS/LABA prescription were identified. In the adult asthma cohort ($N = 41{,}609$), the incidence rate of new adverse outcomes [in 100 patient-years (py)] was significantly lower for FP/FORM (24.75) versus fluticasone/salmeterol metered-dose inhaler [8.86; HR 1.14 (1.04, 1.25)], fluticasone/salmeterol dry powder inhaler [31.19; HR 1.18 (1.08, 1.29)], budesonide/formoterol [25.16; HR: 1.13 (1.03, 1.25)] and beclometasone/formoterol [25.47; HR 1.14 (1.04, 1.25)]. The overall prescribing rate was lower for FP/FORM (13.85 per 1000/py) than licensed FDC ICS/LABA comparators (20.30–28.13 per 1000/py). Of those prescribed FP/FORM, 80.8% were adults with asthma and < 7% were prescribed FP/FORM "off-label".

Conclusions The results suggest that FP/FORM was associated with an overall lower adverse outcome rate than the licensed comparators.

Key Points

This database study using UK primary care data investigated prescribing incidence and adverse outcomes for single-inhaler asthma combination therapies in a "real-life" setting over 36 months.

The prescribing rate was lower for the combination of fluticasone/formoterol than other combinations (fluticasone/salmeterol, budesonide/formoterol and beclometasone/formoterol) and "off-label" prescribing of fluticasone/formoterol was low (< 7%).

The incidence of adverse outcomes in patients receiving fluticasone/formoterol was similar to, or lower than, the incidence among patients receiving licensed comparators.

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1 Introduction

Asthma is the most prevalent chronic disease affecting the lungs and the most common chronic disease affecting children [1]. In 2017, it was estimated that asthma affected 235 million people globally [1]. In the UK, more than 270 people are admitted to hospital each day as a result of asthma attacks, which, in addition to around 6.4 million physician consultations, prescription costs and disability claims, means that the total direct costs of asthma care exceed £1 billion per year [2]. Furthermore, asthma places a substantial health burden on patients by reducing ability to participate in sports and increasing the risk of sleep disruption, depression, emergency room visits, frequent sick days from work [3].

Patients with asthma should be treated with a reliever medication and most will also be treated with a controller medication [4]. Reliever medications are used "as needed" for the relief of breakthrough symptoms including worsening of asthma symptoms and exacerbations, whereas controller medications are used regularly to reduce airway inflammation, *control* symptoms and reduce risk of exacerbations. If good control of the symptoms of asthma is not achieved, then a step-up approach to management is to provide a combination inhaled corticosteroid/long-acting beta$_2$-agonist (ICS/LABA) inhaler [4].

The combination ICS/LABA fluticasone propionate/formoterol fumarate (FP/FORM) as a fixed-dose combination (FDC) in a pressurised metered-dose inhaler (pMDI) was introduced in the UK in late 2012 for the regular treatment of adolescents (aged ≥ 12 to < 18 years) and adults (aged ≥ 18 years) with asthma. FP/FORM is indicated either as a step-up therapy for those who have inadequately controlled asthma with an inhaled corticosteroid, or as a maintenance therapy for those who are controlled on both an ICS and a LABA. Previous trials in asthmatic patients have demonstrated that the FP/FORM inhaler, when administered twice daily over 12 months, has a positive risk-benefit profile [5]. FP/FORM has been shown to have a comparable safety and tolerability profile to that of fluticasone plus formoterol when administered separately [6, 7] and to fluticasone/salmeterol (FP/SAL; Seretide®) [8] and budesonide/formoterol (BUD/FORM; Symbicort®) [9] in randomised controlled trials (RCTs) of up to 12 weeks' duration each enrolling between approximately 200 and 600 patients. However, RCTs are rarely representative of the patient populations likely to receive treatment and the quality of care seldom reflects what would be received in the real world. Therefore, observational studies in the post-authorisation phase of drug development provide a means to study and better understand medicine safety, prescribing practices, adherence to guidelines and licence indications in real-life clinical practice.

Based on this, the Medicines and Healthcare products Regulatory Agency (MHRA) recommended that a post-authorisation observational study of FP/FORM be performed using the Clinical Practice Research Datalink (CPRD) to evaluate the safety of FP/FORM over a longer period (> 1 year) in patients for whom the drug is licensed, and to evaluate off-label use of the drug. The aims of this study were to: (1) describe demographic, medication and disease-related characteristics of patients prescribed FP/FORM and other FDC ICS/LABA therapies for both licensed and off-label groups within 36 months post-FP/FORM launch; (2) estimate the incidence and hazard ratios (HRs) of possible adverse outcomes in patients prescribed FP/FORM versus other FDC ICS/LABA therapies for both licensed and off-label groups within the 36 months post-FP/FORM launch, and (3) quantify the prevalence of on- and off-label prescribing of FP/FORM and other FDC ICS/LABA therapies over 36 months post-FP/FORM launch.

2 Patients and Methods

2.1 Data Source

This study was conducted using linked data from the CPRD. In brief, CPRD is an electronic, longitudinal, health records database containing anonymised primary care data on patients registered with over 600 general practices in the UK. CPRD contains data on demographics, diagnoses, symptoms, prescriptions, referrals, immunisations, behavioural factors and test results for approximately 7% of the UK population. CPRD has been shown to be representative of the wider UK population in terms of age, sex and ethnicity [10]. Over half of all patients in CPRD have their primary care medical records linked with hospital discharge diagnosis data from secondary care [i.e. Hospital Episodes Statistics (HES)] and mortality data from the UK's national death registry [Office for National Statistics (ONS)] [10]. The CPRD database has been extensively validated for use in epidemiological research and is one of the most comprehensive longitudinal primary care databases available for healthcare research [11]. CPRD data can be obtained directly from CPRD subject to the custodian's policies for scientific, data governance, and financial approvals [12].

Ethics approval for use of the CPRD database is granted by the National Research Ethics Service Committee (NRES) for purely observational research using the primary care data and established data linkages. Ethics approval for this study was not required because these were secondary analyses of anonymised data. The protocol for this study was approved by the Independent Scientific Advisory Committee (ISAC) of the CPRD (protocol-number: 16_086). This study is

registered on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) website (study ID no. EUPAS12330), the aim of which is to necessitate transparency and scientific independence throughout the research process [13].

2.2 Study Design and Population

A historical cohort of patients prescribed an FDC ICS/LABA was constructed for this study. For the evaluation of prescribing prevalence, all patients who initiated on, or switched to an FDC ICS/LABA during the 36-month period between 25th September 2012 and 24th September 2015 were included. For the evaluation of adverse outcomes and patient characteristics, patients were required to have ≥ 12 months of data available prior to initiation or switch (initiation and first switch are hereon referred to as initiation, unless stated otherwise). The date of a first FDC ICS/LABA prescription or the date of switching to a different FDC ICS/LABA was defined as the index date; the 12-month period prior to the index date formed the baseline period for patient characterisation and confounder definition. Patients exited the study at the earliest date of either leaving their general practice, the end of the study period, death, or a record of one of the study adverse outcomes of interest.

For the evaluation of patient characteristics and adverse outcomes, patients were stratified into groups comprising: (1) patients diagnosed with asthma aged ≥ 18 years (adult asthma cohort); (2) patients diagnosed with asthma aged 12–17 years (adolescent asthma cohort); (3) patients diagnosed with asthma aged 4–11 years (paediatric asthma cohort); (4) patients diagnosed with asthma aged ≥ 18 years who were prescribed ICS/LABA as the maintenance and reliever therapy (MART) regimen, had a self-management plan (e.g. "as needed") at the index date and absence of a prescription for a short-acting beta$_2$-agonist (SABA) in the 12 months after the index date and presence of a SABA in the 12 months prior to the index date (self-management cohort) and (5) patients aged ≥ 31 years diagnosed with chronic obstructive pulmonary disease (COPD), no asthma and a forced expiratory volume in the first second (FEV_1)/forced vital capacity (FVC) ratio < 0.7 or no FEV_1/FVC recording (COPD cohort). The primary cohort of interest for adverse outcomes was the adult asthma cohort. The paediatric, self-management and COPD cohorts, and prescribing of the high dose in adolescent patients, were all unlicensed (i.e. "off-label") uses of FP/FORM (Table 1). Evaluation of prescribing incidence considered the adult, adolescent and paediatric asthma cohorts and the COPD cohort (the COPD cohort for prescribing incidence included patients with COPD and no asthma; an FEV_1/FVC ratio was not required).

2.3 Exposure

FDC ICS/LABA prescriptions were identified in the CPRD database by using product codes in CPRDs code browser. The included FDC ICS/LABAs were: FP/FORM pMDI (100/10, 250/10 or 500/20 µg twice daily), FP/SAL [dry power inhaler (DPI) or metered-dose inhaler (MDI)], BUD/FORM DPI and beclomethasone/formoterol (BDP/FORM, DPI or MDI), all of which could be administered with or without a spacer (Table 1). The identified codes were then cross-checked with Quality and Outcomes Framework (QOF) Read code lists (where available) and amended as appropriate. A list of search terms and the code lists used for this study are available in Online Resource 1.

2.4 Outcomes and Covariates

The primary safety outcome of interest was a composite of all adverse outcomes (i.e. the total accumulative number of events occurring in the patient's record) for each analysis group that occurred after initiation on an FDC ICS/LABA. Adverse outcomes included: COPD exacerbations, lower respiratory tract infections (LRTI), pneumonia, pulmonary embolism, tuberculosis, oral candidiasis, dysphonia/hoarse voice, other local oral adverse outcomes, adrenal failure, cardiac arrhythmias and ischaemia, hyperglycaemia, type 2 diabetes, anaphylactic reaction, cataract, glaucoma, hypokalaemia, anxiety or depression, growth retardation and reduced bone mineral density (including osteoporosis, osteoporosis-related fracture or osteopenia). The pre-defined adverse outcomes reflect the known and potential risks associated with the use of FP/FORM, which are also known risks for most other ICS/LABA therapies. All adverse outcomes were identified from primary care records, hospital episode statistics (HES) and Office for National Statistics (ONS) mortality data using the diagnostic codes shown in Online Resource 2. Each adverse outcome was also analysed separately (a) regardless of the number of events prior to the index date (for LRTIs, pneumonia, pulmonary embolism and tuberculosis) or (b) only if the event had not occurred in the year prior to the index date (for oral candidiasis through osteoporosis-related fracture or osteopenia). Serious adverse outcomes were those that were recorded in medical records as causes of death or inpatient hospitalisation. For prescribing incidence, the number of patients prescribed FDC ICS/LABA was obtained from patient data and the total number of person-years of patients prescribed FDC ICS/LABA was obtained as aggregate data for each subgroup over the time period of interest.

Table 1 Fixed-dose combination ICS/LABA comparison groups

FP/FORM pMDI and dose	Licensed comparator and dose
Patients aged ≥ 18 years with asthma	
Licensed: 50/5, 125/5, 250/10	1. Seretide DPI (FP/SAL) 100/50, 250/50, 500/50 2. Seretide MDI (FP/SAL) 50/25, 125/25, 250/25 3. Symbicort Turbohaler (BUD/FORM) 100/6, 200/6, 400/12 4. Fostair MDI or NEXThaler[a] (BDP/FORM) 100/6, 200/6[b]
Patients aged 12–17 years with asthma	
Licensed: 50/5, 125/5 Off-label: 250/10	Licensed comparators: 1. Seretide DPI (FP/SAL) 100/50, 250/50, 500/50 2. Seretide MDI (FP/SAL) 50/25, 125/25, 250/25 3. Symbicort Turbohaler (BUD/FORM) 100/6, 200/6, 400/12
Patients aged 4–11 years with asthma	
Off-label: 50/5, 125/5, 250/10	Licensed comparators: 1. Seretide DPI (FP/SAL) 100/50 2. Seretide MDI (FP/SAL) 50/25 3. Symbicort Turbohaler (BUD/FORM) 100/6 (aged 6–12 only)
Patients with COPD (and no asthma)	
Off-label: 50/5, 125/5, 250/10	Licensed comparators: 1. Seretide DPI (FP/SAL) 500/50 2. Symbicort Turbohaler (BUD/FORM) 200/6, 400/12 3. Fostair MDI[c] or NEXThaler[d] (BDP/FORM) 100/6
Patients prescribed FDC ICS/LABA as the "MART" regimen self-managing their condition	
Off-label: 50/5, 125/5, 250/10	1. Symbicort Turbohaler (BUD/FORM) 100/6, 200/6 2. Fostair MDI (BDP/FORM) 100/6

BDP beclomethasone, *BUD* budesonide, *COPD* chronic obstructive pulmonary disease, *DPI* dry powder inhaler, *FDC* fixed-dose combination, *FORM* formoterol, *FP* fluticasone, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LTRA* leukotriene receptor antagonist, *MART* maintenance and reliever therapy, *MDI* metered-dose inhaler, *PEF* peak expiratory flow, *pMDI* pressurised metered-dose inhaler, *SAL* salmeterol, *SD* standard deviation

[a]Licensed use of Fostair NEXThaler 100/6 in patients aged ≥ 18 years with asthma from October 2014

[b]Licensed use of Fostair MDI and Fostair NEXThaler 200/6 in patients aged ≥ 18 years with asthma from December 2015

[c]Licensed use of Fostair MDI 100/6 in COPD from April 2014

[d]Licensed use of Fostair NEXThaler 100/6 in COPD from December 2015

2.5 Study Size

An initial feasibility count from the CPRD database identified 239,176 acceptable patients with a prescription for an FDC ICS/LABA (including 10,589 patients prescribed FP/FORM) during the study period. The estimated power to detect a two-fold increase in risk of adverse outcomes for each cohort based on this initial count (assuming the smallest licensed comparator group had three times as many patients in it as the FP/FORM group) is presented in Table 2.

2.6 Statistical Analyses

The cohort of patients included in the study were categorised by first FDC ICS/LABA prescription using means for normally distributed data (± standard deviation), medians for non-normally distributed data (inter-quartile ranges) or frequencies.

Incidence rates with 95% confidence intervals (CI) were evaluated using a Poisson distribution for each adverse outcome for each FDC ICS/LABA. If there were fewer than 20 adverse outcomes in the FP/FORM group, results were summarised but not analysed. The HR (95% CI) for the comparison of FP/FORM (reference group) and each FDC ICS/LABA comparator (see Table 1 for FP/FORM dose and the corresponding comparator and dose) was estimated for the pre-defined adverse outcomes of interest using Cox regression models. Unadjusted HRs were estimated along with adjusted HRs from two further models. Model 1 adjusted for a priori confounders including age (at index date; continuous), sex, body mass index (closest measure to index date; continuous), percentage predicted peak expiratory flow (PEF) for asthma subgroups (closest measure to index date; continuous) or percentage predicted FEV_1 for COPD subgroups (closest measure to index date; continuous), smoking status (closest measure to index date; categorised as: current smoker, ex-smoker or never smoker), initiator or switch status (at index date) and prescribed FDC ICS/LABA dose per day (at index date; calculated as dose per puff × number of puffs/day minus FP equivalent)

Table 2 Estimated power to detect potential differences in adverse outcome incidence rates

Population	Estimated proportion of patients prescribed FP/FORM (%)	Estimated number of patients on FP/FORM in population	Estimated number in smallest FDC ICS/LABA comparator group	Power		
				Adverse event with incidence rate of 0.2 per 100 py (%)	Adverse event with incidence rate of 2 per 100 py (%)	Adverse event with incidence rate of 30 per 100 py (%)
On-label asthma patients	82	8683	26,049	78	99	99
Off-label asthma patients	1	106	318	< 10	< 10	81
COPD	7	741	2224	< 10	71	99
MART	2.5	264	794	< 10	23	99

COPD chronic obstructive pulmonary disease, *FDC* fixed-dose combination, *FORM* formoterol, *FP* fluticasone, *ICS* inhaled corticosteroid, *LABA* long-acting beta$_2$-agonist, *MART* maintenance and reliever therapy, *py* person-years

(except when the outcomes were pulmonary embolism, tuberculosis, cardiac arrhythmias/ischaemia or hypokalaemia). Model 2 also adjusted, dependent on the outcome, for a selection of other *potential* confounders including long-acting muscarinic antagonist (LAMA) prescriptions in the baseline period or at index date, ICS prescriptions in the baseline period or at index date, COPD diagnosis (yes/no), respiratory GP consultations without prescription for an oral corticosteroid, LRTIs during baseline, history of ischaemic heart disease (yes/no), history of hypertension (yes/no), pain-relief medication prescriptions (categorised), pneumonia adverse outcomes during baseline, and ICS prescriptions in the baseline period or at index date (see Table 5 footnotes a to l for full details).

To evaluate whether initiation/switch status influenced the FP/FORM versus other FDC ICS/LABA comparisons, an interaction between treatment and initiation/switch status was added into the adjusted model. Estimates of the HRs were presented for each comparison.

When missing, data on daily dose for FP/FORM, FP/SAL MDI and FP/SAL dry-powder inhaler (DPI) were imputed, based on a priori reasoning, as two × puffs/twice daily for MDIs and one × puff/twice daily for DPI. Missing data on dose for BDP/FORM or BUD/FORM were not imputed as these FDC ICS/LABAs can be prescribed as part of the MART regimen. Imputation of missing values was performed to preserve patient numbers and to minimise possible selection bias.

Prescribing incidence was presented as the number and percentage of patients receiving each FDC ICS/LABA in each subgroup. The rate per 1000-person years (TPY) of patients prescribed each FDC ICS/LABA was estimated for each subgroup as (number of patients prescribed FDC ICS/LABA divided by total number of person years) × 1000.

All statistical analyses were conducted using STATA version 14 (StataCorp, College Station, TX, USA: StataCorp LP) and SAS version 9.3 (SAS Institute, Cary, NC, USA).

3 Results

3.1 Patients Included in the Analysis

In total, 241,007 patients from the CPRD database were identified as having been prescribed an FDC ICS/LABA between 25th September 2012 and the 24th September 2015. Of these, 41,609 adults aged ≥ 18 years had a diagnosis of asthma and were prescribed either FP/FORM or another licensed comparator (main adult asthma cohort). A further 1865 patients were included in the adolescent asthma cohort and 1458 patients were included in the paediatric asthma cohort; the number of patients prescribed FP/FORM in the paediatric asthma cohort ($N = 27$) was too low to allow meaningful comparisons to be made, therefore no results are presented for this cohort. A total of 641 patients were included in the self-management cohort and 8212 patients were included in the COPD cohort. A total of 11,187 patients did not have an asthma or COPD diagnosis at the index date, most of these patients were initiators (94%) and had no further or only one further prescription of the FDC ICS/LABA in the outcome period (95%) (Fig. 1).

A total of 87,466 patients met the inclusion criteria to be analysed for prescribing incidence; 57,543 patients had a diagnosis of asthma (52,970 aged ≥ 18 years, 2470 aged 12–17 years and 2103 aged 4–11 years) and 15,742 had a diagnosis of COPD and were aged ≥ 31 years. 14,177 patients did not have a recorded diagnosis of asthma or COPD (Fig. 2).

3.2 Patient Characterisation

The characteristics of patients in the adult asthma cohort, grouped by different FDC ICS/LABAs medications, are shown in Table 3. Patient characteristics at baseline were broadly comparable across the different FDC ICS/LABA treatment groups, although patients prescribed FP/SAL

DPI tended to be older, and to have more severe asthma, ischaemic heart disease and hypertension than the comparator groups. The FP/SAL DPI group also experienced more exacerbations and attended more respiratory GP consultations. Patients prescribed FP/FORM tended to have slightly milder asthma compared with the other FDC ICS/LABA groups in terms of higher mean FEV_1 and PEF % predicted, and a lower number of respiratory GP consultations and exacerbations. Across all subgroups, FP/FORM patients were more likely to be switchers rather than initiators of their FDC ICS/LABA therapy for all subgroups; in the adult asthma cohort, 67% of patients prescribed FP/FORM had an FDC ICS/LABA prescription prior to the index date compared with 31–58% of patients prescribed the licensed comparators. Mean daily ICS dose (in FP equivalents) was highest for patients prescribed FP/SAL DPI (765 µg), followed by FP/FORM (652 µg), FP/SAL MDI (617 µg), BDP/FORM (429 µg) and BUD/FORM (302 µg). The patient characteristics for the adolescent asthma cohort, self-management cohort and COPD cohort are shown in Online Resource 3–5.

3.3 Adverse Outcomes

In the main adult asthma cohort, most adverse outcomes, and rate of occurrence of first outcome, were similar between FP/FORM and the other licensed comparators (Table 4). Where the rates of occurrence of first adverse outcome differed, these were generally lower for FP/FORM than licenced comparators. Adjusted HRs for the adult asthma cohort, comparing each FDC ICS/LABA with FP/FORM as the reference treatment, are shown in Table 5. Consistent with the rates of adverse outcomes observed for the different FDC ICS/LABAs, the adjusted HRs tended to be in favour of FP/FORM. The risk of adverse outcomes was significantly lower for patients prescribed FP/FORM compared with all

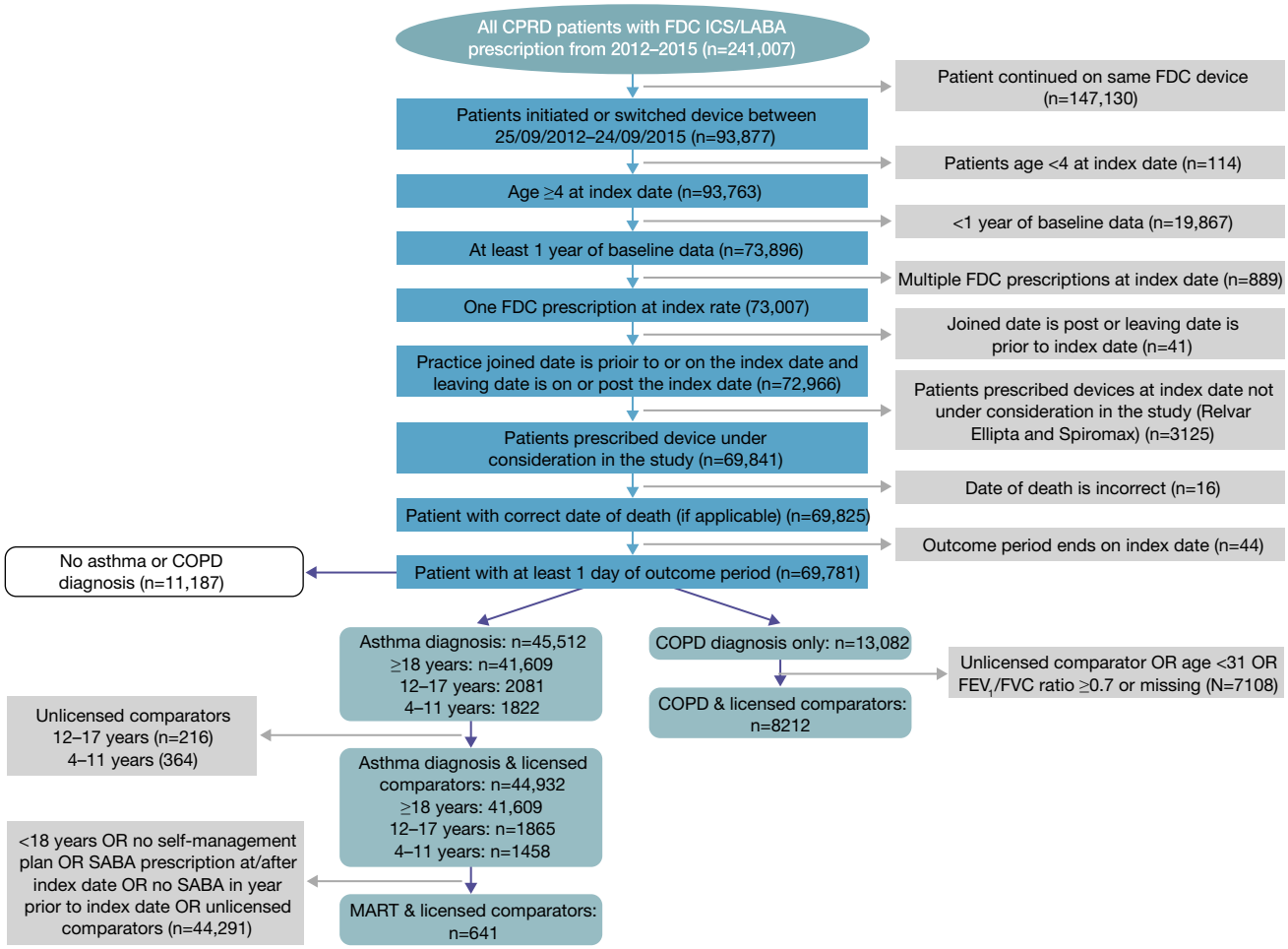

Fig. 1 Patient flowchart of patients prescribed an FDC ICS/LABA: 2012–2015 (Patient Characterisation and Analysis of Adverse Outcomes). *COPD* chronic obstructive pulmonary disease, *CPRD* Clinical Practice Research Datalink, *FDC* fixed-dose combination, *FEV_1* forced expiratory volume in the first second, *FVC* forced vital capacity, *ICS* inhaled corticosteroid, *LABA* long-acting beta2 agonist, *MART* maintenance and reliever therapy, *SABA* short-acting beta2 agonist

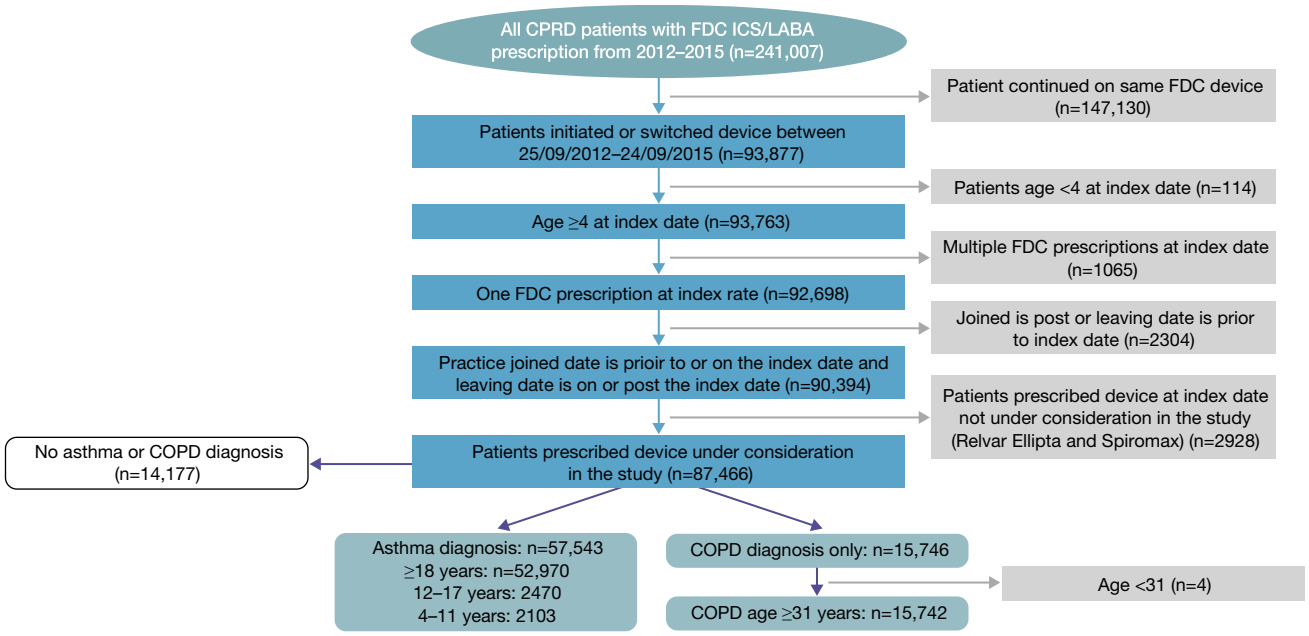

Fig. 2 Patient Flowchart of patients prescribed an FDC ICS/LABA 2012–2015 (Prescribing Incidence). *COPD* chronic obstructive pulmonary disease, *CPRD* Clinical Practice Research Datalink, *FDC* fixed-dose combination, *ICS* inhaled corticosteroid, *LABA* long-acting beta2 agonist

licensed comparators for "any new adverse outcome" and "anxiety/depression", as well as compared with FP/SAL DPI, FP/SAL MDI and BUD/FORM MDI for "LRTIs" and compared with BUD/FORM MDI and BDP/FORM for "oral candidiasis". In the sub-analysis split by initiators and switchers, the only adverse outcomes with a higher rate of occurrence for FP/FORM were "dysphonia/hoarse voice" (higher for FP/FORM than FP/SAL DPI in initiators) and "other local oral adverse events" (higher for FP/FORM than BUD/FORM in initiators) (Online Resource 6).

For the adolescent asthma cohort and COPD cohort, no significant differences between FP/FORM and the licensed FDC ICS/LABA comparators were observed for the incidence of "any new adverse outcome". The incidence of "any new adverse outcome" was too low for comparison of FP/FORM with licensed FDC/LABA comparators in the self-management cohort (analysis was only undertaken for categories with ≥ 20 patients with adverse outcomes observed in the FP/FORM group). Similarly, the incidence of most individual adverse outcomes was too low for analysis; however, in the COPD cohort no significant differences were observed for "COPD exacerbations", "LRTI" or "cardiac arrhythmias and ischaemia". All other analysis groups had < 20 patients with adverse outcomes in the FP/FORM group. The sub-analysis split by initiators and switchers suggested that the rate of occurrence of "COPD exacerbation" was higher for FP/FORM than FP/SAL DPI in those that switched FDC ICS/LABA, although this difference was not seen when compared with BUD/FORM or BDP/FORM and the reverse was observed for initiators when compared with BUD/FORM and BDP/FORM (Online Resource 7).

Considering serious adverse outcomes associated with inpatient hospitalisation in the adult asthma cohort, FP/FORM incidence rates were similar to or lower than the comparators for all adverse outcomes (Table 6). The rate of occurrence of first inpatient hospitalisation associated with an adverse outcome was significantly higher for FP/SAL MDI versus FP/FORM (HR 1.29; 95% CI 1.04, 1.61) and BUD/FORM versus FP/FORM (HR 1.43; 95% CI 1.12, 1.84). The rate of occurrence of first inpatient hospitalisation associated with cardiac arrhythmia and ischaemia was significantly higher for FP/SAL DPI (HR 1.53; 95% CI 1.17, 2.01), FP/SAL MDI (HR 1.56; 95% CI 1.18, 2.05) and BUD/FORM (HR 1.62; 95% CI 1.22, 2.14) compared with FP/FORM, while the rate of occurrence of first inpatient hospitalisation associated with anxiety/depression was significantly higher for FP/SAL MDI (HR 1.56; 95% CI 1.03, 2.37), BUD/FORM (HR 1.72; 95% CI 1.07, 2.78) and BDP/FORM (HR 1.80; 95% CI 1.16, 2.81) compared with FP/FORM. The number of deaths associated with adverse outcomes in patients prescribed FP/FORM in the adult asthma cohort ($n < 5$) was too low for incidence rates to be calculated. Incidence rates of serious adverse outcomes in the adolescent and paediatric asthma cohorts and the self-management cohort were also too low for analysis. In the COPD cohort, the incidence rate of inpatient hospitalisations associated with an adverse outcome was similar for FP/FORM and licensed comparators (FP/

Table 3 Patient characteristics (adult asthma cohort)

Characteristic	Measure	FP/FORM	FP/SAL DPI	FP/SAL MDI	BUD/FORM	BDP/FORM	*P* value
Age at index date (years)	*N* (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10,941 (100.0)	<0.001[a]
	Mean (SD)	54.3 (17.4)	59.7 (17.4)	54.4 (18.4)	52.0 (17.9)	53.4 (17.9)	
	Median (IQR)	55 (42, 68)	62 (48, 73)	55 (41, 69)	52 (38, 66)	54 (40, 67)	
Sex	*N* (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10,941 (100.0)	<0.001[b]
	Female, *n* (%)	3514 (61.4)	4103 (59.8)	5618 (62.8)	5460 (59.8)	6743 (61.6)	
	Male, *n* (%)	2213 (38.6)	2762 (40.2)	3330 (37.2)	3668 (40.2)	4198 (38.4)	
Body mass index (kg/m^2)	*N* (% not missing)	5547 (96.9)	6682 (97.3)	8554 (95.6)	8713 (95.5)	10,546 (96.4)	<0.001[a]
	Mean (SD)	29.2 (6.6)	28.8 (6.8)	29.0 (6.7)	28.9 (6.7)	29.2 (6.8)	
	Median (IQR)	28.1 (24.6, 32.9)	27.9 (24.0, 32.5)	27.9 (24.3, 32.6)	27.8 (24.2, 32.5)	28.1 (24.5, 32.8)	
FEV_1 % predicted	*N* (% not missing)	2378 (41.5)	4163 (60.6)	4040 (45.1)	4148 (45.4)	4850 (44.3)	<0.001[a]
	Mean (SD)	80.2 (23.5)	68.6 (24.3)	76.2 (23.5)	76.2 (23.6)	78.0 (23.6)	
	Median (IQR)	82 (65, 97)	68 (51, 86)	77 (60, 92)	78 (60, 93)	80 (63, 94)	
PEF % predicted[c]	*N* (% not missing)	5176 (90.4)	6019 (87.7)	7625 (85.2)	7602 (83.3)	9606 (87.8)	<0.001[a]
	Mean (SD)	96.5 (26.2)	85.0 (28.3)	92.4 (26.9)	94.0 (26.9)	94.5 (26.9)	
	Median (IQR)	97.4 (78.2, 115.6)	85.0 (64.2, 105.4)	92.9 (73.5, 113.1)	95.2 (74.8, 114.7)	95.3 (75.0, 115.6)	
Smoking status	*N* (% not missing)	5727 (100.0)	6864 (100.0)	8945 (100.0)	9124 (100.0)	10,941 (100.0)	<0.001[b]
	Non-smoker, *n* (%)	2912 (50.8)	2579 (37.6)	4185 (46.8)	4390 (48.1)	5206 (47.6)	
	Current smoker, *n* (%)	1014 (17.7)	1650 (24.0)	1837 (20.5)	1841 (20.2)	2223 (20.3)	
	Ex-smoker, *n* (%)	1801 (31.4)	2635 (38.4)	2923 (32.7)	2893 (31.7)	3512 (32.1)	
History of ischaemic heart disease	*N* (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10,941 (100.0)	<0.001[b]
	No, *n* (%)	5267 (92.0)	5948 (86.6)	8085 (90.4)	8399 (92.0)	10,072 (92.1)	
	Yes, *n* (%)	460 (8.0)	917 (13.4)	863 (9.6)	729 (8.0)	869 (7.9)	
History of hypertension	*N* (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10,941 (100.0)	<0.001[b]
	No, *n* (%)	4125 (72.0)	4486 (65.3)	6464 (72.2)	6911 (75.7)	7997 (73.1)	
	Yes, *n* (%)	1602 (28.0)	2379 (34.7)	2484 (27.8)	2217 (24.3)	2944 (26.9)	
Charlson Comorbidity Index (CCI)	*N* (% not missing)	5727 (100.0)	6865 (100.0)	8947 (100.0)	9127 (100.0)	10,940 (100.0)	<0.001[a]
	Mean (SD)	3.8 (2.6)	3.7 (3.2)	3.8 (2.7)	3.7 (2.7)	3.9 (2.4)	
	Median (IQR)	4 (4, 4)	4 (3, 4)	4 (4, 4)	4 (4, 4)	4 (4, 4)	
Year of first recorded asthma diagnosis	*N* (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10,941 (100.0)	<0.001[a]
	Mean (SD)	1996.0 (13.4)	1997.1 (13.6)	1998.3 (12.8)	1998.7 (12.9)	1997.9 (13.1)	
	Median (IQR)	1998 (1990, 2005)	2000 (1991, 2006)	2000 (1992, 2008)	2001 (1992, 2009)	2000 (1991, 2008)	
Length of follow-up (months)	*N* (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10,941 (100.0)	<0.001[a]
	Mean (SD)	12.7 (10.4)	13.4 (12.5)	13.5 (11.9)	13.7 (12.0)	13.0 (11.0)	
	Median (IQR)	10.9 (2.7, 19.0)	9.6 (2.0, 22.7)	10.1 (2.1, 21.8)	10.7 (2.0, 22.1)	10.6 (2.9, 19.4)	
	Min, max	(0.0, 42.5)	(0.0, 43.7)	(0.0, 44.0)	(0.0, 44.0)	(0.0, 44.0)	
Respiratory GP consultations without prescription for an oral corticosteroid (categorised)	*N* (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10,941 (100.0)	<0.001[b]
	0, n (%)	1660 (29.0)	1557 (22.7)	2271 (25.4)	2269 (24.9)	2829 (25.9)	
	1, *n* (%)	1871 (32.7)	2046 (29.8)	2620 (29.3)	2631 (28.8)	3390 (31.0)	
	2, *n* (%)	1110 (19.4)	1400 (20.4)	1758 (19.6)	1844 (20.2)	2242 (20.5)	
	3+, *n* (%)	1086 (19.0)	1862 (27.1)	2299 (25.7)	2384 (26.1)	2480 (22.7)	
Asthma GP consultations without prescription for an oral corticosteroid (categorised)	*N* (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10,941 (100.0)	<0.001[b]
	0, *n* (%)	2547 (44.5)	3401 (49.5)	4181 (46.7)	4477 (49.0)	4959 (45.3)	
	1, *n* (%)	2213 (38.6)	2370 (34.5)	3170 (35.4)	3065 (33.6)	3963 (36.2)	
	2, *n* (%)	695 (12.1)	765 (11.1)	1052 (11.8)	1059 (11.6)	1404 (12.8)	
	3+, *n* (%)	272 (4.7)	329 (4.8)	545 (6.1)	527 (5.8)	615 (5.6)	

Table 3 (continued)

Characteristic	Measure	FP/FORM	FP/SAL DPI	FP/SAL MDI	BUD/FORM	BDP/FORM	*P* value
Asthma or COPD exacerbations (categorised)	*N* (% not missing)	2685 (100.0)	4221 (100.0)	5187 (100.0)	5166 (100.0)	6101 (100.0)	<0.001[b]
	0, *n* (%)	1230 (45.8)	1431 (33.9)	2016 (38.9)	1962 (38.0)	2693 (44.1)	
	1, *n* (%)	755 (28.1)	1071 (25.4)	1507 (29.1)	1458 (28.2)	1662 (27.2)	
	2+, *n* (%)	700 (26.1)	1719 (40.7)	1664 (32.1)	1746 (33.8)	1746 (28.6)	
Prescribed FDC ICS/LABA dosing (FP equivalent dose per day)	*N* (% not missing)	4928 (86.0)	3186 (46.4)	7557 (84.5)	6525 (71.5)	7827 (71.5)	<0.001[a]
	Mean (SD)	652.1 (283.3)	764.8 (349.7)	617.0 (294.8)	301.6 (137.7)	428.6 (112.0)	
	Median (IQR)	500 (500, 1000)	1000 (500, 1000)	500 (500, 1000)	300 (200, 400)	500 (375, 500)	
	Min, max	100, 2000	150, 2000	50, 2000	50, 1200	125, 1000	
Prescribed FDC ICS/LABA (FP equivalent dose per day) (categorised) at index date	*N* (% not missing)	4928 (86.0)	3186 (46.4)	7557 (84.5)	6525 (71.5)	7827 (71.5)	<0.001[b]
	≥50 and ≤100, *n* (%)	10 (0.2)	*n*<5	22 (0.3)	*n*≥5	*n*<5	
	>100 and ≤200, *n* (%)	369 (7.5)	*n*≥5	1145 (15.2)	*n*≥5	*n*≥5	
	>200 and ≤400, *n* (%)	330 (6.7)	*n*≥5	206 (2.7)	*n*≥5	*n*≥5	
	>400 and <600, *n* (%)	2310 (46.9)	*n*≥5	3608 (47.7)	*n*≥5	*n*≥5	
	≥600 and <1000, *n* (%)	124 (2.5)	*n*≥5	29 (0.4)	*n*≥5	*n*≥5	
	≥1000, *n* (%)	1785 (36.2)	*n*≥5	2547 (33.7)	*n*<5	*n*≥5	
Other medication prescribed at index date	ICS inhaler, *n* (%)	44 (0.8)	48 (0.7)	100 (1.1)	89 (1.0)	119 (1.1)	0.023[b]
	SABA inhaler, *n* (%)	942 (16.4)	1198 (17.5)	1460 (16.3)	1399 (15.3)	1748 (16.0)	0.008[b]
	SAMA inhaler, *n* (%)	53 (0.9)	85 (1.2)	61 (0.7)	47 (0.5)	62 (0.6)	<0.001[b]
	LABA inhaler, *n* (%)	6 (0.1)	21 (0.3)	13 (0.1)	8 (0.1)	6 (0.1)	<0.001[b]
	LAMA inhaler, *n* (%)	156 (2.7)	767 (11.2)	289 (3.2)	334 (3.7)	313 (2.9)	<0.001[b]
	Theophylline, *n* (%)	48 (0.8)	83 (1.2)	33 (0.4)	42 (0.5)	62 (0.6)	<0.001[b]
	LTRA, *n* (%)	268 (4.7)	194 (2.8)	169 (1.9)	249 (2.7)	272 (2.5)	<0.001[b]

BDP beclomethasone, *BUD* budesonide, *COPD* chronic obstructive pulmonary disease, *DPI* dry powder inhaler, *FDC* fixed-dose combination, FEV_1 forced expiratory volume in the first second, *FORM* formoterol, *FP* fluticasone, *ICS* inhaled corticosteroid, *IQR* inter-quartile range, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *LTRA* leukotriene receptor antagonist, *MDI* metered-dose inhaler, *PEF* peak expiratory flow, *SABA* short-acting β_2-agonist, *SAL* salmeterol, *SAMA* short-acting muscarinic antagonist, *SD* standard deviation

[a]Kruskal–Wallis test

[b]Chi-square test

[c]PEF calculated using Roberts' Equations for adults and Rosenthal's Equations for paediatrics (and incorporating Robinson's Equation for paediatrics ≤1.1 m tall)

FORM: 20.49 per 100/py, FP/SAL DPI: 22.57 per 100/py, FP/SAL MDP: 19.44 per 100/py and BDP/FORM: 16.50 per 100/py; HRs and 95% CIs including 1 for all comparisons) and the number of deaths associated with adverse outcomes was too low for incidence rates to be calculated.

3.4 Prescribing Incidence

The prescribing incidence rate of FP/FORM (13.85 per TPY) was lower than the comparator FDC ICS/LABAs (20.30–28.13 per TPY) in the adult asthma cohort (Table 7). The prescribing incidence rate for FP/FORM was particularly low for the off-label groups with asthma aged <18 years. Of those patients prescribed FP/FORM, 80.8% were aged ≥18 years with asthma, 9.2% were without a recorded diagnosis of asthma or COPD, 6.2% had COPD and 3.8% were aged <18 years with asthma. Across the comparator FDC ICS/LABA groups, the incidence of off-label prescribing ranged from <2% for BUD/FORM and BDP FORM, 7.6% for FP/SAL DPI to 17.2% for FP/SAL MDI.

Table 4 Adverse outcomes for adult asthma cohort (incidence rate [95% confidence interval] per 100-person years)

Adverse outcome	FP/FORM $n=5727$	FP/SAL DPI $n=6865$	FP/SAL MDI $n=8948$	BUD/FORM $n=9128$	BDP/FORM $n=10{,}941$
Any new adverse outcome	24.75 (23.22, 26.37)	31.19 (29.64, 32.82)	28.86 (27.56, 30.23)	25.16 (24.00, 26.39)	25.47 (24.35, 26.65)
Lower respiratory tract infection	15.34 (14.18, 16.58)	25.24 (23.86, 26.69)	17.72 (16.74, 18.74)	16.63 (15.72, 17.60)	14.51 (13.70, 15.37)
Pneumonia	0.56 (0.38, 0.82)	1.34 (1.08, 1.65)	0.82 (0.65, 1.05)	0.67 (0.52, 0.87)	0.63 (0.49, 0.81)
Pulmonary embolism	0.13 (0.07, 0.26)	0.31 (0.21, 0.47)	0.28 (0.19, 0.40)	0.29 (0.20, 0.41)	0.19 (0.13, 0.29)
Tuberculosis	NA	NA	NA	NA	NA
Oral candidiasis	0.96 (0.74, 1.25)	1.47 (1.22, 1.78)	1.23 (1.03, 1.47)	1.15 (0.96, 1.38)	1.35 (1.15, 1.58)
Dysphonia/hoarse voice	1.13 (0.89, 1.43)	0.82 (0.64, 1.05)	1.44 (1.22, 1.70)	0.81 (0.66, 1.01)	0.77 (0.62, 0.94)
Other local oral adverse outcomes	1.46 (1.18, 1.80)	1.47 (1.22, 1.77)	1.53 (1.31, 1.80)	1.31 (1.10, 1.55)	1.41 (1.21, 1.65)
Adrenal failure	NA	NA	NA	NA	NA
Cardiac arrhythmias and ischaemia	1.81 (1.49, 2.19)	3.34 (2.94, 3.80)	2.40 (2.10, 2.73)	1.93 (1.68, 2.23)	1.87 (1.63, 2.14)
Hyperglycaemia	2.01 (1.67, 2.42)	2.86 (2.49, 3.30)	2.21 (1.93, 2.54)	1.76 (1.51, 2.04)	1.96 (1.71, 2.24)
Diagnosis of type 2 diabetes mellitus	1.13 (0.89, 1.44)	1.57 (1.31, 1.88)	1.23 (1.03, 1.47)	1.03 (0.85, 1.25)	1.12 (0.94, 1.33)
Anaphylactic reactions	NA	NA	NA	NA	NA
Cataract	1.06 (0.83, 1.36)	1.67 (1.40, 1.99)	1.14 (0.95, 1.38)	0.71 (0.57, 0.90)	0.91 (0.76, 1.11)
Glaucoma	0.13 (0.07, 0.27)	0.33 (0.22, 0.48)	0.20 (0.13, 0.31)	0.12 (0.07, 0.20)	0.21 (0.14, 0.31)
Hypokalaemia	NA	NA	NA	NA	NA
Anxiety/depression	5.72 (5.11, 6.41)	6.87 (6.26, 7.54)	6.87 (6.33, 7.45)	6.54 (6.03, 7.10)	6.91 (6.41, 7.45)
Reduced bone mineral density	0.85 (0.65, 1.12)	1.13 (0.92, 1.40)	0.79 (0.63, 0.99)	0.83 (0.67, 1.03)	0.77 (0.62, 0.94)

BDP beclomethasone, *BUD* budesonide, *DPI* dry powder inhaler, *FORM* formoterol, *FP* fluticasone, *MDI* metered-dose inhaler, *NA* number of events < 5, *SAL* salmeterol

A large proportion of patients prescribed FDC ICS/LABA (9.2–22.1% across the groups) had no recorded asthma or COPD diagnosis.

4 Discussion

In this large-scale cohort of patients in UK primary care comprising nearly 45,000 diagnosed asthma patients who received a prescription for an FDC ICS/LABA, we show that for all adverse outcomes examined, FP/FORM had a similar or lower adverse outcome rate than the licensed comparators. This conclusion held regardless of whether patients were FDC ICS/LABA initiators or switchers, with the exception of a higher rate of first dysphonia for FP/FORM versus FP/SAL DPI and first other local oral adverse event for FP/FORM versus BUD/FORM in initiators in the adult asthma cohort, and a higher rate of first COPD exacerbation for FP/FORM versus FP/SAL DPI in switchers in the COPD cohort. Demographic data showed that patients prescribed FP/FORM generally had milder asthma at baseline compared with patients prescribed other FDC ICS/LABAs; however, the mean prescribed dose of FP/FORM (in FP equivalents) was comparable to the other FDC ICS/LABA groups. The prescribing rate was lower for FP/FORM than licensed comparators (13.85 vs 20.30–28.13 per TPY in the adult asthma cohort), and of those patients prescribed FP/FORM, 80.8% were adults with asthma.

To the best of our knowledge, this is the largest observational medical records database study which has examined the comparative safety profile of FDC ICS/LABAs among asthma patients, and outside of the asthma indication, in the UK. Clinical trials have demonstrated that FP/FORM has a good benefit/risk ratio at the recommended doses and have reported the occurrence of only mild adverse outcomes. In a 12-month study of FP/FORM in mild-to-moderate asthmatic patients aged ≥ 12 years treated with FP/FORM, the most commonly reported adverse outcomes were nasopharyngitis, dyspnoea, pharyngitis and headache, the large majority of which were mild or moderate in severity [5]. Only 3.8% of adverse outcomes were considered study drug-related and none of the outcomes deemed to be serious were considered study drug related [5]. These findings broadly agree with our current study. A 12-week RCT comparing FP/FORM and FP/SAL in children aged 4–12 years with asthma

Table 5 Adverse outcomes for adult asthma cohort (treatment comparisons)

	Model	Number of observations in model	Comparison hazard ratio (95% confidence interval)			
			FP/SAL DPI vs FP/FORM	FP/SAL MDI vs FP/FORM	BUD/FORM vs FP/FORM	BDP/FORM vs FP/FORM
Any new adverse outcomes	Unadjusted	18,981	**1.26 (1.16, 1.37)**	**1.17 (1.08, 1.26)**	1.02 (0.94, 1.10)	1.03 (0.95, 1.11)
	Model 1	14,165	**1.17 (1.07, 1.28)**	**1.19 (1.09, 1.30)**	**1.16 (1.05, 1.28)**	**1.15 (1.05, 1.26)**
	Model 2[a]	14,165	**1.14 (1.04, 1.25)**	**1.18 (1.08, 1.29)**	**1.13 (1.03, 1.25)**	**1.14 (1.04, 1.25)**
Lower respiratory tract infection	Unadjusted	18,981	**1.68 (1.53, 1.85)**	**1.18 (1.08, 1.30)**	**1.11 (1.01, 1.22)**	0.96 (0.87, 1.06)
	Model 1	14,165	**1.37 (1.23, 1.51)**	**1.26 (1.14, 1.40)**	**1.53 (1.36, 1.73)**	**1.22 (1.09, 1.36)**
	Model 2[b]	14,165	**1.13 (1.02, 1.26)**	**1.11 (1.00, 1.23)**	**1.23 (1.09, 1.39)**	1.07 (0.95, 1.20)
Pneumonia	Unadjusted	18,981	**2.34 (1.51, 3.60)**	1.45 (0.93, 2.26)	1.18 (0.75, 1.86)	1.12 (0.71, 1.76)
	Model 1	14,165	1.31 (0.83, 2.06)	1.30 (0.82, 2.07)	**1.94 (1.14, 3.32)**	1.45 (0.86, 2.44)
	Model 2[c]	14,165	1.08 (0.68, 1.72)	1.07 (0.67, 1.72)	1.52 (0.88, 2.62)	1.26 (0.75, 2.13)
Oral candidiasis	Unadjusted	41,008	**1.60 (1.16, 2.20)**	1.31 (0.96, 1.80)	1.23 (0.90, 1.69)	**1.42 (1.05, 1.92)**
	Model 1	30,256	**1.64 (1.15, 2.34)**	**1.54 (1.08, 2.19)**	**1.94 (1.29, 2.92)**	**2.26 (1.57, 3.25)**
	Model 2[d]	30,256	1.41 (0.98, 2.02)	1.38 (0.97, 1.97)	**1.62 (1.07, 2.46)**	**2.04 (1.42, 2.95)**
Dysphonia/hoarse voice	Unadjusted	41,137	0.74 (0.52, 1.05)	1.29 (0.96, 1.73)	0.73 (0.53, 1.01)	**0.68 (0.49, 0.93)**
	Model 1	30,353	**0.69 (0.48, 1.00)**	1.27 (0.93, 1.74)	0.84 (0.57, 1.26)	0.74 (0.51, 1.07)
	Model 2[e]	30,353	0.71 (0.49, 1.03)	1.23 (0.90, 1.68)	0.83 (0.55, 1.24)	0.72 (0.50, 1.05)
Other local oral adverse outcomes	Unadjusted	40,844	1.03 (0.78, 1.37)	1.07 (0.82, 1.40)	0.91 (0.70, 1.20)	0.97 (0.75, 1.27)
	Model 1	30,129	1.14 (0.84, 1.53)	1.10 (0.82, 1.47)	0.87 (0.61, 1.22)	1.02 (0.75, 1.38)
	Model 2[f]	30,129	1.07 (0.79, 1.45)	1.04 (0.78, 1.40)	0.80 (0.57, 1.14)	0.97 (0.72, 1.32)
Cardiac arrhythmias and ischaemia	Unadjusted	40,165	**1.88 (1.49, 2.37)**	**1.34 (1.06, 1.69)**	1.09 (0.86, 1.38)	1.03 (0.82, 1.31)
	Model 1	34,238	**1.30 (1.02, 1.65)**	1.25 (0.97, 1.59)	1.15 (0.89, 1.48)	1.05 (0.83, 1.34)
	Model 2[g]	34,238	1.14 (0.89, 1.46)	1.10 (0.86, 1.41)	1.07 (0.83, 1.39)	1.01 (0.79, 1.29)
Hyperglycaemia	Unadjusted	38,393	**1.48 (1.17, 1.87)**	1.13 (0.90, 1.43)	0.90 (0.71, 1.15)	0.99 (0.78, 1.24)
	Model 1	28,208	1.20 (0.93, 1.54)	1.09 (0.85, 1.40)	1.16 (0.86, 1.55)	1.17 (0.90, 1.52)
	Model 2[h]	28,208	1.15 (0.89, 1.48)	1.06 (0.82, 1.37)	1.10 (0.82, 1.48)	1.14 (0.87, 1.49)
Diagnosis of type 2 diabetes mellitus	Unadjusted	41,022	**1.42 (1.05,1.92)**	1.10 (0.82,1.49)	0.93 (0.68,1.26)	1.00 (0.74,1.34)
	Model 1	30,266	1.31 (0.94, 1.81)	1.16 (0.84, 1.61)	1.11 (0.76, 1.62)	1.10 (0.78, 1.56)
	Model 2[i]	30,266	1.26 (0.90, 1.76)	1.14 (0.82, 1.58)	1.07 (0.73, 1.57)	1.08 (0.76, 1.52)
Cataract	Unadjusted	41,064	**1.57 (1.16, 2.12)**	1.07 (0.79, 1.46)	**0.67 (0.48, 0.94)**	0.86 (0.63, 1.17)
	Model 1	30,282	1.07 (0.78, 1.49)	0.94 (0.68, 1.32)	0.79 (0.52, 1.18)	0.97 (0.67, 1.39)
	Model 2[j]	30,282	1.02 (0.73, 1.43)	0.90 (0.65, 1.26)	0.74 (0.49, 1.12)	0.93 (0.64, 1.33)
Anxiety/depression	Unadjusted	37,282	**1.23 (1.06, 1.43)**	**1.22 (1.06, 1.40)**	**1.17 (1.01, 1.34)**	**1.21 (1.06, 1.39)**
	Model 1	27,491	**1.28 (1.09, 1.51)**	**1.27 (1.09, 1.49)**	**1.26 (1.05, 1.50)**	**1.30 (1.10, 1.52)**
	Model 2[k]	27,491	**1.28 (1.09, 1.51)**	**1.27 (1.09, 1.49)**	**1.26 (1.05, 1.50)**	**1.30 (1.10, 1.52)**
Reduced bone mineral density	Unadjusted	41,193	1.34 (0.94, 1.89)	0.93 (0.65, 1.32)	0.98 (0.69, 1.38)	0.90 (0.64, 1.28)
	Model 1	30,378	1.13 (0.78, 1.64)	0.95 (0.65, 1.39)	1.40 (0.92, 2.15)	1.26 (0.84, 1.87)
	Model 2[l]	30,378	1.06 (0.73, 1.55)	0.91 (0.62, 1.33)	1.21 (0.79, 1.87)	1.17 (0.78, 1.75)

Values in bold are statistically significant at the 5% level

Treatment comparisons were only performed for adverse outcomes reported for ≥ 20 patients in the FP/FORM group

Model 1 adjusted for a priori confounders. Model 2 adjusted for a priori confounders and selected potential confounders as described in footnotes a to l

BDP beclomethasone, *BUD* budesonide, *DPI* dry powder inhaler, *FORM* formoterol, *FP* fluticasone, *MDI* metered-dose inhaler, *SAL* salmeterol

[a]Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, COPD diagnosis

[b]Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, COPD diagnosis, respiratory GP consultations without prescription for an oral corticosteroid, LRTI adverse event during baseline

[c]Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, history of ischaemic heart disease, history of hypertension, COPD diagnosis, pain-relief medication prescriptions (categorised), respiratory GP consultations without prescription for an oral corticosteroid, pneumonia adverse event during baseline

[d]Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, COPD diagnosis, pain-relief medication pre-

Table 5 (continued)

scriptions (categorised), respiratory GP consultations without prescription for an oral corticosteroid

[e]Selected potential confounders adjusted for: ICS only prescriptions in baseline period or index date, COPD diagnosis, respiratory GP consultations without prescription for an oral corticosteroid

[f]Selected potential confounders adjusted for: respiratory GP consultations without prescription for an oral corticosteroid

[g]Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, history of ischaemic heart disease, history of hypertension, COPD diagnosis, pain-relief medication prescriptions (categorised)

[h]Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, history of ischaemic heart disease, history of hypertension, COPD diagnosis, pain-relief medication prescriptions (categorised)

[i]Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, history of ischaemic heart disease, history of hypertension, COPD diagnosis, pain-relief medication prescriptions (categorised)

[j]Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, history of ischaemic heart disease, history of hypertension, COPD diagnosis, pain-relief medication prescriptions (categorised)

[k]No further confounders selected in addition to a priori confounders

[l]Selected potential confounders adjusted for: LTRA prescriptions in baseline period or index date, LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, history of hypertension, COPD diagnosis, pain-relief medication prescriptions (categorised), respiratory GP consultations without prescription for an oral corticosteroid

Table 6 Serious adverse outcomes (associated with inpatient hospitalisation) for adult asthma cohort [incidence rate (95% confidence interval) per 100-person years]

Adverse outcome	FP/FORM $n=5727$	FP/SAL DPI $n=6865$	FP/SAL MDI $n=8948$	BUD/FORM $n=9128$	BDP/FORM $n=10{,}941$
Any adverse outcome	6.59 (5.56, 7.81)	13.48 (12.27, 14.81)	9.14 (8.23, 10.15)	7.48 (6.68, 8.36)	6.42 (5.73, 7.20)
Lower respiratory tract infection	2.34 (1.77, 3.09)	5.35 (4.64, 6.17)	3.38 (2.86, 4.00)	2.93 (2.46, 3.49)	1.97 (1.61, 2.41)
Pneumonia	0.87 (0.56, 1.37)	2.15 (1.73, 2.69)	1.67 (1.32, 2.12)	1.29 (0.99, 1.67)	0.90 (0.67, 1.21)
Cardiac arrhythmias and ischaemia	2.84 (2.27, 3.56)	7.43 (6.65, 8.30)	5.25 (4.66, 5.92)	4.16 (3.65, 4.75)	3.29 (2.86, 3.78)
Diagnosis of type 2 diabetes mellitus	1.63 (1.22, 2.20)	3.55 (3.03, 4.16)	2.28 (1.90, 2.73)	1.85 (1.52, 2.25)	1.79 (1.48, 2.15)
Anxiety/depression	1.29 (0.93, 1.80)	2.70 (2.25, 3.23)	2.05 (1.70, 2.48)	1.76 (1.44, 2.15)	1.92 (1.60, 2.30)
Reduced bone mineral density	0.44 (0.25, 0.77)	0.99 (0.73, 1.33)	0.82 (0.61, 1.10)	0.48 (0.32, 0.70)	0.29 (0.18, 0.46)

BDP beclomethasone, *BUD* budesonide, *DPI* dry powder inhaler, *FORM* formoterol, *FP* fluticasone, *MDI* metered-dose inhaler, *SAL* salmeterol

demonstrated no notable differences in safety between the two treatments and no safety concerns were identified with long-term FP/FORM therapy [14], a finding which is consistent with our results. No studies of the use of FP/FORM in the MART regimen were identified and so we could not assess our results in the context of other studies for this subgroup of patients.

A substantial proportion of patients ($n=11{,}187$, 16%) did not have either a COPD or asthma diagnosis recorded by the time of their initiation or switch to FDC ICS/LABA (index date). The majority were initiators (94%) and had no further or only one further prescription of the FDC ICS/LABA in the outcome period (95%). A limited number of patients had codes referring to the monitoring/management of asthma or COPD, which were not included in our code lists because the diagnostic Read code lists were based on QOF to identify asthma and COPD diagnosis. QOF is part of the UK national quality improvement initiative and pay-for-performance scheme, ensuring good reporting of these diseases. Furthermore, a very small proportion of these patients without a diagnosis were prescribed FP/FORM (6%), with the majority being prescribed FP/SAL (43%) or BUD/FORM (35%). We assume that this was a trial of treatment for patients where GPs were unsure of their diagnosis or wanted to see if treatment could improve outcomes, despite absence of a given diagnosis.

Important strengths of our study include use of a large representative population database with up to 3 years of follow-up data among all patients treated with an FDC ICS/LABA. Additionally, use of a publicly available medical records database, inclusion of an in-depth statistical analysis strategy and a participant flow diagram, means that our findings can be replicated and repeated in future analyses. There are several limitations of our study which need to be considered. Data on medications given during hospitalisation, medications provided in specialist care, and medications provided by a hospital following patient discharge are not recorded in patients' medical records. Spacer use would

Table 7 Percentage of patients prescribed FDC ICS/LABA and prescribing incidence rate by FDC ICS/LABA

	FP/FORM $n=7713$	FP/SAL DPI $n=18,761$	FP/SAL MDI $n=21,966$	BUD/FORM $n=22,283$	BDP/FORM $n=16,743$
Number (%) prescribed[a]					
No diagnosis	706 (9.2%)	2948 (15.7%)	3553 (16.2%)	4916 (22.1%)	2058 (12.3%)
Patients aged ≥ 18 years with asthma	6229 (80.8%)	9130 (48.7%)	12,485 (56.8%)	12,654 (56.8%)	12,472 (74.5%)
Patients aged ≥ 12 and < 18 years with asthma	242 (3.1%)	352 (1.9%)	936 (4.3%)	675 (3.0%)	243 (1.5%)[b]
	22 (0.3%)[b]				
Patients aged ≥ 4 and < 12 years with asthma	32 (0.4%)[b]	167 (0.9%)	1203 (5.5%)	266 (1.2%)	38 (0.2%)[b]
		15 (0.1%)[b]	327 (1.5%)[b]	55 (0.2%)[b]	
Patients with COPD only	482 (6.2%)[b]	4736 (25.2%)	3462 (15.8%)[b]	3356 (15.1%)	1932 (11.5%)
Prescribing incidence rate[c]					
Patients aged ≥ 18 years with asthma	13.85	20.30	27.75	28.13	27.72
Patients aged ≥ 12 and < 18 years with asthma	4.84	7.04	18.73	13.51	4.86[b]
	0.44[b]				
Patients aged ≥ 4 and < 12 years with asthma	0.75[b]	3.89	28.02	6.20	0.89[b]
		0.35[b]	7.62[b]	1.28[b]	
Patients with COPD only	10.18[b]	100.04	73.13[b]	70.89	40.81
		29.85[b]		7.63[b]	

BDP beclomethasone, *BUD* budesonide, *DPI* dry powder inhaler, *FDC* fixed-dose combination, *FORM* formoterol, *FP* fluticasone, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist; *MDI* metered-dose inhaler, *SAL* salmeterol

[a]Number (%) prescribed FDC ICS/LABA of all prescribed FDC ICS/LABA within subgroup

[b]Off-label dosage

[c]Prescribing incidence rate by FDC ICS/LABA (per 1000-person years)

be expected to affect adverse outcomes, particularly local effects; however, spacer prescription at index date was not captured in this analysis, and in any case may not accurately reflect spacer use in this real-life population where patients might buy devices over-the-counter or use old devices. The analyses were limited by low numbers of patients prescribed FP/FORM, particularly in certain subgroups such as children aged 12–17 years with asthma and patients on the MART regimen. Furthermore, due to this study being conducted with use of retrospective data from a database, we are unable to assess the direction of causality between the different FDC ICS/LABAs and the adverse outcomes. The analysis only captured pre-defined known adverse outcomes for FP/FORM, and treatment differences for other potential adverse outcomes may have been overlooked. We also acknowledge that "mild" adverse outcomes are unlikely to be reported by a patient to their GP (e.g. headache); however, it is unlikely that underreporting of such outcomes will be differential across the different FDC ICS/LABAs medications.

In conclusion, our analysis of a large-scale cohort of patients in UK primary care, comprising nearly 45,000 diagnosed asthma patients who received a prescription for an FDC ICS/LABA, and who were followed-up for up to 36 months, suggest that FP/FORM was associated with an overall lower adverse outcome rate than the licensed comparators, but was used in patients with milder disease.

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Compliance with Ethical Standards

Conflict of interest David Price has board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp, Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals, Theravance, UK National Health Service, Zentiva (Sanofi Generics); payment for lectures/speaking engagements from Almirall,

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Ethics approval This article is based on previously conducted studies, and does not involve any new studies of human subjects performed by any of the authors.

Data availability The dataset analysed during the current study is available from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) at: https://www.cprd.com/dataAccess/.

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References

1. World Health Organization. 10 facts on asthma; 2017. http://www.who.int/features/factfiles/asthma/en/. Accessed 28 March 2019.
2. Mukherjee M, Stoddart A, Gupta RP, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. BMC Med. 2016;14:113. https://doi.org/10.1186/s12916-016-0657-8.
3. Healthline. Complications of Asthma; 2017. https://www.healthline.com/health/asthma-complications. Accessed 28 March 2019.
4. GINA 2018 Report, Global Strategy for Asthma Management and Prevention. https://ginasthma.org/gina-reports/. Accessed 28 March 2019.
5. Mansur AH, Kaiser K. Long-term safety and efficacy of fluticasone/formoterol combination therapy in asthma. J Aerosol Med Pulm Drug Deliv. 2013;26:190–9.
6. Bodzenta-Lukaszyk A, Pulka G, Dymek A, et al. Efficacy and safety of fluticasone and formoterol in a single pressurized metered dose inhaler. Respir Med. 2011;105:674–82.
7. Bodzenta-Lukaszyk A, van Noord J, Schroder-Babo W, McAulay K, McIver T. Efficacy and safety profile of fluticasone/formoterol combination therapy compared to its individual components administered concurrently in asthma: a randomised controlled trial. Curr Med Res Opin. 2013;29:579–88.
8. Bodzenta-Lukaszyk A, Dymek A, McAulay K, Mansikka H. Fluticasone/formoterol combination therapy is as effective as fluticasone/salmeterol in the treatment of asthma, but has a more rapid onset of action: an open-label, randomized study. BMC Pulm Med. 2011;11:28.
9. Bodzenta-Lukaszyk A, Buhl R, Balint B, Lomax M, Spooner K, Dissanayake S. Fluticasone/formoterol combination therapy versus budesonide/formoterol for the treatment of asthma: a randomized, controlled, non-inferiority trial of efficacy and safety. J Asthma. 2012;49:1060–70.
10. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44:827–36.
11. Walley T, Mantgani A. The UK General Practice Research Database. Lancet. 1997;350:1097–9.
12. Clinical Practice Research Datalink. https://www.cprd.com/. Accessed 28 March 2019.
13. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). http://www.encepp.eu/. Accessed 28 March 2019.
14. Płoszczuk A, Bosheva M, Spooner L, McIver T, Dissanayake S. Efficacy and safety of fluticasone propionate/formoterol fumarate in pediatric asthma patients: a randomized controlled trial. Ther Adv Respir Dis. 2018;12:1753466618777924. https://doi.org/10.1177/1753466618777924.