

## ORIGINAL ARTICLE

# Asthma control with extrafine-particle hydrofluoroalkane–beclometasone vs. large-particle chlorofluorocarbon–beclometasone: a real-world observational study

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## Clinical & Experimental Allergy

### Summary

**Background** The extrafine-particle formulation of hydrofluoroalkane–beclometasone (EF HFA–BDP; Qvar<sup>®</sup>) demonstrates improved total and small airway deposition compared with large-particle chlorofluorocarbon (CFC)–BDP. In some short-term studies, EF HFA–BDP provides greater effects on lung function than CFC–BDP, and hence is recommended to be prescribed at a lower dose, but whether there are differences in asthma outcomes during long-term treatment is unknown.

**Objective** To compare the effectiveness of EF HFA–BDP vs. CFC–BDP over 1 year.

**Methods** This retrospective matched cohort study examined outcomes in a large primary care database for patients aged 5–60 years with asthma receiving their first inhaled corticosteroid (ICS) prescription (initiation population) or first ICS dose increase (step-up population) by a pressurized metered-dose inhaler (pMDI) as EF HFA–BDP or CFC–BDP. Patients were matched on baseline demographic and asthma severity measures in EF HFA–BDP:CFC–BDP ratios of 1 : 3 and 1 : 2 for initiation and step-up populations, respectively. Step-up patients were matched also on ICS dose during a baseline year. Co-primary endpoints were asthma control (composite measure comprising no recorded hospital attendance for asthma, oral corticosteroids, or antibiotics for lower respiratory infection) and exacerbation rate during the outcome year.

**Results** For the initiation population (EF HFA–BDP *n* = 2882; CFC–BDP *n* = 8646), adjusted odds of achieving asthma control with EF HFA–BDP vs. CFC–BDP was 1.15 (95% CI 1.02–1.28). For the step-up population (*n* = 258 and 516), adjusted odds of asthma control with EF HFA–BDP was 1.72 (95% CI 1.14–2.56). EF HFA–BDP was prescribed at a median dose half that of CFC–BDP.

**Conclusion and Clinical Relevance** During 1 year after initiating or stepping up ICS therapy by pMDI, patients who received EF HFA–BDP were more likely to achieve asthma control than those receiving CFC–BDP. These findings suggest that ICS formulation, particle size, and deposition characteristics play important roles in real-life effectiveness of asthma therapy. This study shows that an EF-particle formulation of beclometasone can be used at half the dose of the large-particle formulation with at least as good clinical outcomes.

**Keywords** asthma, beclometasone dipropionate, inhaled corticosteroid, lung deposition, observational study, particle size

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### Introduction

Several hydrofluoroalkane (HFA) propellant formulations of inhaled corticosteroids (ICS) have been developed in

response to the required phasing out of ozone-depleting chlorofluorocarbon (CFC) propellants. Some HFA products are formulated with the same particle size and administered at the same dose as the original CFC product.

An exception is the extrafine (EF)-particle HFA-beclometasone dipropionate (BDP) formulation sold under the brand name Qvar<sup>®</sup>. By license, this product is recommended to be administered at approximately one half the dose of CFC-BDP. For this reason, clinical guidance in the United Kingdom recommends that inhaled beclometasone products be prescribed by name [1–3].

Qvar<sup>®</sup> (EF HFA-BDP) by a pressurized metered dose inhaler (pMDI) is BDP formulated as a solution, unlike CFC-BDP pMDIs, which are formulated as suspensions. The EF HFA-BDP pMDI solution produces an aerosol spray with a particle mass median aerodynamic diameter of 1.1 µm as compared with 3.5 µm for CFC-BDP [4–6]. The EF HFA-BDP pMDI also has a softer spray, warmer spray temperature, and longer spray duration than CFC-BDP pMDIs [5]. These characteristics result in increased total and peripheral lung deposition and decreased oropharyngeal deposition of EF HFA-BDP [6, 7].

ICS are effective anti-inflammatory agents for asthma therapy that work at the site of deposition in the lung [8]. As airway inflammation in asthma involves both large and small airways [9, 10], increasing the total lung deposition of an ICS, as well as its deposition throughout large and small airways, could influence asthma outcomes. In randomized controlled trials (RCTs) of beclometasone formulations for asthma, the short-term efficacy of EF HFA-BDP is equivalent to that of CFC-BDP administered at twice the dose [11, 12]. A rigorous dose-response study has confirmed that EF HFA-BDP provides significantly greater effects on lung function than comparable doses of CFC-BDP [13].

Patients enrolled in RCTs, however, may not be representative of those seen in everyday clinical practice. Fewer than 10% of primary-care patients with asthma are eligible for the typical RCT because of selective trial enrolment criteria [14, 15]. Moreover, RCTs likely do not capture the effects of suboptimal adherence as well as of poor inhaler technique that are commonplace in real-world practice [16]. Nonetheless, in 6-month and 12-month RCTs, improvements in asthma symptoms and quality of life tended to be better with EF HFA-BDP than CFC-BDP at twice the dose [17–19], suggesting that there may be clinically meaningful differences between the EF-particle and large-particle formulations.

We undertook this observational study to investigate the real-world effectiveness of EF HFA-BDP as compared with CFC-BDP for patients with asthma who were new to ICS therapy or receiving their first increase in ICS dose. In an identically designed companion study comparing EF HFA-BDP and fluticasone, we found that patients receiving EF HFA-BDP had similar or better odds of achieving asthma control at lower prescribed doses than those receiving fluticasone, a large-particle ICS [20]. The objective of the present study was to compare formulations with different particle sizes of the same ICS molecule,

namely, EF as compared with large-particle beclometasone. We hypothesized that differences in effectiveness might become apparent over 1 year for the diverse patients with asthma seen in primary care.

## Methods

### *Database and study population*

The General Practice Research Database (GPRD) has approximately 500 participating practices throughout the United Kingdom and contains deidentified clinical and prescribing information for 12 million patients overall, including active records for 4.9 million patients, or about 8% of the UK population [21]. This large, well-maintained database is used routinely for pharmaco-epidemiologic research and has been described elsewhere [20, 22, 23].

We studied patients with asthma aged 5–60 years at the time they were prescribed a pMDI containing either EF HFA-BDP (as Qvar<sup>®</sup>, Teva Pharmaceutical Industries Ltd, Petach Tikva, Israel) or CFC-BDP as their first ICS prescription (initiation population) or their first increase in ICS dose (step-up population). Eligible patients were continuously registered at the same practice for 1 year before (baseline year) and 1 year after (outcome year) the index date of the EF HFA-BDP or CFC-BDP prescription; and the practice had to be judged by the GPRD as having up-to-standard data during that time [21]. The period of study was January 1997 through June 2007.

A diagnosis of asthma was defined as a medical database code consistent with an asthma diagnosis or two or more prescriptions for asthma therapy, including one ICS prescription, at different time-points during the outcome year. Patients in the step-up population had at least one prescription for ICS by pMDI during the baseline year and a minimum dose increase of 50% on the index date, captured in the database as an increase in prescribed number of puffs or formulation strength. Patients with a recorded diagnosis of chronic obstructive pulmonary disease (COPD) or chronic respiratory disease other than asthma were excluded from study, as were patients in the step-up population who received a combination inhaler or any add-on asthma controller agent during the baseline year. The search strategy and medical database codes used for diagnostic, consultation and pharmacotherapy searches are available on request.

Approval was given for this study by the GPRD Independent Scientific Advisory Committee (ISAC protocol number 07\_083). The trial registration number was Clinicaltrial.gov number NCT01141439.

### *Outcome measures*

Data from the baseline year were used for patient characterization and confounder definition. Comorbidities

were accounted for by the Charlson comorbidity index score [24], calculated for each patient using ICD-9-matching algorithms produced by CliniClue software (<http://www.cliniclue.com/software>). The socio-economic status assigned to patients was that assigned, in quintiles, to their practices by the GPRD, using the Index of Multiple Deprivation as a proxy measure [21, 25].

The two co-primary end-points were the primary measure of asthma control and exacerbation rate during the outcome year. The 'primary measure of asthma control' was a composite measure, designed to capture available data indicative of control, in accordance with asthma guidelines and international consensus [2, 26], and defined as:

1. no recorded hospital attendance for asthma (including admission or A&E department, out of hours, or out-patient department attendance);
2. no prescription for oral corticosteroid;
3. no consultation, hospital admission, or A&E department attendance for lower respiratory tract infection requiring antibiotics.

An exacerbation was defined as a hospital admission or A&E department attendance for asthma or a course of oral corticosteroids during the outcome year; exacerbations on the index date were included with the baseline data.

Two other composite measures evaluated different aspects of asthma control. 'Asthma control plus short-acting  $\beta_2$  agonist (SABA) use' included an average prescribed daily dose of salbutamol of  $\leq 200 \mu\text{g}$  or terbutaline  $\leq 500 \mu\text{g}$  as a fourth outcome in addition to the three criteria defining the primary measure of asthma control. 'Asthma control plus no additional or change in therapy' was defined as no exacerbation and no change in therapy, where a change in therapy could be any of the following:

1. increase in ICS dose;
2. change in ICS or inhaler device;
3. use of additional therapy for asthma.

### Statistical analyses

All outcome measures were specified *a priori* before the analyses were performed, and all analyses took account of any residual confounding variables using multiple regression methods according to the study group's standard operating procedures [27]. For the primary outcomes, a *P*-value of  $\leq 0.05$  was used to denote statistical significance. For secondary outcomes, a more stringent *P*-value of  $\leq 0.01$  was used to denote statistical significance because of potential multiple testing and the associated increased chance of a type 1 error. Data were analysed using SPSS version 17 (SPSS Inc., Chicago, IL, USA) and SAS version 9.2 (SAS Software Ltd, Marlow, UK).

Treatment cohorts were compared at baseline using the Mann-Whitney test for continuous variables and the  $\chi^2$ -test for categorical variables. Continuous variables showing a skewed distribution were categorized appropriately, as follows: SABA daily doses (0, 1–100, 101–200, 201–300, 301–400 and  $> 400 \mu\text{g}$ ); ICS daily doses (as the CFC-BDP doses, with EF HFA-BDP doses matched to double the dose of CFC-BDP, as per licensing recommendations, of 0–199, 200–399, 400–599, 600–799, 800–1199, 1200–1599 and  $\geq 1600 \mu\text{g}$ ); and number of oral corticosteroid prescriptions (0, 1, 2 and  $\geq 3$ ) and hospitalizations (0 and  $\geq 1$ ).

The baseline analysis highlighted significant differences between patients in the two treatment cohorts; therefore, to better account for and examine differences between cohorts, we elected to use both a matched analysis (reported here) and an adjusted but unmatched analysis (unmatched data are included as supporting information).

Patients in the two cohorts were matched in EF HFA-BDP:CFC-BDP ratios of 1 : 3 for the initiation population and 1 : 2 for the step-up population to maximize sample sizes and the power of statistical tests. We matched on key demographic and clinically relevant characteristics to minimize the potential for confounding in the outcomes. Matching variables included age, sex and non-collinear criteria indicative of baseline asthma control, namely, number of oral corticosteroid prescriptions, SABA daily dose and number of asthma consultations without oral corticosteroids. For the step-up population, matching also took into account the mean ICS daily dose during the baseline year, with EF HFA-BDP doses matched to double the dose of CFC-BDP, as per licensing recommendations. Patient ages were matched within 1 year for children aged 5 years, within 3 years for children aged 6–12 years and within 5 years for patients aged 13 years and older.

Conditional logistic regression was used to compare baseline characteristics between matched cohorts. Any variables that remained potentially different between matched cohorts at baseline ( $P < 0.10$ ) were included as potential confounding factors in the outcome analysis. Conditional logistic regression was used to compare cohorts for binary outcomes; and a conditional Poisson regression model (adjusted for over-dispersion and using empirical standard error estimates for more robust confidence intervals) was used to compare outcome exacerbation rates.

For the unmatched analyses, a binary logistic regression model was used to compare cohorts for binary outcomes, and a Poisson regression model (adjusted for over-dispersion using robust standard errors) was used to obtain estimates of exacerbation rates during the outcome period in the EF HFA-BDP cohorts relative to the CFC-BDP cohorts. All models included adjustments for potential baseline confounders. Those variables that were

potentially different between treatment cohorts at baseline (assuming that they were not collinear with each other, in which case the one most likely to be clinically meaningful was used) or that were predictive of outcome in a multivariate analysis were included as potential confounding factors. In a *post hoc* sensitivity analysis, we also compared the co-primary outcome measures for matched cohorts of ages 5–12 and 18–60 years.

## Results

During the study period from 1997 to 2007, 56 513 of 156 003 patients (36.2%) in the GPRD receiving a first prescription of ICS had valid inclusion criteria and 9369 of 27 396 patients (34.2%) receiving a first increase in dose of ICS had valid inclusion criteria. Of these, 36 864 of 56 513 patients (65%) initiating ICS and 3988 of 9369 patients (43%) receiving an increased ICS dose were prescribed either EF HFA-BDP or CFC-BDP, had valid inclusion criteria, and were included in the unmatched analyses, as reported in the online supplement (supporting information Fig. S1). In the initiation population, patients had been registered in the GPRD without a previous ICS prescription for a median time of 10.2 years [interquartile range (IQR), 5.1–16.7 years] for the EF HFA-BDP cohort and 8.2 years (IQR, 4.6–14.1) for the CFC-BDP cohort, indicating that the prescription was likely their first for ICS.

### *Baseline demographic and clinical characteristics of matched cohorts*

The matching process is depicted in supporting information Figure S2. There were several statistically significant baseline differences between cohorts after matching, particularly in the initiation population, but they were small and not clinically meaningful (Tables 1 and 2). The year of the index date prescription was generally later for patients in EF HFA-BDP cohorts than CFC-BDP cohorts of both initiation and step-up populations ( $P < 0.001$  for both comparisons; data not shown).

### *Outcomes for the initiation population (matched cohorts)*

Most patients were prescribed a daily dose of EF HFA-BDP  $< 400 \mu\text{g}$  or CFC-BDP  $< 800 \mu\text{g}$  on the index date. Figure 1a shows the distribution of actual index date doses, and Fig. 1c shows the index date dose distribution with EF HFA-BDP doses doubled to depict dose proportionality with CFC-BDP doses as per the 1:2 ratio recommended by licensing.

Over the outcome year, after initiating ICS therapy, the percentage of patients achieving the primary measure of asthma control increased to  $> 80\%$  in both cohorts (Table 3). Exacerbation rates were similar for the two cohorts. After adjustment for potential confounding factors, the

odds of achieving asthma control were significantly higher in the EF HFA-BDP cohort than in the CFC-BDP cohort (Fig. 2). Adjusted exacerbation rates were not significantly different between cohorts.

Disaggregated outcomes for the composite measures (Table 3) and secondary composite measures were similar in the two treatment cohorts (Fig. 2). For patients with changes in therapy, the types of changes were similar in the two cohorts (Table 4).

### *Outcomes for the step-up population (matched cohorts)*

Most patients were prescribed a daily dose of EF HFA-BDP 200–599  $\mu\text{g}$  or CFC-BDP 400–1199  $\mu\text{g}$  on the index date. Figure 1b shows the distribution of actual index date doses, and Fig. 1d shows the index date dose distribution with EF HFA-BDP doses doubled to depict dose proportionality with CFC-BDP doses as per the 1:2 ratio recommended by licensing.

Over the outcome year after the step-up in therapy, the percentage of patients achieving asthma control increased to over 82% in the EF HFA-BDP cohort and to 76% in the CFC-BDP cohort (Table 3). Patients in the CFC-BDP cohort experienced more exacerbations. After adjusting for confounders, the odds of achieving the primary measure of asthma control were significantly greater for the EF HFA-BDP cohort; exacerbation rates were not significantly different between cohorts (Fig. 2).

Disaggregated outcomes for the composite measures were generally similar for the two cohorts (Table 3). Results for the secondary composite measure of asthma control incorporating SABA use significantly favoured the EF HFA-BDP cohort (Fig. 2). Changes in therapy were similar in frequency and type between patients in the two cohorts (Table 4).

### *Sensitivity analysis*

The results of the sensitivity analysis supported the primary analyses (Table 5). The odds of asthma control was significantly better for adults in the EF HFA-BDP cohorts of both initiation and step-up populations, while the rate of exacerbations was significantly lower for those receiving EF HFA-BDP in the step-up population. For children in the initiation population, the odds of asthma control was better but not significantly so, while the rate of exacerbations was significantly lower for those in the EF HFA-BDP cohort than for those in the CFC-BDP cohort. (There were too few children in the EF HFA-BDP cohort of the step-up population to warrant an analysis.)

### *Results of the unmatched analyses*

At baseline, there were several statistically and clinically important differences in demographic characteristics between unmatched treatment cohorts of both initiation and step-up populations (supporting information Table S1).

**Table 1.** Baseline demographic and clinical characteristics of patients initiating ICS by pMDI and those receiving an increased dose of ICS by pMDI: matched analyses

| Characteristics                                              | Initiation population            |                               |                  | Step-up population              |                              |                  |
|--------------------------------------------------------------|----------------------------------|-------------------------------|------------------|---------------------------------|------------------------------|------------------|
|                                                              | EF HFA-BDP<br>( <i>n</i> = 2882) | CFC-BDP<br>( <i>n</i> = 8646) | <i>P</i> -value* | EF HFA-BDP<br>( <i>n</i> = 258) | CFC-BDP<br>( <i>n</i> = 516) | <i>P</i> -value* |
| Male sex, <i>n</i> (%)                                       | 1231 (42.7)                      | 3693 (42.7)                   | n/a              | 107 (41.5)                      | 214 (41.5)                   | n/a              |
| Age, mean (SD)                                               | 32.9 (15.8)                      | 32.6 (15.9)                   | <0.001           | 31.6 (16.8)                     | 31.5 (17.1)                  | 0.446            |
| 5–12 years, <i>n</i> (%)                                     | 379 (13.2)                       | 1351 (15.6)                   | <0.001           | 40 (15.5)                       | 100 (19.4)                   | 0.059            |
| 13–17 years, <i>n</i> (%)                                    | 279 (9.7)                        | 652 (7.5)                     |                  | 37 (14.3)                       | 51 (9.9)                     |                  |
| 18–60 years, <i>n</i> (%)                                    | 2224 (77.2)                      | 6643 (76.8)                   |                  | 181 (70.2)                      | 365 (70.7)                   |                  |
| Weight (kg), mean (SD) <sup>†</sup>                          | 71.9 (23.1)                      | 71.7 (22.8)                   | 0.501            | 69.9 (25.9)                     | 69.6 (25.2)                  | 0.660            |
| Height (m), mean (SD) <sup>†</sup>                           | 1.64 (0.18)                      | 1.63 (0.17)                   | 0.052            | 1.62 (0.19)                     | 1.60 (0.20)                  | 0.027            |
| Body mass index (kg/m <sup>2</sup> ), mean (SD) <sup>†</sup> | 26.1 (7.1)                       | 26.2 (7.2)                    | 1.0              | 25.7 (7.5)                      | 26.0 (7.6)                   | 0.859            |
| SES (logged), mean (SD) <sup>‡</sup>                         | 2.9 (0.7)                        | 2.8 (0.8)                     | 0.001            | 2.9 (0.8)                       | 2.9 (0.8)                    | 0.216            |
| Charlson comorbidity index, <i>n</i> (%)                     |                                  |                               |                  |                                 |                              |                  |
| 0                                                            | 2683 (93.1)                      | 7955 (92.0)                   |                  | 236 (91.5)                      | 475 (92.1)                   |                  |
| 1                                                            | 114 (4.0)                        | 389 (4.5)                     | 0.045            | 4 (1.6)                         | 7 (1.4)                      | 0.665            |
| 2                                                            | 65 (2.3)                         | 217 (2.5)                     |                  | 11 (4.3)                        | 25 (4.8)                     |                  |
| 3                                                            | 20 (0.7)                         | 85 (1.0)                      |                  | 7 (2.7)                         | 9 (1.7)                      |                  |
| Smoking status, <i>n</i> /total <i>n</i> (%) <sup>§</sup>    |                                  |                               |                  |                                 |                              |                  |
| Current                                                      | 652/1872 (34.8)                  | 1726/4393 (39.3)              | <0.001           | 64/180 (35.6)                   | 83/256 (32.4)                | 0.012            |
| Former                                                       | 338/1872 (18.1)                  | 887/4393 (20.2)               |                  | 23/180 (12.8)                   | 60/256 (23.4)                |                  |
| Non-smoker                                                   | 882/1872 (47.1)                  | 1780/4393 (40.5)              |                  | 93/180 (51.7)                   | 113/256 (44.1)               |                  |
| Recorded comorbidity, <i>n</i> (%)                           |                                  |                               |                  |                                 |                              |                  |
| Rhinitis                                                     | 465 (16.1)                       | 1367 (15.8)                   | 0.681            | 50 (19.4)                       | 112 (21.7)                   | 0.454            |
| Cardiac disease                                              | 77 (2.7)                         | 343 (4.0)                     | 0.001            | 8 (3.1)                         | 16 (3.1)                     | 1.0              |
| Gastro-oesophageal reflux disease                            | 208 (7.2)                        | 638 (7.4)                     | 0.769            | 17 (6.6)                        | 39 (7.6)                     | 0.606            |
| 1+prescription in 12 months, <i>n</i> (%)                    |                                  |                               |                  |                                 |                              |                  |
| Non-steroidal anti-inflammatory drug                         | 466 (16.2)                       | 1471 (17.0)                   | 0.283            | 51 (19.8)                       | 96 (18.6)                    | 0.685            |
| Beta blocker                                                 | 94 (3.3)                         | 293 (3.4)                     | 0.734            | 14 (5.4)                        | 14 (2.7)                     | 0.058            |
| Paracetamol                                                  | 384 (13.3)                       | 1419 (16.4)                   | <0.001           | 50 (19.4)                       | 89 (17.2)                    | 0.469            |

\*Conditional logistic regression.

<sup>†</sup>Not all patients had recorded weight and height data. For weight, initiation population *n* = 2379 (82.5%) and *n* = 7228 (83.6%) for EF HFA-BDP and CFC-BDP cohorts, respectively; step-up population *n* = 224 (86.8%) and *n* = 447 (86.6%), respectively. For height, initiation population *n* = 2536 (88.0%) and *n* = 7535 (87.2%), respectively; step-up population *n* = 240 (93.0%) and *n* = 470 (91.1%), respectively. For body mass index, initiation population *n* = 2323 (80.6%) and *n* = 7045 (81.5%), respectively; step-up population *n* = 221 (85.7%) and *n* = 433 (83.9%), respectively.

<sup>‡</sup>Socio-economic status was that assigned, in quintiles, by the GPRD to each practice using the Index of Multiple Deprivation as a proxy measure.

<sup>§</sup>The likelihood of smoking status being recorded increased with later years of the study; therefore, as patients in the EF HFA-BDP cohorts had later index dates, they were more likely to have recorded smoking status. Data were available for 65.0% and 50.8% of patients in EF HFA-BDP and CFC-BDP cohorts, respectively, of the initiation population, and for 69.8% and 49.6%, respectively, in the step-up population.

CFC-BDP, chlorofluorocarbon beclometasone; EF HFA, extra-fine hydrofluoroalkane; ICS, inhaled corticosteroid; pMDI, pressurized metered-dose inhaler; n/a, not applicable (matching criterion); SES, socio-economic status.

The adjusted outcomes for the unmatched populations were similar to those of the matched populations, with significantly higher odds of asthma control for patients receiving EF HFA-BDP (supporting information Tables S2–S4). As for the matched populations, the differences between treatment cohorts were greatest for the step-up population.

## Discussion

For primary-care patients, initiating ICS therapy or stepping up to a higher ICS dose with EF HFA-BDP or CFC-BDP effectively improved asthma control over the

1-year period evaluated in this observational study. More than three quarters of patients in each cohort achieved asthma control as defined by the proxy asthma control measure, and nine in 10 had no exacerbation during the outcome year. These findings provide real-world support for asthma guideline recommendations to initiate ICS monotherapy, with the option of stepping up, as necessary, to a higher dose [2].

We found that the effectiveness of this strategy was significantly better, as measured by the composite asthma control measure, for patients who were prescribed EF HFA-BDP as compared with large-particle CFC-BDP. While the effect size for the primary end-point was not

**Table 2.** Asthma-related medical resource use during the baseline year for patients initiating ICS by pMDI and those receiving an increased dose of ICS by pMDI: matched analyses

| Characteristic                                            | Initiation population    |                       |                  | Step-up population      |                      |                  |
|-----------------------------------------------------------|--------------------------|-----------------------|------------------|-------------------------|----------------------|------------------|
|                                                           | EF HFA-BDP<br>(n = 2882) | CFC-BDP<br>(n = 8646) | <i>P</i> -value* | EF HFA-BDP<br>(n = 258) | CFC-BDP<br>(n = 516) | <i>P</i> -value* |
| Recorded asthma diagnosis, <i>n</i> (%)                   | 2682 (93.1)              | 8016 (92.7)           | 0.515            | 250 (96.9)              | 504 (97.7)           | 0.495            |
| Mean SABA daily dose, <i>n</i> (%) <sup>†</sup>           |                          |                       |                  |                         |                      |                  |
| 0                                                         | 1347 (46.7)              | 4041 (46.7)           | n/a              | 9 (3.5)                 | 18 (3.5)             | n/a              |
| 1–100 µg                                                  | 893 (31.0)               | 2679 (31.0)           |                  | 74 (28.7)               | 148 (28.7)           |                  |
| 101–200 µg                                                | 449 (15.6)               | 1347 (15.6)           |                  | 98 (38.0)               | 196 (38.0)           |                  |
| 201–300 µg                                                | 97 (3.4)                 | 291 (3.4)             |                  | 41 (15.9)               | 82 (15.9)            |                  |
| 301–400 µg                                                | 36 (1.2)                 | 107 (1.2)             |                  | 12 (4.7)                | 24 (4.7)             |                  |
| ≥ 400 µg                                                  | 60 (2.1)                 | 180 (2.1)             |                  | 24 (9.3)                | 48 (9.3)             |                  |
| Oral corticosteroid courses, <i>n</i> (%) <sup>‡</sup>    |                          |                       |                  |                         |                      |                  |
| 0                                                         | 2413 (83.7)              | 7239 (83.7)           | n/a              | 219 (84.9)              | 438 (84.9)           | n/a              |
| 1                                                         | 398 (13.8)               | 1194 (13.8)           |                  | 30 (11.6)               | 60 (11.6)            |                  |
| 2                                                         | 63 (2.2)                 | 189 (2.2)             |                  | 8 (3.1)                 | 16 (3.1)             |                  |
| ≥ 3                                                       | 8 (0.3)                  | 24 (0.3)              |                  | 1 (0.4)                 | 2 (0.4)              |                  |
| Asthma consultations, <i>n</i> (%)                        |                          |                       |                  |                         |                      |                  |
| 0                                                         | 1386 (48.1)              | 4130 (47.8)           | 0.055            | 65 (25.2)               | 124 (24.0)           | 0.684            |
| 1                                                         | 1179 (40.9)              | 3533 (40.9)           |                  | 87 (33.7)               | 175 (33.9)           |                  |
| 2                                                         | 250 (8.7)                | 730 (8.4)             |                  | 54 (20.9)               | 117 (22.7)           |                  |
| ≥ 3                                                       | 67 (2.3)                 | 253 (2.9)             |                  | 52 (20.2)               | 100 (19.4)           |                  |
| Asthma consultations, no OCS, <i>n</i> (%)                |                          |                       |                  |                         |                      |                  |
| 0                                                         | 1580 (54.8)              | 4740 (54.8)           | n/a              | 77 (29.8)               | 154 (29.8)           | n/a              |
| 1                                                         | 1057 (36.7)              | 3171 (36.7)           |                  | 83 (32.2)               | 166 (32.2)           |                  |
| ≥ 2                                                       | 245 (8.5)                | 735 (8.5)             |                  | 98 (38.0)               | 196 (38.0)           |                  |
| Mean ICS daily dose during baseline year <sup>‡</sup>     |                          |                       |                  |                         |                      |                  |
| 1–199 µg                                                  | –                        | –                     | –                | 215 (83.3)              | 430 (83.3)           | n/a              |
| 200–399 µg                                                |                          |                       |                  | 35 (13.6)               | 70 (13.6)            |                  |
| 400–599 µg                                                |                          |                       |                  | 6 (2.3)                 | 12 (2.3)             |                  |
| 600–799 µg                                                |                          |                       |                  | 2 (0.8)                 | 4 (0.8)              |                  |
| ≥ 800 µg                                                  |                          |                       |                  | 0                       | 0.0                  |                  |
| Asthma prescriptions, <i>n</i> (%)                        |                          |                       |                  |                         |                      |                  |
| 1                                                         | 955 (33.1)               | 2867 (33.2)           | 0.917            | 0                       | 0                    | 0.331            |
| 2                                                         | 922 (32.0)               | 2773 (32.1)           |                  | 42 (16.3)               | 72 (14.0)            |                  |
| ≥ 3                                                       | 1005 (34.9)              | 3006 (34.8)           |                  | 216 (83.7)              | 444 (86.0)           |                  |
| Courses of antibiotics for LRTI, <i>n</i> (%)             |                          |                       |                  |                         |                      |                  |
| 0                                                         | 2346 (81.4)              | 6866 (79.4)           | 0.026            | 203 (78.7)              | 403 (78.1)           | 0.802            |
| 1                                                         | 412 (14.3)               | 1375 (15.9)           |                  | 40 (15.5)               | 81 (15.7)            |                  |
| 2                                                         | 98 (3.4)                 | 301 (3.5)             |                  | 10 (3.9)                | 21 (4.1)             |                  |
| ≥ 3                                                       | 26 (0.9)                 | 104 (1.2)             |                  | 5 (1.9)                 | 11 (2.1)             |                  |
| ≥ 1 Hospitalization for asthma, <i>n</i> (%) <sup>§</sup> | 8 (0.3)                  | 52 (0.6)              | 0.040            | 0                       | 10 (1.9)             | 0.194            |
| Asthma control status, <i>n</i> (%) <sup>¶</sup>          | 2024 (70.2)              | 5926 (68.5)           | 0.024            | 181 (70.2)              | 351 (68.0)           | 0.437            |

\*Conditional logistic regression.

<sup>†</sup>The SABA dose is the salbutamol dose equivalent. To cope with a variety of ICS prescribed during the baseline year, the ICS dose in the table is the doubled EF HFA-BDP dose matched to the actual CFC-BDP dose, as per licensing, which calls for EF HFA-BDP to be prescribed at approximately half the dose of CFC-BDP.<sup>‡</sup>In both initiation and step-up populations, the numbers of patients in the EF HFA-BDP cohort who experienced an exacerbation during the baseline year were exactly the same as those receiving oral steroids, while in the CFC-BDP cohort, the percentages of patients experiencing 0–2 exacerbations were similar (within 0.4 percentage points) to those receiving oral steroids.<sup>§</sup>Recorded hospital attendance for asthma including admission, A&E attendance, out-of-hours attendance, or outpatient attendance.<sup>¶</sup>The primary measure of asthma control was defined as no hospital attendance for asthma, oral corticosteroid course, or antibiotics for lower respiratory infection.

Percentages may not total 100 because of rounding.

CFC-BDP, chlorofluorocarbon beclometasone; EF HFA, extra-fine hydrofluoroalkane; ICS, inhaled corticosteroid; LRTI, lower respiratory tract infection; pMDI, pressurized metered-dose inhaler; n/a, not applicable (matching criterion); OCS, oral corticosteroid; SABA, short-acting  $\beta_2$  agonist.

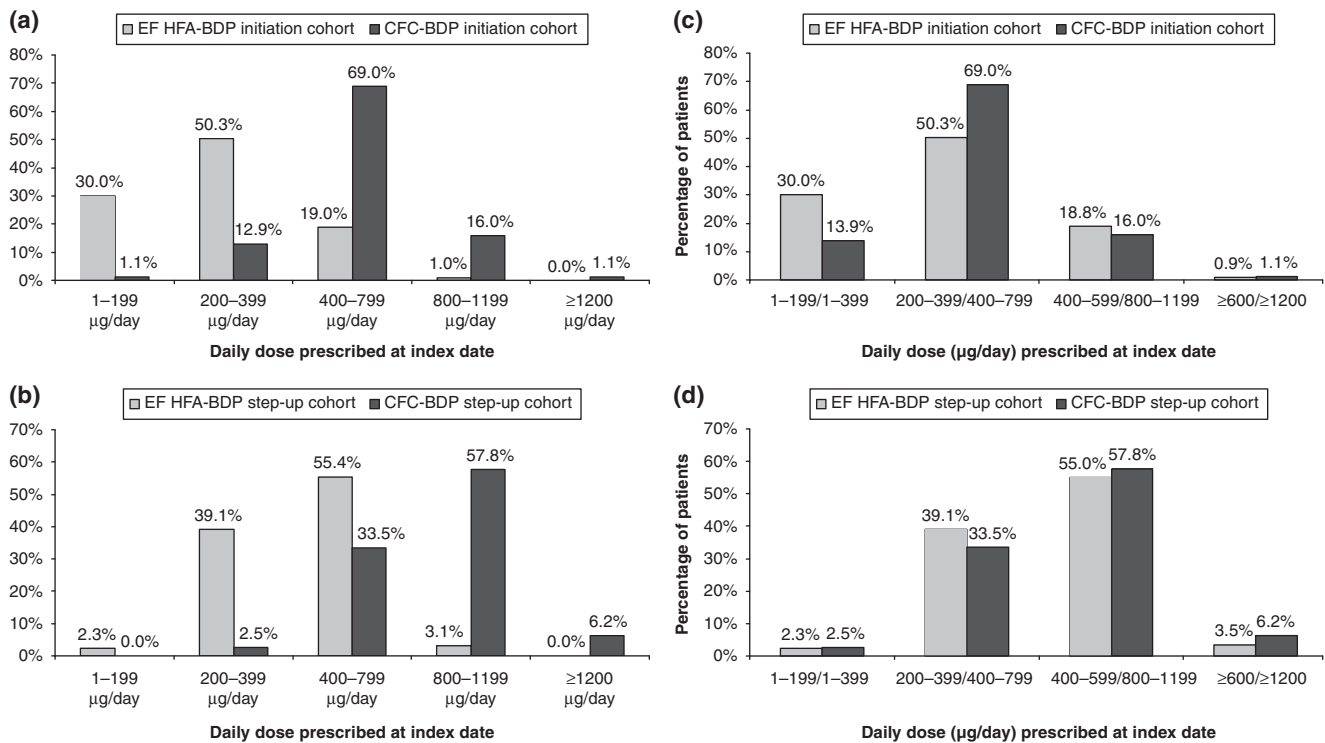


Fig. 1. Two representations of the index date ICS doses are depicted. (a, b) Depict the nominal (actual) ICS dose on the index date for patients (a) initiating ICS or (b) receiving a step-up in dose of ICS. (c and d) Depict the index date doses for initiation and step-up populations, respectively, with the EF HFA-BDP dose doubled to show it in proportion to the dose of CFC-BDP, as per licensing recommendations, which call for the dose of EF HFA-BDP to be approximately half that of CFC-BDP. CFC-BDP, chlorofluorocarbon beclometasone; EF HFA, extrafine hydrofluoroalkane; ICS, inhaled corticosteroid.

Table 3. Outcomes for patients initiating ICS and those receiving an increased dose of ICS: matched analyses

| Outcome                                                | Initiation population    |                       |                      | Step-up population      |                      |                      |
|--------------------------------------------------------|--------------------------|-----------------------|----------------------|-------------------------|----------------------|----------------------|
|                                                        | EF HFA-BDP<br>(n = 2882) | CFC-BDP<br>(n = 8646) | P-value <sup>†</sup> | EF HFA-BDP<br>(n = 258) | CFC-BDP<br>(n = 516) | P-value <sup>†</sup> |
| Asthma control status, n (%)                           |                          |                       |                      |                         |                      |                      |
| Primary measure of asthma control                      | 2407 (83.5)              | 7057 (81.6)           |                      | 213 (82.6)              | 391 (75.8)           |                      |
| Asthma control plus SABA use                           | 1786 (62.0)              | 5228 (60.5)           |                      | 127 (49.2)              | 210 (40.7)           |                      |
| Asthma control plus no additional or change in therapy | 2186 (75.9)              | 6622 (76.6)           |                      | 196 (76.0)              | 374 (72.5)           |                      |
| Asthma exacerbations, n (%)                            |                          |                       |                      |                         |                      |                      |
| 0                                                      | 2610 (90.6)              | 7774 (89.9)           |                      | 233 (90.3)              | 442 (85.7)           |                      |
| 1                                                      | 195 (6.8)                | 649 (7.5)             |                      | 18 (7.0)                | 47 (9.1)             |                      |
| 2                                                      | 53 (1.8)                 | 141 (1.6)             |                      | 4 (1.6)                 | 16 (3.1)             |                      |
| ≥ 3                                                    | 24 (0.8)                 | 82 (0.9)              |                      | 3 (1.2)                 | 11 (2.1)             |                      |
| Daily ICS dose (µg), median (IQR)*                     | 82 (55–165)              | 137 (55–274)          |                      | 165 (96–274)            | 329 (164–548)        |                      |
| Disaggregated outcomes of the composite measures       |                          |                       |                      |                         |                      |                      |
| Change in therapy, n (%)                               | 546 (18.9)               | 1524 (17.6)           | 0.107                | 48 (18.6)               | 94 (18.2)            | 0.899                |
| ≥ One oral corticosteroid course, n (%)                | 272 (9.4)                | 867 (10.0)            | 0.350                | 25 (9.7)                | 72 (14.0)            | 0.084                |
| ≥ One hospital admission, n (%)                        | 28 (1.0)                 | 89 (1.0)              | 0.787                | 1 (0.4)                 | 9 (1.7)              | 0.154                |
| ≥ One course antibiotics for LRTI, n (%)               | 273 (9.5)                | 896 (10.4)            | 0.171                | 27 (10.5)               | 74 (14.3)            | 0.129                |
| Mean SABA dose > 200 µg/day, n (%)                     | 813 (28.2)               | 2517 (29.1)           | 0.333                | 113 (43.8)              | 248 (48.1)           | 0.200                |

\*The daily ICS dose during the outcome year was calculated as the dispensed amount divided by 365. (The licensed recommended dose of EF HFA-BDP is approximately half that of CFC-BDP).

<sup>†</sup>Conditional logistic regression.

Percentages may not total 100 because of rounding.

CFC-BDP, chlorofluorocarbon beclometasone; EF HFA, extrafine hydrofluoroalkane; ICS, inhaled corticosteroid; IQR, interquartile range; LRTI, lower respiratory tract infection; SABA, short-acting  $\beta_2$  agonist.

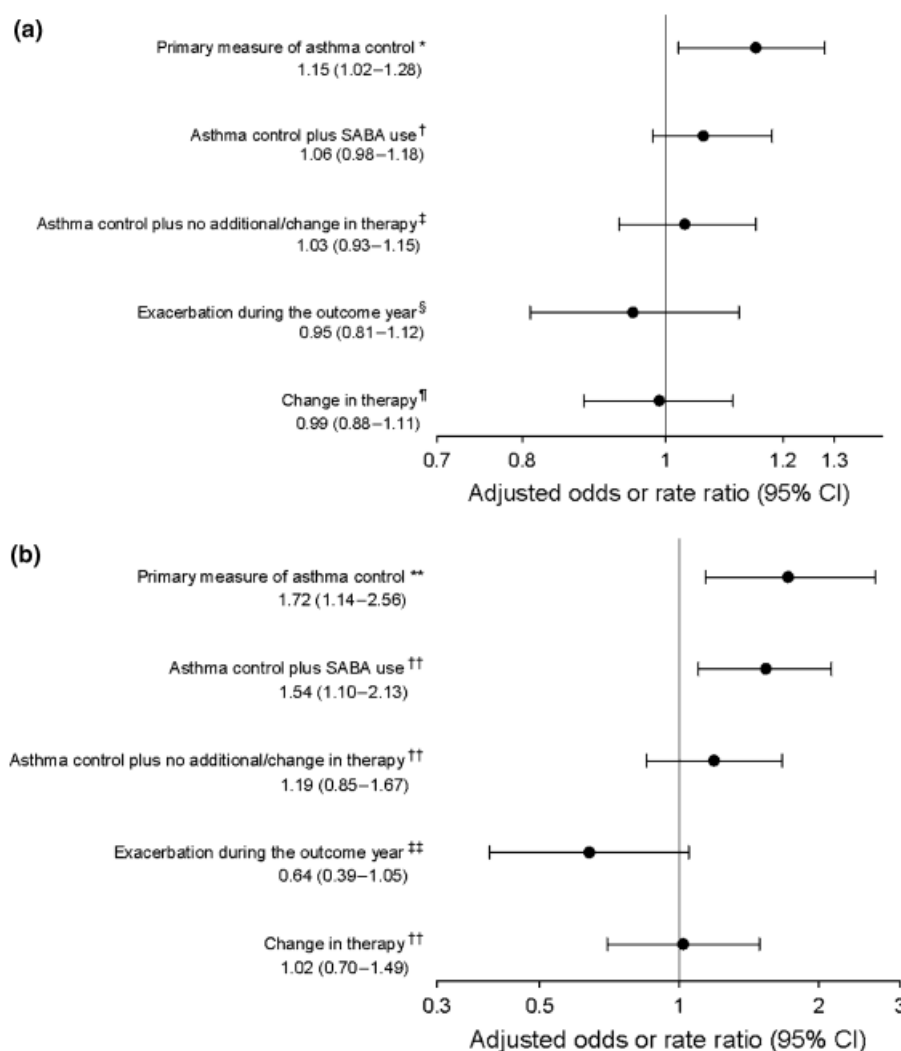


Fig. 2. Adjusted odds ratios (95% CI) for measures of asthma control and change in therapy, and adjusted rate ratios (95% CI) for exacerbations, in the EF HFA-BDP cohorts of initiation (a) and step-up populations (b) during the outcome year, with the CFC-BDP cohort set as the reference group (odds ratio/rate ratio = 1.0). \*Adjusted for age and baseline paracetamol prescriptions, antibiotics and number of non-asthma-related consultations. <sup>†</sup>Adjusted for age, SES (logged) and baseline paracetamol prescriptions, antibiotics and number of non-asthma-related consultations. <sup>‡</sup>Adjusted for SES (logged), CCI score, index date ICS dose, and baseline antibiotics and number of non-asthma-related consultations. <sup>§</sup>Adjusted for age and baseline antibiotics and number of non-asthma-related consultations. <sup>¶</sup>Adjusted for SES (logged), CCI score, index date ICS dose, and baseline paracetamol prescriptions, antibiotics and number of non-asthma-related consultations. \*\*Adjusted for number of non-asthma-related consultations. <sup>††</sup>No significant effects (unadjusted OR). <sup>‡‡</sup>Adjusted for beta blockers at baseline. CCI, Charlson comorbidity index; CFC-BDP, chlorofluorocarbon beclometasone; EF HFA, extrafine hydrofluoroalkane; ICS, inhaled corticosteroid; SES socio-economic status.

large for the initiation population, this was not surprising, as large differences between cohorts would not be expected for matched patients initiating ICS. The difference between treatment cohorts in achieving asthma control was most marked for the step-up population. Although patients in the EF HFA-BDP step-up cohort had fewer exacerbations, the difference in exacerbation rates between cohorts was not statistically significant.

Study results indicate that UK general practitioners are administering the EF formulation according to licensing recommendations. The initiation and step-up cohorts were prescribed half or less than half the dose of EF HFA-BDP

than that of CFC-BDP for patients matched on markers of asthma control. The licensing recommendations are further supported by the findings of this study, which show that patients prescribed EF HFA-BDP at lower doses did at least as well as those prescribed CFC-BDP. In a dose-ranging study, it was shown that 2.6 times the dose of CFC-BDP (95% CI, 1.1–11.6) would be required to achieve the same improvements in forced expiratory volume in 1 s (FEV<sub>1</sub>) percent predicted as with EF HFA-BDP [13], suggesting that, at least in terms of lung function and accepting the wide variability of this measure, the dose ratio for CFC-BDP relative to EF HFA-BDP may actually be more than double.

**Table 4.** Change in therapy by type for patients initiating ICS and those receiving an increased dose of ICS

| Outcome                         | Initiation population         |                            | Step-up population           |                           |
|---------------------------------|-------------------------------|----------------------------|------------------------------|---------------------------|
|                                 | EF HFA-BDP ( <i>n</i> = 2882) | CFC-BDP ( <i>n</i> = 8646) | EF HFA-BDP ( <i>n</i> = 258) | CFC-BDP ( <i>n</i> = 516) |
| Increase in ICS dose            | 169 (5.9)                     | 579 (6.7)                  | 4 (1.6)                      | 12 (2.3)                  |
| Change in inhaler device        | 123 (4.3)                     | 423 (4.9)                  | 10 (3.9)                     | 20 (3.9)                  |
| Change in ICS drug              | 33 (1.1)                      | 227 (2.6)                  | 4 (1.6)                      | 11 (2.1)                  |
| Additional therapy              | 279 (9.7)                     | 608 (7.0)                  | 33 (12.8)                    | 64 (12.4)                 |
| Fluticasone+salmeterol          | 122 (4.2)                     | 286 (3.3)                  | 15 (5.8)                     | 22 (4.3)                  |
| Budesonide+formoterol           | 47 (1.6)                      | 79 (0.9)                   | 3 (1.2)                      | 9 (1.7)                   |
| Long-acting $\beta_2$ agonist   | 146 (5.1)                     | 342 (4.0)                  | 17 (6.6)                     | 38 (7.4)                  |
| Leukotriene receptor antagonist | 55 (1.9)                      | 95 (1.1)                   | 9 (3.5)                      | 7 (1.4)                   |
| Theophylline                    | 5 (0.2)                       | 27 (0.3)                   | 0                            | 1 (0.2)                   |

Values shown are number (%). Patients could have more than one change in therapy; thus, the numbers are not additive. Because of rounding, percentages may not total 100.

CFC-BDP, chlorofluorocarbon beclometasone; EF HFA, extra-fine hydrofluoroalkane; ICS, inhaled corticosteroid.

**Table 5.** Co-primary outcome measures for matched cohorts: all patients, adults, and children, with the CFC-BDP cohort set as the reference group (odds ratio/rate ratio = 1.0)

|                            | Initiation population          | Step-up Population             |
|----------------------------|--------------------------------|--------------------------------|
| Asthma control OR (95% CI) | For EF HFA-BDP                 | For EF HFA-BDP                 |
| All patients               | 1.15 (1.02–1.28)*              | 1.72 (1.14–2.56)**             |
| Ages 18–60                 | 1.15 (1.01–1.30) <sup>†</sup>  | 1.72 (1.06–2.78) <sup>††</sup> |
| Ages 5–12                  | 1.27 (0.86–1.85) <sup>‡</sup>  | –                              |
| Exacerbation RR (95% CI)   |                                |                                |
| All patients               | 0.95 (0.81–1.12) <sup>§</sup>  | 0.64 (0.39–1.05) <sup>‡‡</sup> |
| Ages 18–60                 | 1.01 (0.85–1.20) <sup>¶</sup>  | 0.60 (0.34–1.04) <sup>§§</sup> |
| Ages 5–12                  | 0.54 (0.32–0.91) <sup>  </sup> | –                              |

\*Adjusted for age and baseline paracetamol prescriptions, antibiotics, and number of non-asthma-related consultations.

<sup>†</sup>Adjusted for age, SES (logged), number of asthma consults, number of non-asthma consults and antibiotics.

<sup>‡</sup>Adjusted for baseline asthma control status and paracetamol prescriptions.

<sup>§</sup>Adjusted for age and baseline antibiotics and number of non-asthma-related consultations.

<sup>¶</sup>Adjusted for age, SES (logged), number of non-asthma consults and antibiotics.

<sup>||</sup>Adjusted for baseline revised primary outcome status and paracetamol prescriptions.

\*\*Adjusted for number of non-asthma-related consultations.

<sup>††</sup>Adjusted for number of non-asthma consults.

<sup>‡‡</sup>Adjusted for beta blockers at baseline.

<sup>§§</sup>Adjusted for number of non-asthma consults and beta blockers. CFC-BDP, chlorofluorocarbon beclometasone; EF HFA, extra-fine hydrofluoroalkane; OR, odds ratio; RR, rate ratio.

There are several possible reasons for the better effectiveness of EF HFA-BDP under real-world conditions. The EF HFA-BDP inhaler is considered a relatively 'forgiving' device, as good lung deposition is recorded even with poor inhaler technique [5]. This is an important consideration, because incorrect inhaler use is very common in clinical

practice [16]. Improved lung deposition likely relates to both smaller particle size *per se* and inhaler spray characteristics (softer and of longer duration). Moreover, EF HFA-BDP shows even deposition throughout the lungs, extending to the small airways [6, 7], a site of airway inflammation in asthma [9, 10].

Studies have also shown that EF HFA-BDP has a significant effect on markers of small airway function, whereas large-particle ICS do not [28–31]. Intriguing work has suggested that air trapping, possibly related to uncontrolled small airway inflammation, might contribute to difficulties in controlling asthma and recurrent exacerbations [32, 33]. The benefits of an EF ICS that can control large and small airway inflammation thus might not be fully captured by spirometry measures. If small airway deposition by an ICS does indeed provide benefit, it might manifest in reduced asthma symptoms (improved asthma control and fewer exacerbations). To an extent this is true as data from this study suggest that the deposition characteristics of an ICS are important in real-life asthma therapy [7]. Results of the companion study in which patients receiving EF HFA-BDP had similar or better odds of achieving asthma control at lower prescribed doses than those receiving fluticasone, a large-particle ICS, provide further support for this hypothesis [20]. The present study extends this observation by limiting the comparison to EF and large-particle formulations of the same molecule.

The three composite outcome measures in this study were designed to capture different aspects of asthma control, as per current consensus [26], and within the limitations of the clinical and prescribing information that is available in the GPRD. The primary measure of asthma control comprised outcomes indicating occurrence of an asthma exacerbation, including unplanned medical care or hospitalization for asthma as well as antibiotic prescribing for lower respiratory tract infection, as acute asthma may be confused in practice for respiratory

infection [34, 35]. The other composite measures captured reliever use (SABA), a proxy for active asthma symptoms, and changes in therapy that could potentially indicate uncontrolled asthma. While symptoms and objective measures of lung function are not available from a primary-care database, the use of these composite measures gives an indication of the risk of future asthma-related adverse events, an important aspect of asthma control [26]. We chose the patient age range of 5–60 years to optimize the chance of identifying patients with asthma, as those below 5 years of age could have infant wheeze, while those over 60 could have COPD. Evaluation of outcomes over a full year after the index prescription minimizes the effects of seasonal variations on asthma symptoms.

As for all observational studies, a limitation is the possibility of unmeasured or unrecognized confounding factors, including selection bias and practice/physician bias. During the study period, CFC-BDP was widely used across the United Kingdom as a whole; so while we cannot rule out physician or practice bias, we would not expect it to be substantial during the analysis period. Nonetheless, we cannot rule out the possibility of residual confounding by selection bias. The matching process was used to reduce this possibility by comparing results for patients with similar asthma severity and control at baseline, as reflected in asthma-related measures recorded in the database [21]. Although there remained differences at baseline between EF HFA-BDP and CFC-BDP cohorts in both initiation and step-up populations, they were small and were not considered clinically meaningful.

While rigorous, however, the matched approach may exclude important groups of patients who are not represented in both populations; thus, we report the unmatched analyses for comparison. Results of unmatched vs. matched analyses were generally consistent within each population, as were the findings for the three composite measures, suggesting that the findings are robust. Furthermore, the results for adult and paediatric patients of the *post hoc* sensitivity analysis also supported the primary findings.

Study findings are dependent on the quality and availability of data in the GPRD. Some data, such as smoking status, were missing for some patients, and the GPRD contains limited information on hospitalizations. Lung function data would have added value as a study assessment; however, lung function is not often measured in UK primary care. Nonetheless, the GPRD is accepted as a high-quality database with the advantages of large size and inclusion of a representative sample of the UK population [22, 23]. Medical care and prescribing in the United Kingdom are centralized in general practice; thus, general practice data reflect actual clinical practice. Treatment changes, when they occurred, were similar for both treatment cohorts and both populations, indicating that

physician behaviour was consistent and supporting the validity of the data.

In conclusion, we found that patients receiving a first prescription or first increase in dose of ICS as an EF formulation of beclometasone had significantly better odds of achieving asthma control, and at approximately half the dose, as compared with those prescribed large-particle CFC-BDP, particularly when stepping up to a higher ICS dose. The results of this observational study illustrate real-world effectiveness over 1 year of these two formulations of beclometasone in a broad and diverse patient population receiving asthma therapy in primary care. These data support the guideline-recommended strategy of first implementing ICS monotherapy, with the option of stepping up, as necessary, to a higher dose. Results suggest furthermore that ICS formulation, particle size, and deposition characteristics play important roles in real-world effectiveness of asthma therapy.

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G. C. has served as a consultant/speaker for Teva, Dey, BI, GlaxoSmithKline, Vatera, Skye Pharma and Med-Immune and has served as an expert witness on the topic of long-acting  $\beta$ -agonists.

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R. J. M. is a lecturer and consultant for Teva; a consultant for AstraZeneca, Novartis/Genentech, Schering, Cypress BioScience, Phase to Phase and Common Health and the National Heart, Lung, and Blood Institute (NHLBI)/National Institutes of Health (NIH); and has received research support from the NHLBI/NIH.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Study flow diagram showing identification in the GPRD of patients aged 5–60 years with asthma who received a first prescription or first increase in dose of ICS as EF HFA-BDP or CFC-BDP between January 1, 1998, and June 30, 2006 (full study period, January 1997 through June 2007).

BAI, breath-actuated inhaler; CFC-BDP, chlorofluorocarbon beclomethasone; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; EF HFA, extrafine hydrofluoroalkane; ICS, inhaled corticosteroid; pMDI, pressurised metered-dose inhaler

**Figure S2.** Selection of eligible patients in the database: matching of the cohorts (A) initiating ICS therapy (initiation population) or (B) receiving their first increase in dose of ICS (step-up population) as EF HFA-BDP or CFC-BDP by metered-dose inhaler.

CFC-BDP, chlorofluorocarbon beclomethasone; COPD, chronic obstructive pulmonary disease; DPI, dry powder

inhaler; EF HFA, extrafine hydrofluoroalkane; ICS, inhaled corticosteroid; SABA, short-acting  $\beta_2$  agonist

**Table S1.** Unmatched analysis: baseline characteristics of patients initiating ICS by pMDI and those receiving an increased dose of ICS by pMDI.

**Table S2.** Unmatched analysis: outcomes for patients initiating ICS and those receiving an increased dose of ICS.

**Table S3.** Unmatched analysis: odds ratios (95% CI) for measures of asthma control and change in therapy, and rate ratios (95% CI) for exacerbations, in the EF HFA-BDP cohorts of initiation and step-up populations during the outcome year, with the CFC-BDP cohort set as the reference group (OR = 1.0).

**Table S4.** Unmatched analysis: change in therapy by type for patients initiating ICS and those receiving an increased dose of ICS.

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## **Asthma control with extrafine-particle HFA-beclometasone versus large-particle CFC-beclometasone: a real-world observational study**

Barnes et al.

### **Figure legends**

**Fig. S1.** Study flow diagram showing identification in the GPRD of patients aged 5–60 years with asthma who received a first prescription or first increase in dose of ICS as EF HFA-BDP or CFC-BDP between January 1, 1998, and June 30, 2006 (full study period, January 1997 through June 2007).

BAI, breath-actuated inhaler; CFC-BDP, chlorofluorocarbon beclometasone; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; EF HFA, extrafine hydrofluoroalkane; ICS, inhaled corticosteroid; pMDI, pressurised metered-dose inhaler

**Fig. S2.** Selection of eligible patients in the database: matching of the cohorts (A) initiating ICS therapy (initiation population) or (B) receiving their first increase in dose of ICS (step-up population) as EF HFA-BDP or CFC-BDP by metered-dose inhaler.

CFC-BDP, chlorofluorocarbon beclometasone; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; EF HFA, extrafine hydrofluoroalkane; ICS, inhaled corticosteroid; SABA, short-acting  $\beta_2$  agonist

**Table S1.** Unmatched analysis: baseline characteristics of patients initiating ICS by pMDI and those receiving an increased dose of ICS by pMDI

| Characteristic                                   | Initiation population    |                         | <i>P</i> -value* | Step-up population      |                       | <i>P</i> -value* |
|--------------------------------------------------|--------------------------|-------------------------|------------------|-------------------------|-----------------------|------------------|
|                                                  | EF HFA-BDP<br>(n = 2938) | CFC-BDP<br>(n = 33 926) |                  | EF HFA-BDP<br>(n = 364) | CFC-BDP<br>(n = 3624) |                  |
| Male sex, n (%)                                  | 1259 (42.9)              | 14 756 (43.5)           | 0.500            | 158 (43.4)              | 1617 (44.6)           | 0.657            |
| Age, mean (SD)                                   | 32.9 (15.8)              | 28.2 (16.9)             | <0.001           | 33.9 (16.9)             | 27.7 (18.1)           | <0.001           |
| 5–12 years, n (%)                                | 385 (13.1)               | 9138 (26.9)             |                  | 46 (12.6)               | 1175 (32.4)           |                  |
| Weight (kg)†, mean (SD)                          | 72.0 (23.1)              | 67.1 (25.3)             | <0.001           | 71.4 (24.9)             | 64.2 (27.7)           | <0.001           |
| Height (m)†, mean (SD)                           | 1.64 (0.18)              | 1.59 (0.21)             | <0.001           | 1.63 (0.18)             | 1.54 (0.23)           | <0.001           |
| Body mass index (kg/m <sup>2</sup> )†, mean (SD) | 26.1 (7.1)               | 25.4 (8.7)              | <0.001           | 26.1 (7.2)              | 25.0 (8.2)            | 0.002            |
| Socioeconomic status‡, median (IQR)              | 16.4 (11.2–28.8)         | 17.9 (9.8–31.4)         | 0.659            | 18.2 (11.4–32.1)        | 20.1 (10.7–33.9)      | 0.572            |
| Charlson comorbidity index, n (%)                |                          |                         |                  |                         |                       |                  |
| 0                                                | 2733 (93.0)              | 31 708 (93.5)           | 0.702            | 337 (92.6)              | 3333 (92.0)           | 0.975            |
| 1                                                | 120 (4.1)                | 1315 (3.9)              |                  | 6 (1.6)                 | 70 (1.9)              |                  |
| 2                                                | 65 (2.2)                 | 659 (1.9)               |                  | 14 (3.8)                | 149 (4.1)             |                  |
| ≥3                                               | 20 (0.7)                 | 244 (0.7)               |                  | 7 (1.9)                 | 72 (2.0)              |                  |
| Smoking status, n/total n (%)                    |                          |                         |                  |                         |                       |                  |
| Current                                          | 671/1912 (35.1)          | 5888/15 842 (37.2)      | 0.126            | 89/265 (33.6)           | 559/1746 (32.0)       | 0.698            |
| Former                                           | 345/1912 (18.0)          | 2901/15 842 (18.3)      |                  | 42/265 (15.8)           | 312/1746 (17.9)       |                  |
| Never                                            | 896/1912 (46.9)          | 7053/15 842 (44.5)      |                  | 134/265 (50.6)          | 875/1746 (50.1)       |                  |
| Recorded comorbidity, n (%)                      |                          |                         |                  |                         |                       |                  |
| Rhinitis                                         | 479 (16.3)               | 5275 (15.5)             | 0.279            | 81 (22.3)               | 732 (20.2)            | 0.354            |
| Cardiac disease                                  | 81 (2.8)                 | 1082 (3.2)              | 0.198            | 14 (3.8)                | 125 (3.4)             | 0.694            |
| Gastro-oesophageal reflux disease                | 213 (7.2)                | 2145 (6.3)              | 0.049            | 26 (7.1)                | 291 (8.0)             | 0.551            |
| 1+ prescription in 12 mo, n (%)                  |                          |                         |                  |                         |                       |                  |
| Nonsteroidal anti-inflammatory drug              | 481 (16.4)               | 5098 (15.0)             | 0.051            | 70 (19.2)               | 578 (15.9)            | 0.106            |
| Beta blocker                                     | 97 (3.3)                 | 945 (2.8)               | 0.105            | 16 (4.4)                | 72 (2.0)              | 0.003            |
| Paracetamol                                      | 392 (13.3)               | 5418 (16.0)             | <0.001           | 69 (19.0)               | 776 (21.4)            | 0.274            |
| Recorded asthma diagnosis, n (%)                 | 2735 (93.1)              | 31 610 (93.2)           | 0.864            | 356 (97.8)              | 3550 (98.0)           | 0.842            |
| SABA dose,§ median (IQR)                         | 55 (0–55)                | 55 (0–55)               | 0.177            | 110 (55–274)            | 164 (55–274)          | 0.333            |
| Oral corticosteroid courses, n (%)               |                          |                         |                  |                         |                       |                  |
| 0                                                | 2415 (82.2)              | 28 709 (84.6)           | <0.001           | 279 (76.6)              | 2561 (70.7)           | 0.023            |
| 1                                                | 415 (14.1)               | 4372 (12.9)             |                  | 51 (14.0)               | 754 (20.8)            |                  |

|                                        |             |               |       |              |              |       |
|----------------------------------------|-------------|---------------|-------|--------------|--------------|-------|
| 2                                      | 82 (2.8)    | 688 (2.0)     |       | 22 (6.0)     | 202 (5.6)    |       |
| ≥3                                     | 26 (0.9)    | 157 (0.5)     |       | 12 (3.3)     | 107 (3.0)    |       |
| Asthma consultations, median (range)   | 1 (0-6)     | 1 (0-10)      | 0.024 | 1 (0-9)      | 1 (0-12)     | 0.372 |
| ICS dose during baseline year§         | n/a         | n/a           | n/a   | 110 (55-219) | 110 (55-219) | 0.001 |
| Asthma prescriptions, median (IQR)     | 2 (1-3)     | 2 (1-3)       | 0.840 | 5 (3-8)      | 5 (3-7)      | 0.939 |
| Courses of antibiotics for LRTI, n (%) |             |               |       |              |              |       |
| 0                                      | 2379 (81.0) | 27 254 (80.3) | 0.811 | 281 (77.2)   | 2775 (76.6)  | 0.986 |
| 1                                      | 425 (14.5)  | 5127 (15.1)   |       | 60 (16.5)    | 605 (16.7%)  |       |
| 2                                      | 102 (3.5)   | 1160 (3.4)    |       | 16 (4.4)     | 165 (4.6)    |       |
| ≥3                                     | 32 (1.1)    | 385 (1.1)     |       | 7 (1.9)      | 79 (2.2)     |       |
| Hospitalisation for asthma,¶ 1+        | 9 (0.3)     | 187 (0.6)     | 0.080 | 2 (0.5)      | 58 (1.6)     | 0.116 |
| Asthma control status**, n (%)         | 2026 (69.0) | 23 631 (69.7) | 0.431 | 232 (63.7)   | 2059 (56.8)  | 0.011 |

Percentages may not total 100 because of rounding.

\* $\chi^2$  analysis for categorical variables and Mann-Whitney for continuous variables. Variables that were significantly different were included in the regression analyses.

†Not all patients had recorded weight and height data. For weight, initiation population n=2426 and n=26 896 for EF HFA-beclometasone and CFC-beclometasone cohorts, respectively; step-up population n=314 and n=3023, respectively. For height, initiation population n=2585 and n=28 701, respectively; step-up population n=337 and n=3270, respectively. For body mass index, initiation population n=2368 and n=26 108, respectively; step-up population n=310 and n=2948, respectively.

‡Socioeconomic status was that assigned, in quintiles, by the GPRD to each practice using the Index of Multiple Deprivation (IMD) as a proxy measure.

§The SABA dose is the albuterol dose equivalent; the ICS dose is the actual CFC-BDP dose or the doubled EF HFA-BDP dose, as per licensing, which calls for EF HFA-BDP to be prescribed at approximately half the dose of CFC-BDP.

¶Recorded hospital attendance for asthma including admission, A&E attendance, out-of-hours attendance, or outpatient attendance.

\*\* The primary measure of asthma control was defined as no hospital attendance for asthma, oral corticosteroid course, or antibiotics for lower respiratory infection.

CFC-BDP, chlorofluorocarbon beclometasone; EF HFA, extrafine hydrofluoroalkane; ICS, inhaled corticosteroid; IQR, interquartile range; LRTI, lower respiratory tract infection; pMDI, pressurised metered-dose inhaler; n/a, not applicable; SABA, short-acting  $\beta_2$  agonist.

**Table S2.** Unmatched analysis: outcomes for patients initiating ICS and those receiving an increased dose of ICS

| Outcome                                                  | Initiation population |               |               | Step-up population |               |               |
|----------------------------------------------------------|-----------------------|---------------|---------------|--------------------|---------------|---------------|
|                                                          | EF HFA-BDP            | CFC-BDP       |               | EF HFA-BDP         | CFC-BDP       |               |
|                                                          | (n = 2938)            | (n = 33 926)  |               | (n = 364)          | (n = 3624)    |               |
| Asthma control status, n (%)                             |                       |               |               |                    |               |               |
| Primary measure of asthma control                        | 2444 (83.2)           | 27 686 (81.6) |               | 292 (80.2)         | 2653 (73.2)   |               |
| Asthma control plus SABA use                             | 1812 (61.7)           | 20 317 (59.9) |               | 163 (44.8)         | 1413 (39.0)   |               |
| Asthma control plus no additional or change              |                       |               |               |                    |               |               |
| in therapy                                               | 2222 (75.6)           | 25 976 (76.6) |               | 266 (73.1)         | 2477 (68.3)   |               |
| Asthma exacerbations, n (%)                              |                       |               |               |                    |               |               |
| 0                                                        | 2651 (90.2)           | 30 495 (89.9) |               | 317 (87.1)         | 2980 (82.2)   |               |
| 1                                                        | 201 (6.8)             | 2608 (7.7)    |               | 33 (9.1)           | 424 (11.7)    |               |
| 2                                                        | 57 (1.9)              | 522 (1.5)     |               | 7 (1.9)            | 125 (3.4)     |               |
| ≥3                                                       | 29 (1.0)              | 301 (0.9)     |               | 7 (1.9)            | 95 (2.6)      |               |
| ICS dose at index date (µg/d), n (%)†                    |                       |               |               |                    |               |               |
| 1-199 EF HFA-/ 1-399 CFC-BDP                             | 875 (29.8)            | 6685 (19.7)   |               | 6 (1.6)            | 184 (5.1)     |               |
| 200-399 EF HFA-/ 400-799 CFC-BDP                         | 1482 (50.4)           | 22 167 (65.3) |               | 119 (32.7)         | 1433 (39.5)   |               |
| 400-599 EF HFA-/ 800-1199 CFC-BDP                        | 555 (18.9)            | 4741 (14.0)   |               | 216 (59.3)         | 1769 (48.8)   |               |
| ≥600 EF HFA-/ ≥1200 CFC-BDP                              | 26 (0.9)              | 333 (1.0)     |               | 23 (6.3)           | 238 (6.6)     |               |
| Daily ICS dose (µg), median (IQR)‡                       | 82 (55–164)           | 110 (55–274)  |               | 192 (110–329)      | 329 (164–658) |               |
|                                                          |                       |               | <i>P-</i>     |                    |               | <i>P-</i>     |
|                                                          |                       |               | <i>value*</i> |                    |               | <i>value*</i> |
| <i>Disaggregated outcomes of the composite measures:</i> |                       |               |               |                    |               |               |
| Change in therapy, n (%)                                 | 556 (18.9)            | 5887 (17.4)   | 0.031         | 72 (19.8)          | 731 (20.2)    | 0.859         |
| ≥1 oral corticosteroid course, n (%)                     | 287 (9.8)             | 3421 (10.1)   | 0.586         | 47 (12.9)          | 641 (17.7)    | 0.022         |
| ≥1 hospital admission, n (%)                             | 28 (1.0)              | 294 (0.9)     | 0.629         | 2 (0.5)            | 51 (1.4)      | 0.173         |
| ≥1 course antibiotics for lower respiratory tract        |                       |               |               | 36 (9.9)           | 494 (13.6)    |               |
| infection, n (%)                                         | 283 (9.6)             | 3529 (10.4)   | 0.189         |                    |               | 0.045         |
| Mean SABA dose >200 µg/d, n (%)                          | 835 (28.4)            | 10 097 (29.8) | 0.127         | 173 (47.5)         | 1840 (50.8)   | 0.238         |

Percentages may not total 100 because of rounding.

\* $\chi^2$  analysis for categorical variables and Mann-Whitney for continuous variables.

†Nominal (actual) ICS dose on the index date. EF HFA-BDP dose is shown in proportion to double the dose of CFC-BDP, as per licensing recommendations, which call for the dose of EF HFA-BDP to be approximately half that of CFC-BDP.

‡The daily ICS dose during the outcome year was calculated as the dispensed amount divided by 365. (The licensed recommended dose of EF HFA-BDP is approximately half that of CFC-BDP.)

**Table S3.** Unmatched analysis: odds ratios (95% CI) for measures of asthma control and change in therapy, and rate ratios (95% CI) for exacerbations, in the EF HFA-BDP cohorts of initiation and step-up populations during the outcome year, with the CFC-BDP cohort set as the reference group (OR = 1.0).

|                                                                     | Initiation Population | Step-Up Population  |
|---------------------------------------------------------------------|-----------------------|---------------------|
|                                                                     | EF HFA-BDP            | EF HFA-BDP          |
|                                                                     | (N = 2938)            | (N = 364)           |
| Primary measure of asthma control, OR (95% CI)                      |                       |                     |
| Unadjusted                                                          | 1.12 (1.01-1.23)      | 1.48 (1.14-1.94)    |
| Adjusted for residual confounders                                   | 1.25 (1.14-1.39)*     | 1.56 (1.18-2.04)**  |
| Asthma control plus SABA use, OR (95% CI)                           |                       |                     |
| Unadjusted                                                          | 1.08 (1.00-1.17)      | 1.27 (1.02-1.58)    |
| Adjusted for residual confounders                                   | 1.15 (1.06-1.25)†     | 1.45 (1.15-1.82)††  |
| Asthma control plus no additional or change in therapy, OR (95% CI) |                       |                     |
| Unadjusted                                                          | 0.95 (0.87-1.04)      | 1.26 (0.99-1.60)    |
| Adjusted for residual confounders                                   | 1.08 (0.98-1.18)‡     | 1.30 (1.01-1.67)‡‡  |
| Exacerbation during the outcome year, rate ratio (95% CI)           |                       |                     |
| Unadjusted                                                          | 1.09 (0.93-1.28)      | 0.79 (0.53-1.18)    |
| Adjusted for residual confounders                                   | 0.96 (0.83-1.11)§     | 0.74 (0.52-1.05)§§  |
| Change in therapy, OR (95% CI)                                      |                       |                     |
| Unadjusted                                                          | 1.11 (1.01-1.22)      | 0.98 (0.75-1.28)    |
| Adjusted for residual confounders                                   | 0.98 (0.88-1.08)¶     | 0.94 (0.71-1.25) §§ |

\*Adjusted for age, baseline asthma consultations with no oral corticosteroid prescription, baseline non-asthma-related consultations, GERD, NSAIDs, paracetamol, oral corticosteroid courses and hospital admissions.

†Adjusted for age, year of index date, baseline asthma consultations with no oral corticosteroid prescription, baseline non-asthma-related consultations, GERD, NSAIDs, paracetamol, oral corticosteroid courses and hospital admissions.

‡Adjusted for age, ICS dose at index date, age by ICS dose at index date interaction, baseline asthma consultations with no oral corticosteroid prescription, baseline non-asthma-related consultations, GERD, NSAIDs, oral corticosteroid courses and hospital admissions.

§Adjusted for age, ICS dose at index date, age by ICS dose at index date interaction, baseline asthma consultations with no oral corticosteroid prescription, baseline non-asthma-related consultations, paracetamol, oral corticosteroid courses and hospital admissions.

¶Adjusted for age, ICS dose at index date, year of index date, baseline asthma consultations with no oral corticosteroid prescription, baseline non-asthma-related consultations, GERD, NSAIDs, oral corticosteroid courses and hospital admissions.

\*\*Adjusted for baseline non-asthma-related consultations, baseline asthma control status and average ICS daily dose.

††Adjusted for height, baseline asthma control status and average ICS daily dose.

‡‡Adjusted for baseline non-asthma-related consultations, average ICS daily dose, baseline exacerbations and ICS dose at index date.

¶¶Adjusted for baseline non-asthma-related consultations,  $\beta$ -blockers, average ICS daily dose, baseline exacerbations and ICS dose at index date.

§§Adjusted for baseline non-asthma-related consultations, baseline exacerbations and year of index date.

**Table S4.** Unmatched analysis: change in therapy by type for patients initiating ICS and those receiving an increased dose of ICS

|                                                     | Initiation population |                   | Step-up population |                  |
|-----------------------------------------------------|-----------------------|-------------------|--------------------|------------------|
|                                                     | EF HFA-BDP            | CFC-BDP           | EF HFA-BDP         | CFC-BDP          |
| Outcome                                             | (n = 2938)            | (n = 33 926)      | (n = 364)          | (n = 3624)       |
| Increase in ICS dose                                | 170 (5.8)             | 2250 (6.6)        | 6 (1.6)            | 121 (3.3)        |
| Change in inhaler device                            | 123 (4.2)             | 1631 (4.8)        | 15 (4.1)           | 147 (4.1)        |
| Change in ICS type                                  | 33 (1.1)              | 840 (2.5)         | 8 (2.2)            | 90 (2.5)         |
| Change to combination therapy or additional therapy | 288 (9.8)             | 2230 (6.6)        | 47 (12.9)          | 469 (12.9)       |
| Fluticasone+salmeterol                              | 125 (4.3) [43.4]*     | 1030 (3.0) [46.2] | 18 (4.9) [38.3]    | 160 (4.4) [34.1] |
| Budesonide+formoterol                               | 48 (1.6) [16.7]       | 281 (0.8) [12.6]  | 7 (1.9) [14.9]     | 43 (1.2) [9.2]   |
| Long-acting $\beta_2$ agonist                       | 153 (5.2) [53.1]      | 1257 (3.7) [56.4] | 26 (7.1) [55.3]    | 284 (7.8) [60.6] |
| Leukotriene receptor antagonist                     | 56 (1.9) [19.4]       | 353 (1.0) [15.8]  | 13 (3.6) [27.7]    | 65 (1.8) [13.9]  |
| Theophylline                                        | 5 (0.2) [1.7]         | 81 (0.2) [3.6]    | 1 (0.3) [2.1]      | 12 (0.3) [2.6]   |

Values shown are number (%). Patients could have more than one change in therapy; thus, the numbers are not additive. Because of rounding, percentages may not total 100.

\*Percentage in [square brackets] refers to subcohort receiving additional therapy.

CFC-BDP, chlorofluorocarbon beclometasone; EF HFA, extra-fine hydrofluoroalkane; ICS, inhaled corticosteroid

Figure S1

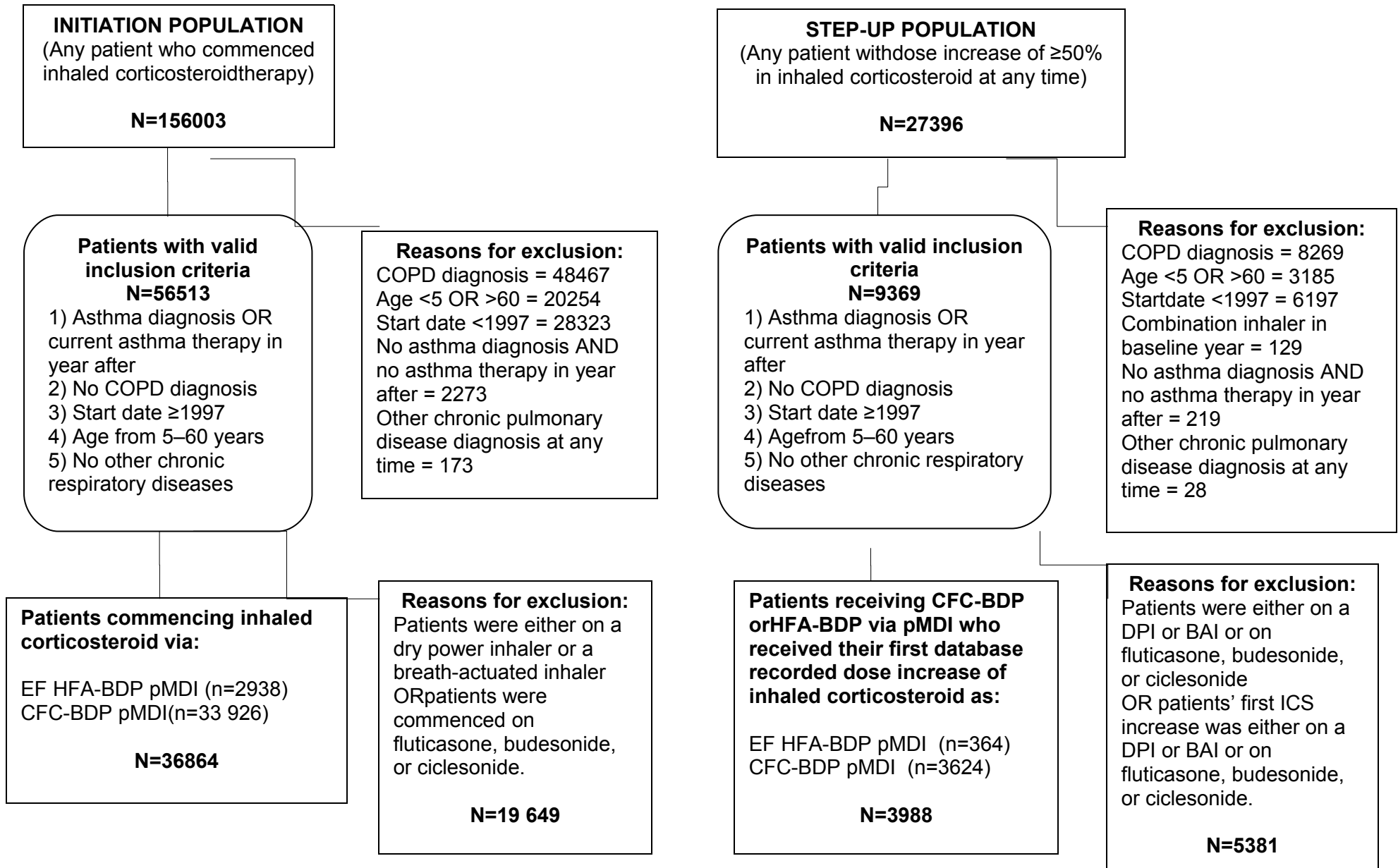


Figure S2

