RESEARCH PAPER

Clinical and cost effectiveness of switching asthma patients from fluticasone-salmeterol to extra-fine particle beclometasone-formoterol: a retrospective matched observational study of real-world patients

***David Price[1,2], Iain Small[3], John Haughney[1], Dermot Ryan[4], Kevin Gruffydd-Jones[5], Federico Lavorini[6], Tim Harris[7], Annie Burden[2], Jeremy Brockman[2], Christine King[2], Alberto Papi[8]**

[1] Academic Centre of Primary Care, University of Aberdeen, UK
[2] Research in Real Life Ltd, Cambridge, UK
[3] Peterhead Medical Centre, NHS Grampian, Scotland, UK
[4] Woodbrook Medical Centre, Loughborough, UK
[5] Box Surgery, Box, Corsham, Wiltshire, UK
[6] Department of Experimental and Clinical Medicine, Careggi University Hospital, Florence, Italy
[7] Chiesi UK Ltd, Cheadle, UK
[8] Department of Medical Science, University of Ferrara, Ferrara, Italy

Received 18th June 2013; revised 15th September 2013; accepted 16th September 2013; online 2nd November 2013

Abstract

Background: Efficacy trials suggest that extra-fine particle beclometasone dipropionate-formoterol (efBDP-FOR) is comparable to fluticasone propionate-salmeterol (FP-SAL) in preventing asthma exacerbations at a clinically equivalent dosage. However, switching from FP-SAL to efBDP-FOR has not been evaluated in real-world asthma patients.

Aims: The REACH (Real-world Effectiveness in Asthma therapy of Combination inHalers) study investigated the clinical and cost effectiveness of switching typical asthma patients from FP-SAL to efBDP-FOR.

Methods: A retrospective matched (1:3) observational study of 1,528 asthma patients aged 18–80 years from clinical practice databases was performed. Patients remaining on FP-SAL (n=1,146) were compared with those switched to efBDP-FOR at an equivalent or lower inhaled corticosteroid (ICS) dosage (n=382). Clinical and economic outcomes were compared between groups for the year before and after the switch. Non-inferiority (at least equivalence) of efBDP-FOR was tested against FP-SAL by comparing exacerbation rates during the outcome year.

Results: efBDP-FOR was non-inferior to FP-SAL (adjusted exacerbation rate ratio 1.01 (95% CI 0.74 to 1.37)). Switching to efBDP-FOR resulted in significantly better ($p<0.05$) odds of achieving overall asthma control (no asthma-related hospitalisations, bronchial infections, or acute oral steroids; salbutamol ≤200µg/day) and lower daily short-acting β_2-agonist usage at a lower daily ICS dosage (mean –130µg/day FP equivalents; $p<0.001$). It also reduced mean asthma-related healthcare costs by £93.63/patient/year ($p<0.001$).

Conclusions: Asthma patients may be switched from FP-SAL to efBDP-FOR at an equivalent or lower ICS dosage with no reduction in clinical effectiveness but a significant reduction in cost.

D Price *et al*. *Prim Care Respir J* 2013; **22**(4): 439-448
http://dx.doi.org/10.4104/pcrj.2013.00088

Keywords asthma, extra-fine particle, beclometasone, formoterol, fluticasone, salmeterol

*** Corresponding author:** Professor David Price, Academic Centre of Primary Care, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen AB25 2ZD, UK. Tel: +44 (0)1224 554588 Fax: +44 (0)1224 550683 E-mail: david@respiratoryresearch.org

The full version of this paper, with online appendices, is available online at www.thepcrj.org

Introduction

Asthma is a complex and costly disease to manage, particularly in patients with moderate-to-severe persistent asthma who require combination therapy with an inhaled corticosteroid (ICS) and long-acting β_2-receptor agonist (LABA) for daily asthma control. For example, in the East of England, a region of approximately 5.85 million people,[1] the Strategic Health Authority reported in 2011 that it spends approximately £55.5 million annually on low- and moderate-dose combination ICS-LABA inhalers.[2] Any measure that reduces the cost of asthma therapy without reducing the effectiveness or increasing the risk is therefore worthy of consideration.

In January 2008 an extra-fine particle formulation of beclometasone dipropionate (efBDP) and formoterol (FOR) was licensed in the UK as a fixed-dose combination (FDC) inhaler for use in the treatment of asthma in adults.[3] Extra-fine particle BDP-FOR has several advantages over larger particle ICS-LABA combinations such as fluticasone propionate and salmeterol (FP-SAL), the efBDP and FOR components each contributing a clinical advantage.

First, pulmonary distribution – especially to the small airways – is greater for extra-fine particle formulations than for larger particle formulations.[4-13] Second, and no doubt consequentially, efBDP is as effective for asthma control as larger particle ICS formulations, at a lower ICS dosage. For example, the clinical equivalence of efBDP and FP in asthma patients can be described as a ratio of approximately 0.8:1, so 400µg of efBDP is clinically equivalent to 500µg of FP.[12-15] A third and probably related advantage is that extra-fine particle inhalers may be less dependent on good inhaler technique – or more tolerant of poor technique – than larger particle formulations.[7,16,17] Lastly, formoterol relieves bronchoconstriction more quickly than salmeterol[18,19] and almost as quickly as short-acting β_2-receptor agonists (SABA) such as salbutamol,[19-21] potentially improving patient compliance and allowing the efBDP-FOR inhaler to be used for both maintenance and reliever therapy (MART) if the patient and physician elect this approach.[22]

In various studies, efBDP-FOR was at least as effective at improving lung function and measures of asthma control while preventing acute asthma exacerbations as (1) larger particle BDP with FOR delivered via separate inhalers;[23] (2) FP-SAL;[12-16,24,25] and (3) budesonide with formoterol (BUD-FOR).[16,24,26,27] As further evidence, in studies of ICS alone, efBDP was at least as effective for asthma control as larger particle formulations of BDP[28-30] and fluticasone.[31] However, the greater clinical effectiveness of efBDP may have been understated in efficacy studies involving randomised controlled trials (RCTs), which have shown no clear clinical advantage of any one ICS.[32-34] In real-world asthma patients, efBDP provides equivalent – and, in some cases, better – asthma control at a lower daily ICS dosage,[31,35] and therefore lower risk for adverse effects[31] and lower asthma-related healthcare costs[35] – attributes considered important by physicians and respiratory specialists alike when choosing an ICS-LABA combination.[36]

Product approval for the efBDP-FOR inhaler was granted in the UK based on RCTs in Europe which showed non-inferiority in morning pre-dose peak expiratory flow and no significant difference in the number of symptom-free days or adverse events, including acute exacerbations, compared with FP-SAL[15] and BUD-FOR.[26] Because efBDP-FOR costs less than other FDC inhalers and has been shown to be of comparable efficacy in asthma management, the UK National Health Service (NHS) in some regions encouraged physicians to switch patients to the efBDP-FOR inhaler in an effort to lower the costs of ongoing ICS-LABA therapy.[2] This switch was estimated to save between £3 and £16 per patient per month (depending on the inhaler) for low- and moderate-dose ICS-LABA therapy.[2]

However, despite the reasonable assumption of greater cost effectiveness with the efBDP-FOR inhaler, to date no studies have investigated the outcome of such a switch under real-world conditions of use. The clinical efficacy of switching from FP-SAL to efBDP-FOR, with[14] or without[25] a step-down in ICS dosage, has been shown in two recent RCTs, but it has yet to be demonstrated under less controlled conditions.

We therefore undertook a retrospective study of typical asthma patients seen in routine clinical practice in the UK, investigating both the clinical and cost effectiveness of switching from FP-SAL to efBDP-FOR at an equivalent or lower ICS dosage. Using nationwide patient databases, we sought to generate as large and representative a population of asthma patients as possible given the study aims, including patients with significant co-morbidities, a past or current smoking habit, and less than ideal adherence to their ICS prescriptions.

Our aims were twofold: (1) to determine whether efBDP-FOR is at least equivalent (non-inferior) to FP-SAL for exacerbation prevention when typical asthma patients are switched from FP-SAL to efBDP-FOR; and (2) to determine whether switching from FP-SAL to efBDP-FOR is cost-effective or represents a trade-off (lower cost but lower effectiveness).

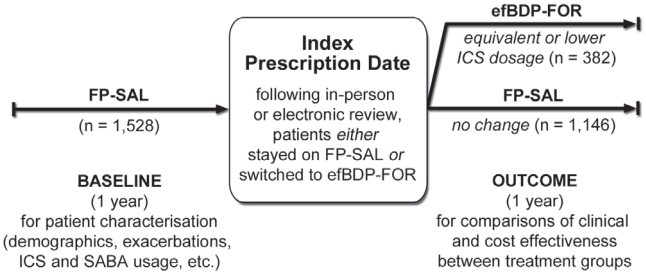
Methods

Study design

A retrospective matched observational study was conducted of asthma patients in the UK treated in primary care practice. An outline of the study design is illustrated in Figure 1. For each patient meeting the inclusion criteria, the medical record was examined for 12 months before ('baseline year') and for 12 months after ('outcome year') the face-to-face or electronic review during which the physician either continued FP-SAL inhaler therapy at the same ICS dosage or switched the patient to efBDP-FOR at an equivalent or lower ICS dosage. The date of this pivotal patient review was designated the index prescription date (IPD). For further explanation, see Supplemental Materials (Appendix 1 available online at www.thepcrj.org).

Raw data were obtained from the UK Optimum Patient Care Research Database (http://www.optimumpatientcare.org/Html_Docs/OPCRD.html) and the Clinical Practice Research Datalink, formerly known as the General Practice Research Database

Figure 1. Schematic of the Real-world Effectiveness in Asthma therapy of Combination inHalers (REACH) study design



efBDP-FOR=extra-fine particle beclometasone and formoterol as fixed-dose combination inhaler, FP-SAL=fluticasone and salmeterol as fixed-dose combination inhaler, ICS=inhaled corticosteroid, SABA=short-acting β_2-receptor agonist.

Box 1. Inclusion criteria for the Real-world Effectiveness in Asthma therapy of Combination inHalers (REACH) study

Age: 18–80 years

Diagnostic code: asthma; no code for chronic obstructive pulmonary disease or other chronic respiratory condition (except asthma)

Smoking status: known

Baseline fluticasone and salmeterol as fixed-dose combination inhaler (FP-SAL) therapy: ≥2 prescriptions for FP-SAL during baseline year

Oral steroids: none for maintenance during baseline year

Evidence of continuing therapy: ≥2 prescriptions for extra-fine particle beclometasone and formoterol as fixed-dose combination inhaler (efBDP-FOR) during outcome year (efBDP-FOR group); no change in therapy (FP-SAL group)

Evidence of switching for reasons other than efficacy: ≥5 patients in a practice switched from FP-SAL to efBDP-FOR, with no increase in inhaled corticosteroid dosage, in a 3-month period

(http://www.cprd.com/intro.asp), spanning the period from January 2007 to August 2012. Inclusion criteria are summarised in Box 1 and further details are given in the online Supplemental Materials, along with a CONSORT diagram illustrating the patient selection process (Figure S1). A total of 50,261 patients met the inclusion criteria, of whom 390 were switched to efBDP-FOR and 49,871 remained on FP-SAL.

The patients switched to efBDP-FOR were then matched as closely as possible in a ratio of 1:3 with those remaining on FP-SAL using the demographic and clinical criteria summarised in Table 1. Using a one-sided test of equivalence based on exacerbation prevention, the 1:3 ratio yielded a statistical power of 95% whereas lesser ratios yielded lower powers (93% and 86% for 1:2 and 1:1 ratios, respectively). A time-frame of ±2 years for the IPD was

Table 1. Matching criteria for the Real-world Effectiveness in Asthma therapy of Combination inHalers (REACH) study

Criteria	Specifics
Age	±5 years, within two subgroups: 18–60 years and 61–80 years
Gender	Male or female
Smoking status	Non-smoker, current smoker, or ex-smoker
Last prescribed ICS dosage prior to IPD	Exact match (µg/day)
Type of consultation/review at IPD	Face-to-face or electronic
Last ICS device prescribed prior to IPD	MDI or DPI
Number of courses of acute oral steroids	0, 1, or 2+
SABA usage, average daily dose	0, 1–200, 201–400, 401–800, 801+ µg
Year of IPD	Closest match within ±2 years

DPI=dry powder inhaler, ICS=inhaled corticosteroid, IPD=index prescription date, MDI=metered dose inhaler, SABA=short-acting β_2-receptor agonist.

deemed optimal for case matching, as a longer interval would have risked placing matched patients in different time periods and a shorter interval would have excluded too many otherwise eligible patients. As it was, eight patients in the efBDP-FOR group were excluded for unmatched data (see Figure S2 in online Supplemental Materials), so the final group numbers were 382 patients switched to efBDP-FOR and 1,146 patients remaining on FP-SAL for the outcome year.

Clinical outcome measures

The primary clinical outcome investigated was the incidence of severe asthma exacerbations, as defined by the American Thoracic Society and European Respiratory Society (ATS/ERS) task force on asthma control and exacerbations, where an exacerbation is defined as an occurrence of asthma-related hospital attendance/admission (including Accident and Emergency attendance) or the use of acute oral steroids.[37] The secondary outcomes investigated are described in Table 2.

Economic outcome measures

Health economic analyses comprised comparisons of asthma-related healthcare costs and assessment of the cost effectiveness of treatment, using exacerbation prevention (ATS/ERS definition) and risk domain asthma control (see Table 2) as measures of treatment effectiveness.

Asthma-related costs included all asthma drug prescriptions: ICS of all kinds including FDC inhalers, oral corticosteroids for acute control, SABA, LABA, leukotriene receptor antagonists, theophylline, and antibiotics prescribed for lower respiratory tract infections. Drug costs were obtained from the 2010 British National Formulary (http://www.bnf.org/bnf/index.htm).

Asthma-related costs also included general practitioner (GP) consultations and respiratory-related hospitalisation costs

Table 2. Secondary outcomes compared between matched treatment groups

Outcome	Definition
Risk domain asthma control	'Controlled' if absence of: • asthma-related hospital attendance/admission,* *and* • GP consultation for LRTI, *and* • prescription for acute course of oral steroids
Overall asthma control (risk and impairment)	'Controlled' if: • risk domain asthma control, *and* • average SABA dosage of ≤200µg/day for salbutamol or ≤500µg/day for terbutaline
Severe exacerbation rate (clinical definition)	'Exacerbation' defined as an occurrence of: • asthma-related hospital attendance/admission *or* • GP consultation for LRTI *or* • use of acute oral steroids
Treatment success	'Successful' if: • risk domain asthma control *and* • no additional or change in therapy†
Asthma-related hospitalisations	Hospital admission‡ within 7 days either side of a lower respiratory code
Average daily SABA usage	0, 1–200, 201–400, 401–800, or 801+ µg
Adherence to ICS therapy§	<50%, 50–69%, 70–99%, or 100+%
Incidence of oral thrush	Diagnostic code for oral candidiasis or prescription for topical/oral antifungal therapy

*Asthma-related hospitalisation included Accident and Emergency, out-of-hours, and Outpatient department attendance.
†Change in asthma therapy included an increase in ICS dose of ≥50% or the addition of theophylline or a leukotriene receptor antagonist.
‡Inpatient asthma-related or vague/uncoded hospitalisation.
§Adherence to ICS therapy was calculated as follows:
days per pack = actuations per pack/actuations per day
total pack days = sum (days per pack) over the year of interest
adherence (%) = (total pack days/365) x 100
GP=general practitioner, ICS=inhaled corticosteroid, LRTI=lower respiratory tract infection, SABA=short-acting β_2-receptor agonist.

(outpatient, inpatient, and Accident and Emergency). Unit costs for GP consultations were derived from the Personal Social Services Research Unit report: *Unit Costs of Health and Social Care 2011*,[38] assuming an average consultation duration of 11.7 minutes. Hospital usage costs were obtained from the NHS Reference Costs 2010–2011.[39]

Statistical analyses

All analyses were carried out using SPSS Statistics Version 20 (IBM, Armonk, New York, USA), SAS Version 9.3 (SAS Institute, Cary, North Carolina, USA), and Microsoft Excel 2007 (Microsoft, Redmond, Washington, USA). Statistically significant results were defined as $p<0.05$, and trends as $p\geq0.05$ but <0.10. All adjusted odds/rate ratios and differences in proportions are presented with their 95% confidence intervals (CI).

Exploratory data analysis was conducted for all variables of interest for the baseline and outcome years. Box 2 in the online Supplemental Materials lists all the potential confounders examined. Summary statistics for all baseline variables for the matched cohorts were compared using conditional logistic regression (for more information, see online Supplemental Materials).

Clinical outcomes

For the primary outcome, the total number of exacerbations in the outcome year was compared between treatment groups using a conditional Poisson regression model to obtain an estimate of relative exacerbation rates (further details are given in online Supplemental Materials).

To show 'at least equivalence' or non-inferiority in exacerbation prevention for efBDP-FOR compared with FP-SAL, the adjusted proportions of patients within each treatment group and the adjusted difference in proportions recording no exacerbations in the outcome year were calculated using a conditional binary logistic regression model. Non-inferiority was defined as the proportion of efBDP-FOR patients recording no exacerbations being no more than 10% lower than the proportion of patients remaining on FP-SAL recording no exacerbations. We chose a threshold of –10% based on clinical experience and available literature. Although there is little agreement among statisticians,[40,41] differences of >10% are widely regarded as clinically important in related respiratory studies.[41]

For the secondary outcomes, adjusted odds and rates of events were compared between matched treatment groups using conditional binary/ordinal logistic regression or conditional Poisson regression models, respectively, as detailed in the online Supplemental Materials.

Economic outcomes

Generalised linear models with a logit link and gamma distribution were used to estimate mean asthma-related healthcare costs. Treatment costs were compared between groups via the differences in mean costs/patient/year, both unadjusted and adjusted for

Table 3a. Clinically important baseline variables in matched treatment groups: variables used in patient matching (see Tables 3b and 3c in online Supplemental Materials for further baseline patient characterisation)

Variable	FP-SAL (n=1,146)	efBDP-FOR* (n=382)	p Value†
Age at index prescription date (years)			
18–60	723 (63.1%)	241 (63.1%)	NA
61–80	423 (36.9%)	141 (36.9%)	
Mean (SD)	53.4 (14.7)	53.4 (14.9)	0.86
Median (IQR)	53 (43, 65)	54 (43, 65)	
Gender			
Male	507 (44.2%)	169 (44.2%)	NA
Female	639 (55.8%)	213 (55.8%)	
Smoking status			
Non-smoker	594 (51.8%)	198 (51.8%)	NA
Current smoker	210 (18.3%)	70 (18.3%)	
Ex-smoker	342 (29.9%)	114 (29.9%)	
Last prescribed ICS dosage (actual FP dosage, µg/day)			
200	99 (8.6%)	33 (8.6%)	NA
250	33 (2.9%)	11 (2.9%)	
500	816 (71.2 %)	272 (71.2%)	
1,000	198 (17.3%)	66 (17.3%)	
Mean (SD)	553.3 (223.6)	553.3 (223.7)	NA
Median (IQR)	500 (500, 500)	500 (500, 500)	
Type of consultation at index prescription date			
Face-to-face	321 (28.0%)	107 (28.0%)	NA
Electronic	825 (72.0%)	275 (72.0%)	
Last prescribed ICS device			
MDI	1,059 (92.4%)	353 (92.4%)	NA
DPI	87 (7.6%)	29 (7.6%)	
Courses of acute oral steroids			
0	936 (81.7%)	312 (81.7%)	NA
1	141 (12.3%)	47 (12.3%)	
2+	69 (6.0%)	23 (6.0%)	
Mean (SD)	0.29 (0.76)	0.34 (1.13)	0.081
Median (IQR)	0 (0, 0)	0 (0, 0)	
SABA usage, average daily dose (µg/day)			
0	216 (18.9%)	72 (18.9%)	NA
1–200	336 (29.3%)	112 (29.3%)	
201–400	291 (25.4%)	97 (25.4%)	
401–800	240 (20.9%)	80 (20.9%)	
801+	63 (5.5%)	21 (5.5%)	
Mean (SD)	279.7 (289.2)	296.4 (348.2)	0.022
Median (IQR)	219 (55, 438)	219 (55, 438)	
Year of index prescription date			
2008	379 (33.0%)	26 (6.8%)	<0.001
2009	702 (61.3%)	178 (46.6%)	
2010	63 (5.5%)	151 (39.5%)	
2011	2 (0.2%)	27 (7.1%)	

Data are shown as n (%) unless otherwise indicated

*These patients were on FP-SAL during their baseline year but were switched to efBDP-FOR at the index prescription date.

†Conditional logistic regression.

DPI=dry powder inhaler, efBDP-FOR=extra-fine particle beclometasone and formoterol as fixed-dose combination inhaler, FP=fluticasone propionate, FP-SAL=fluticasone and salmeterol as fixed-dose combination inhaler, ICS=inhaled corticosteroid, IQR=interquartile range, MDI=metered dose inhaler, NA=not applicable (matching variable), SABA=short-acting β_2-receptor agonist, SD=standard deviation.

potential confounders. Differences in adjusted mean costs are reported with 95% CI found by bootstrapping methods[42] using 1,000 random samples taken, with replacement, from the dataset.

Cost effectiveness was determined using point estimates of differences in treatment cost and effectiveness between efBDP-FOR and FP-SAL using 1,000 replicated samples plotted to create a cost effectiveness plane, with FP-SAL as the reference treatment.

Results

Baseline data

Despite matching for most recent prescribed ICS dosage and several other clinically relevant variables, some significant baseline differences remained between treatment groups (Tables 3a–c). While the rates of rhinitis and cardiac disease were higher in the patients who would remain on FP-SAL, the patients who would be switched to efBDP-FOR appeared to have slightly more severe asthma, as evidenced by a higher rate of multiple asthma consultations, a greater number of respiratory prescriptions (particularly for ICS and SABA), and a higher average daily ICS dosage. The higher controller-to-reliever ratio in the patients who would be switched to efBDP-FOR suggests that these patients may have been more diligent in managing their asthma than those who would remain on FP-SAL. Regardless, there were no significant differences between treatment groups for any of the clinical outcome measures at baseline (see Table 3b in online Supplemental Materials).

Daily ICS dosages at review/switch

At the IPD, the majority of patients (71.2%) were on a prescribed FP dosage of 500µg/day, 11.5% were on 200–250µg/day, and 17.3% were on 1,000µg/day (Figure 2). These proportions did not change going into the outcome year in the patients remaining on FP-SAL. In the group switching to efBDP-FOR, 306 patients (80.1%) were prescribed an efBDP dosage of 400µg/day and 76 patients (19.9%) a dosage of 200µg/day (Figure 2). These dosages were equivalent to the most recent FP-SAL prescription in 296 patients (77.5%), and in the remaining 86 patients (22.5%) they represented a reduction in ICS dosage of at least 50%.

Primary outcome

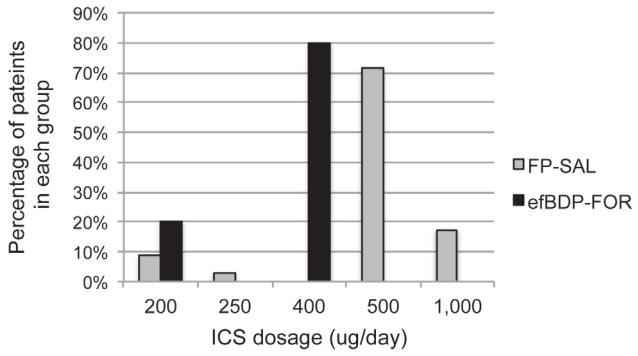
There was no significant difference between treatment groups in the incidence of severe exacerbations during the outcome year (Table 4). The adjusted difference in proportions of patients recording no exacerbations was only 0.02 (95% CI –0.03 to 0.07). As the threshold for non-inferiority was set at a difference of no more than 10% lower (–0.10), efBDP-FOR was shown to be at least equivalent (non-inferior) to FP-SAL in this setting

Secondary outcomes

The efBDP-FOR patients were significantly more likely to achieve overall asthma control, have lower daily SABA usage, and be more adherent to ICS therapy than the FP-SAL patients (Table 5a; Figure 3). In addition, the average daily ICS dosage over the course of the outcome year was significantly lower in the efBDP-FOR group, by a mean of 130µg/day in FP-equivalent doses (Table 6).

There were no significant differences between treatment groups for risk domain asthma control, severe exacerbations (clinical definition), treatment success, inpatient asthma-related

Figure 2. Actual ICS dosage prescribed at the Index Prescription Date in patients remaining on FP-SAL and those switched to efBDP-FOR (values for the efBDP-FOR group are actual BDP dosages, not FP-equivalents)



BDP=beclometasone dipropionate, efBDP-FOR=extra-fine particle beclometasone and formoterol as fixed-dose combination inhaler, FP=fluticasone propionate, FP-SAL=fluticasone and salmeterol as fixed-dose combination inhaler, ICS=inhaled corticosteroid.

Table 5a. Comparison of secondary outcomes between matched treatment groups during the outcome year (for the full version of this table, see Table 5b in online Supplemental Materials)

Outcome	FP-SAL (n=1,146)	efBDP-FOR (n=382)
Overall asthma control (risk and impairment)		
Adjusted odds ratio*	1.00	1.56
(95% CI)		(1.14 to 2.14)
Average daily SABA usage		
Adjusted odds ratio*	1.00	0.74
(95% CI)		(0.60 to 0.91)
Adherence to ICS therapy		
Odds ratio	1.00	1.40
(95% CI)		(1.13 to 1.73)

*Adjusted for baseline confounders (see Table 5b in online Supplemental Materials)

CI=confidence intervals, efBDP-FOR=extra-fine particle beclometasone and formoterol as fixed-dose combination inhaler, FP-SAL=fluticasone and salmeterol as fixed-dose combination inhaler, ICS=inhaled corticosteroid, SABA=short-acting β_2-receptor agonist.

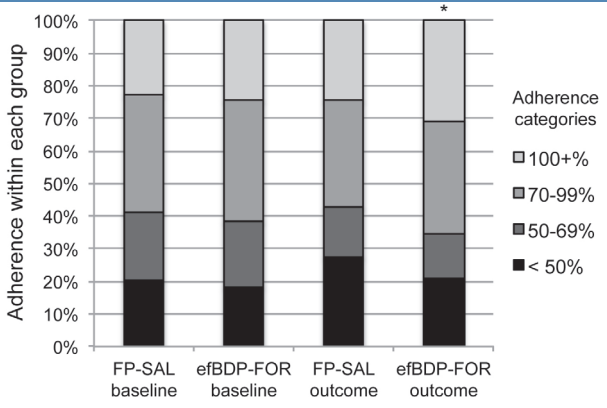
Table 4. Comparison of severe exacerbation rates (ATS/ERS definition) between matched treatment groups during the outcome year

Severe exacerbations	FP-SAL (n=1,146)	efBDP-FOR (n=382)
0, n (%)	918 (80.1%)	309 (80.9%)
1, n (%)	155 (13.5%)	49 (12.8%)
2+, n (%)	73 (6.4%)	24 (6.3%)
p=0.78		
Adjusted rate ratio*	1.00	1.01
95% CI	–	0.74 to 1.37

*Adjusted for baseline confounders: numbers of SABA prescriptions and asthma consultations.

ATS/ERS=American Thoracic Society and European Respiratory Society, CI=confidence intervals, efBDP-FOR=extra-fine particle beclometasone and formoterol as fixed-dose combination inhaler, FP-SAL=fluticasone and salmeterol as fixed-dose combination inhaler, SABA=short-acting β_2-receptor agonist

Figure 3. Adherence to ICS therapy in matched treatment groups during their baseline and outcome years (patients in the 'efBDP-FOR baseline' group were on FP-SAL during their baseline year but were switched to efBDP-FOR at the index prescription date.)



Adherence was categorised as <50%, 50–69%, 70–99%, and 100+% compliance with the prescribed ICS dosage. *Adherence to ICS therapy was significantly greater in the efBDP-FOR patients than in the FP-SAL patients during the outcome year (p=0.001). efBDP-FOR=extra-fine particle beclometasone and formoterol as fixed-dose combination inhaler, FP-SAL=fluticasone and salmeterol as fixed-dose combination inhaler, ICS=inhaled corticosteroid.

hospitalisations, or incidence of oral thrush during the outcome year (see Table 5b in online Supplemental Materials). There were no significant interactions between treatment and smoking status for any outcomes.

Health economic outcomes

During the baseline year there were no significant differences between treatment groups for asthma-related total healthcare or drug costs. However, there was a trend (p=0.061) for higher healthcare costs in the patients who would be switched to efBDP-FOR, driven by significantly higher costs for their FDC inhalers (p=0.016) and asthma consultations (p<0.001).

During the outcome year asthma-related total healthcare and drug costs were both significantly lower in patients switched to efBDP-FOR than in those remaining on FP-SAL (p<0.001 for both indices). Adjusted for baseline costs, the mean asthma-related total healthcare costs for the outcome year were £438.82/patient (95% CI £421.94 to £456.25) for the FP-SAL group and £345.19/patient (95% CI £327.96 to £362.90) for the efBDP-FOR group, a difference of £93.63/patient/year (95% CI £73.65 to £114.27), or £7.89/patient/month.

The single greatest contributor to the total healthcare cost was

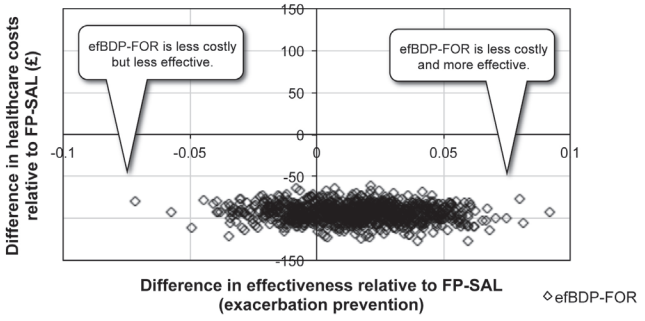
Table 6. Comparison of average daily ICS dose (FP-equivalents) between matched treatment groups during the outcome year

	FP-SAL (n=1,146)	efBDP-FOR (n=382)
Average daily ICS dose, n (%)		
1–200 µg	203 (17.7%)	92 (24.1%)
201–400 µg	350 (30.6%)	197 (51.5%)
401–600 µg	352 (30.7%)	74 (19.4%)
601+ µg	241 (21.0%)	19 (5.0%)
Mean (SD), µg/day	455.0 (304.8)	324.5 (159.3)
Median (IQR) µg/day	411.0 (246.6, 575.4)	295.9 (230.2, 394.5)
p Value*	<0.001	

*Conditional logistic regression.

efBDP-FOR=extra-fine particle beclometasone and formoterol as fixed-dose combination inhaler, FP=fluticasone propionate, FP-SAL=fluticasone and salmeterol as fixed-dose combination inhaler, ICS=inhaled corticosteroid, IQR=interquartile range, SD=standard deviation.

Figure 4. Cost-effectiveness of switching from FP-SAL to efBDP-FOR, with treatment effectiveness based on exacerbation prevention (ATS/ERS definition) during the outcome year. Costs are total asthma-related healthcare costs (£/patient/year), adjusted for baseline differences



ATS/ERS=American Thoracic Society and European Respiratory Society, efBDP-FOR=extra-fine particle beclometasone and formoterol as fixed-dose combination inhaler, FP-SAL=fluticasone and salmeterol as fixed-dose combination inhaler.

the cost of FDC inhaler therapy, so these differences were driven by the significantly lower cost of FDC inhaler therapy in the efBDP-FOR group (p<0.001). All other costs (drugs, consultations, hospitalisations) were comparable between treatment groups. The mean cost of FDC inhaler therapy for the outcome year was £368.20/patient for the FP-SAL group and £280.12/patient for the efBDP-FOR group, a difference of £88.08/patient/year, or £7.34/patient/month.

Based on point estimates of differences in cost and effectiveness using 1,000 replicated samples, efBDP-FOR was both less costly and more effective than FP-SAL in this setting. Using exacerbation prevention (ATS/ERS definition) as the measure of treatment effectiveness, there was a 75% probability that efBDP-FOR is less costly and more effective than FP-SAL (Figure 4). Using risk domain asthma control as the measure of effectiveness, there was an 87% probability that efBDP-FOR is less costly and more effective in this setting.

Discussion

Main findings

In this heterogeneous population of patients requiring ICS-LABA therapy for asthma control, efBDP-FOR was at least as effective as FP-SAL in preventing severe exacerbations. In addition, switching from FP-SAL to efBDP-FOR at an equivalent or lower daily ICS dosage resulted in improved odds of achieving overall asthma control, lower daily SABA usage, and better adherence to ICS therapy, all at a lower daily ICS dosage. Furthermore, switching from FP-SAL to efBDP-FOR was cost-effective, efBDP-FOR being more effective and less costly than FP-SAL in this patient population.

Strengths and limitations of this study

There are three main strengths of our study: (1) its large and diverse patient population, with few clinically relevant exclusion criteria; (2) its relatively long duration; and (3) its non-interventional nature. By including patients with significant co-morbidities, smokers, and patients with poor adherence to their ICS prescription, most of the challenges typically faced in primary asthma care were represented in our study population. In addition, our study examined 12 months of patient data both before and after the index patient review/switch, so the effects of seasonal or other transient confounders – including a change in therapy – were minimised. Furthermore, the retrospective nature of data acquisition meant that our study protocol did not affect patient behaviour in any way, particularly with respect to inhaler use and physician contact.

In contrast, the RCTs which compared efBDP-FOR with FP-SAL[15] and BUD-FOR[26] followed only 114 and 109/110 carefully selected patients, respectively, and for a treatment period of only 12 weeks. Furthermore, those study protocols required frequent clinic visits over the course of the investigation period,[15,26] which likely influenced treatment adherence and thus outcomes.[43,44] Our study showed that efBDP-FOR is comparable to FP-SAL – and in some measures superior – in real-life asthma patients.

The main limitations of our study are those inherent to retrospective studies, and to observational studies of any kind.[43,44] There are trade-offs in the scope and thus the findings of any study. Specifically, our study design precluded a thorough evaluation of adverse effects with either ICS-LABA combination in this patient population. In order to achieve our objectives, it was necessary to include only those patients with complete data for both baseline and outcome years. Our study design thus precluded an evaluation of asthma-related deaths and other rare significant adverse effects with either FDC inhaler.

Another limitation of our study was the need to rely on anonymised medical records for the diagnosis of asthma and the exclusion of other chronic respiratory disorders such as chronic obstructive pulmonary disease (COPD). Using diagnostic spirometry, it has been estimated that about 25% of asthma patients over the age of 40 may have COPD.[45] Given the age distribution and smoking status of the patients in our study, we estimate that a maximum of 10% of the patients may have had COPD instead of – or in addition

to – asthma. As age and smoking status were matching variables, any such patients would have been fairly equally distributed among the two treatment groups.

Interpretation of findings in relation to previously published work

The clinical effectiveness of efBDP-FOR in asthma patients requiring combination ICS-LABA therapy is well established.[12-16,21-27,46,47] However, to our knowledge, no studies have evaluated both the clinical and cost effectiveness of switching from another ICS-LABA combination to efBDP-FOR in the typical asthma patient – a scenario that is likely to be increasingly common in primary care, given the substantially lower cost and comparable effectiveness of the efBDP-FOR inhaler and, in the UK, certain NHS recommendations to physicians.[2]

The effectiveness of stepping down from high-dose FP-SAL to moderate-dose FP-SAL (step-down) or efBDP-FOR (step-down plus switch) was recently shown in a prospective RCT. The study concluded that efBDP-FOR (400µg/day efBDP) was equivalent to moderate-dose FP-SAL (500µg/day FP) in morning pre-dose peak expiratory flow, and asthma control was maintained in 96% of the patients following treatment step-down (from 1,000µg/day FP).[14] In another recent RCT, asthma patients previously controlled with FP-SAL (500µg/day FP) were effectively stepped across or switched to efBDP-FOR (400µg/day efBDP); lung function and asthma control were maintained, no safety issues were reported, and efBDP-FOR was noted to have a relatively rapid (5 min) onset of action.[25] However, those studies involved carefully selected patient populations, as is typical of a RCT, and did not include cost analyses.

An Italian study[48] conducted a *post hoc* cost-effectiveness and cost-utility analysis of the data from the RCT on which the non-inferiority of efBDP-FOR to FP-SAL was based.[15] From the perspective of the Italian NHS, efBDP-FOR was more cost effective than FP-SAL and offered a slight advantage over FP-SAL in weeks spent successfully controlled and in quality-adjusted life years.[48] However, that study involved only 114 carefully selected patients in each treatment group and followed the patients for only 12 weeks of treatment.[15] None of these RCTs examined a broad population of asthma patients.

The PRISMA (PRospectIve Study on asthMA control) study group followed 1,017 real-life asthma patients for 12 months, including smokers, ex-smokers, and patients with co-morbidities.[24,27] Of the 739 patients evaluable after 12 months, 569 patients were treated using an ICS-LABA combination. The patients on efBDP-FOR had significantly better asthma control and quality of life compared with patients on FP-SAL or BUD-FOR.[24] In another study of real-life asthma patients, treatment with efBDP-FOR led to significant improvements in pulmonary function and asthma control, regardless of the patient's smoking status, and the medication was well tolerated.[47] However, while these studies indicate that efBDP-FOR is both safe and effective for asthma control in typical asthma patients, a study of real-life asthma patients switching from FP-SAL to efBDP-FOR was necessary in order to confirm that switching is both clinically and cost effective in this broad patient population.

Implications for future research, policy and practice

One direction for future research is the outcome, in clinical and cost effectiveness, of stepping down the ICS dosage in typical asthma patients switching to efBDP-FOR from another ICS-LABA combination. The British Thoracic Society and Scottish Intercollegiate Guidelines Network recommend stepping down ICS therapy once asthma is controlled, advising a treatment review every three months and a decrease in dosage by approximately 25–50% each time if appropriate.[49] Only 86 patients in our study were switched to efBDP-FOR at an ICS dosage that was substantially lower than their last FP-SAL prescription, so meaningful statistical analysis was not possible.

Another avenue worth exploring is the use of efBDP-FOR as single inhaler MART. A recent RCT found that efBDP-FOR used both for daily maintenance and as-needed reliever therapy was well tolerated and superior to a combination of daily maintenance with efBDP-FOR and as-needed SABA (salbutamol). The MART approach with efBDP-FOR significantly increased the time to first severe exacerbation (ATS/ERS definition) by 75 days, reduced the risk of exacerbation by 36%, and resulted in fewer courses of oral steroids and asthma-related hospitalisations compared with the efBDP-FOR + SABA combination.[22] It would be interesting to evaluate the cost effectiveness of this approach, as it is possible that even further asthma-related cost savings could be realised without a significant reduction in clinical effectiveness or an increase in risk.

Conclusions

Switching asthma patients from FP-SAL to efBDP-FOR at an equivalent or lower ICS dosage is both less costly and more effective.

Handling editor Anthony D'Urzo
Statistical review Gopal Netuveli

Acknowledgements We thank Stan D Musgrave, Julie von Ziegenweidt, Francesca Barion, and Anna Rigazio for help with the statistical and data analyses.

Conflicts of interest DP has consultant arrangements with Almirall, AstraZeneca (AZ), Boehringer Ingelheim, Chiesi, GlaxoSmithKline (GSK), Merck, Mundipharma, Medapharma, Novartis, Napp, Nycomed, Pfizer, Sandoz, and Teva. He or his research team have received grants and support for research in respiratory disease from the following organisations in the last 5 years: UK National Health Service, Aerocrine, AZ, Boehringer Ingelheim, Chiesi, GSK, Merck, Mundipharma, Novartis, Nycomed, Orion, Pfizer and Teva. He has spoken for Almirall, AZ, Activaero, Boehringer Ingelheim, Chiesi, Cipla, GSK, Kyorin, Novartis, Merck, Mundipharma, Pfizer, and Teva. He has shares in AKL Ltd which produces phytopharmaceuticals. He is the sole owner of Research in Real Life Ltd and its subsidiary social enterprise Optimum Patient Care. IS has received honoraria and support to attend international conferences from Almirall, AZ, Boehringer Ingelheim, Chiesi, GSK, NAPP, Novartis, and Orion. He is an Associate editor of the *PCRJ*, but was not involved in the editorial review of, nor the decision to publish, this article. JH has provided occasional consultancy or speaker services for Almirall, AZ, Boehringer Ingelheim, Chiesi, GSK, Merck, Novartis, Sharpe and Dohme, and Teva. DR has lectured on behalf of, received sponsorship from, or provided consultancy services to: AZ, GSK, MSD, Schering Plough, Uriach Pharma, Chiesi, NAPP, Meda Pharmaceuticals, Nycomed, BI, Pfizer, and Novartis Pharma. KG-J has acted as a consultant for and spoken on behalf of GSK, AZ, Chiesi, Boehringer Ingelheim, MSD, Mundi Pharma/Napp, Almirall, Novartis, and Sandoz. FL has been reimbursed for attending conferences and/or giving talks by Chiesi, Farmaceutici, Menarini Industrie Farmaceutiche, Mundipharma, AZ, and Pfizer. TH is an employee of Chiesi UK Ltd. AB and JB are employees of Research in Real Life. CK declares that she has no conflicts of interest in relation to this article. AP (or members of his research team) has received grants for research in respiratory disease and he has received honoraria for participation in scientific meetings and advisory boards from AZ, Boehringer Ingelheim, Chiesi, GSK, MSD, Mundipharma, Novartis, Nycomed, Pfizer, and Zambon.

Contributorship DP, IS, JH, DR, KG-J, FL, and AP conceived and designed the study; AB and JB conducted the statistical and data analyses respectively; and CK

prepared the manuscript. All authors contributed to the interpretation of the data, writing of the manuscript, and review of the final draft. The study guarantor is DP.

Funding The study was sponsored by Chiesi UK Ltd. The funders had no role in the conduct of the study, interpretation of study results, or preparation of the manuscript.

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Appendix 1. Supplemental materials

Materials and methods

The FP-SAL inhalers under investigation were the Seretide® Accuhaler and the Seretide® Evohaler (Allen & Hanburys Ltd, Uxbridge, Middlesex, UK). Each single dose of the Accuhaler contains 100, 250, or 500µg of fluticasone propionate and 50µg of salmeterol xinafoate. Each single actuation of the Evohaler contains 50, 125, or 250µg of fluticasone propionate and 25µg of salmeterol xinafoate. The efBDP-FOR inhaler was Fostair® 100/6 (Chiesi Ltd, Highfield, Cheadle, UK). Each metered dose contains 100µg of extra-fine particle beclometasone dipropionate and 6µg of formoterol fumarate dihydrate. The Fostair inhaler uses Modulite technology, so it generates a slower plume of aerosolised medication than earlier formulations, which may help with pulmonary deposition.[1]

Study design

The baseline year of data collection was used for patient matching, to identify and characterise any confounders, and to allow for seasonal changes in respiratory disease and its related conditions. It also established that the patients were relatively well controlled on FP-SAL at their current dosage, as at the index review the physician saw no need to increase the ICS dosage. This aspect of the study design was important in comparing the two FDC inhalers on equal footing while examining the results of the switch.

Figure S1 summarises the patient selection process prior to case matching. The databases identified 1,113,776 patients who were being treated with ICS therapy. Patients were considered for inclusion if they received a prescription for either FP-SAL or efBDP-FOR as single FDC inhaler therapy after 1 January 2008 and received no other ICS or LABA prescriptions on the same date. On this basis, 930,645 patients were excluded.

Patients further considered for inclusion had a recorded diagnostic code for asthma; no recorded diagnosis for chronic obstructive pulmonary disease or other chronic respiratory disease; at least two prescriptions for FP-SAL as FDC inhaler therapy during their baseline year; either ongoing prescriptions for FP-SAL with no change in ICS dosage or switch to efBDP-FOR at an ICS dosage equivalent to, or lower than, their last FP-SAL prescription (≥2 efBDP-FOR prescriptions) in their outcome year; and attended a practice in which five or more patients were switched from FP-SAL to efBDP-FOR within a three-month period. On this basis, 105,631 patients were excluded.

Even patients who met all other inclusion criteria but whose prescribed ICS dosage was increased at the index prescription date (IPD) were excluded. This step was taken in an effort to determine fairly whether efBDP-FOR was at least equivalent to FP-SAL when patients are switched as recommended by the NHS.[2,3] The study group was limited to the patients of primary care practices switching multiple patients from FP-SAL to efBDP-FOR over a short period of time, as this "wholesale" change in prescribing suggests that the switch was made for reasons other than clinical efficacy, such as lower ICS dosage for safety/tolerance and/or cost.

Of the remaining 77,500 patients under consideration, the final selection process included those who were between 18 and 80 years of age; had complete data for both the baseline and outcome years; whose smoking status was known; and who required no oral corticosteroids for maintenance during their baseline year. A total of 50,261 patients met these last inclusion criteria, of whom 390 were switched to efBDP-FOR and 49,871 remained on FP-SAL for the outcome year. Figure S2 illustrates the subsequent case matching process.

Statistical analysis

Exploratory data analysis was conducted for all variables of interest for both the baseline and outcome years. As a conservative approach, differences between treatment groups were considered possibly important if $p<0.10$. Variables meeting this criterion were examined for co-linearity and clinical importance to select those used as potential confounders (Box 2) in the regression modelling of outcomes.

Data plots

During exploratory data analysis, frequency distribution plots were generated to illustrate the distribution of variables measured on the interval or ratio scale and to determine whether categorisation was necessary (eg, if heavily skewed). Box plots were generated to illustrate the location and spread of the variable and identify potential outliers. Plots by treatment group were used to highlight baseline and outcome differences between treatment groups. For categorical variables, mosaic plots were generated to illustrate distributions and highlight baseline and outcome differences between treatment groups.

Correlations

Spearman correlation coefficients were calculated among all baseline variables to determine strengths of linear relationships between variables. Relationships with rank correlation coefficients >0.30 were considered, in conjunction with clinical interpretation, to identify pairings of variables that may present co-linearity issues at the modelling stage. Scatter plots and error bar plots were used to further investigate non-linear relationships.

Predictive variables

Multivariate analyses were conducted using the full dataset to identify baseline variables that were predictive ($p<0.05$) of outcomes. These variables were then considered as potential confounders when modelling the outcome variables.

Clinical outcomes, primary

Exacerbation rates were compared across treatment arms using a conditional Poisson regression model. The model used empirical standard errors (for more conservative CI estimations), and adjustments were made for potential baseline confounders. Variables that were significantly different – or showed a trend towards significance – between treatment groups at baseline were included as potential confounding factors. Variables that were found to be predictive ($p<0.05$) of the outcome through multivariate analysis were also considered as potential confounders.

Clinical outcomes, secondary

The adjusted odds of achieving risk domain asthma control (RDAC), overall asthma control (OAC), and treatment success (TS) were compared between matched treatment groups using conditional binary logistic regression models. For RDAC and OAC, asthma control status was used as the dependent variable, with treatment and potential confounding factors as explanatory variables. For TS, success status was used as the dependent variable, with treatment and potential confounding factors as explanatory variables.

The total number of exacerbations (clinical definition), hospitalisations (where event numbers were sufficient), and incidents of oral thrush were compared between treatment groups using a conditional Poisson regression model to obtain an estimate of relative exacerbation, hospitalisation, and incident rates. The model used empirical standard errors (for more conservative CI estimations) and adjustments were made for potential baseline confounders.

The adjusted odds of being in a higher ICS adherence or SABA category were compared between matched treatment groups using conditional ordinal logistic regression models. The adherence or SABA category was used as the dependent variable, with treatment and potential confounding factors as explanatory variables.

Variables that were significantly different or showed a trend toward significance ($p<0.10$) between treatment groups at baseline were included as potential confounding factors. In addition, variables that were found to be predictive ($p<0.05$) of the outcome through multivariate analysis were also considered as potential confounders.

Results

Tables 3b and 3c show other clinically important baseline variables for the matched treatment groups. Table 5b provides full details of the secondary clinical outcome measures between matched treatment groups during the outcome year.

References

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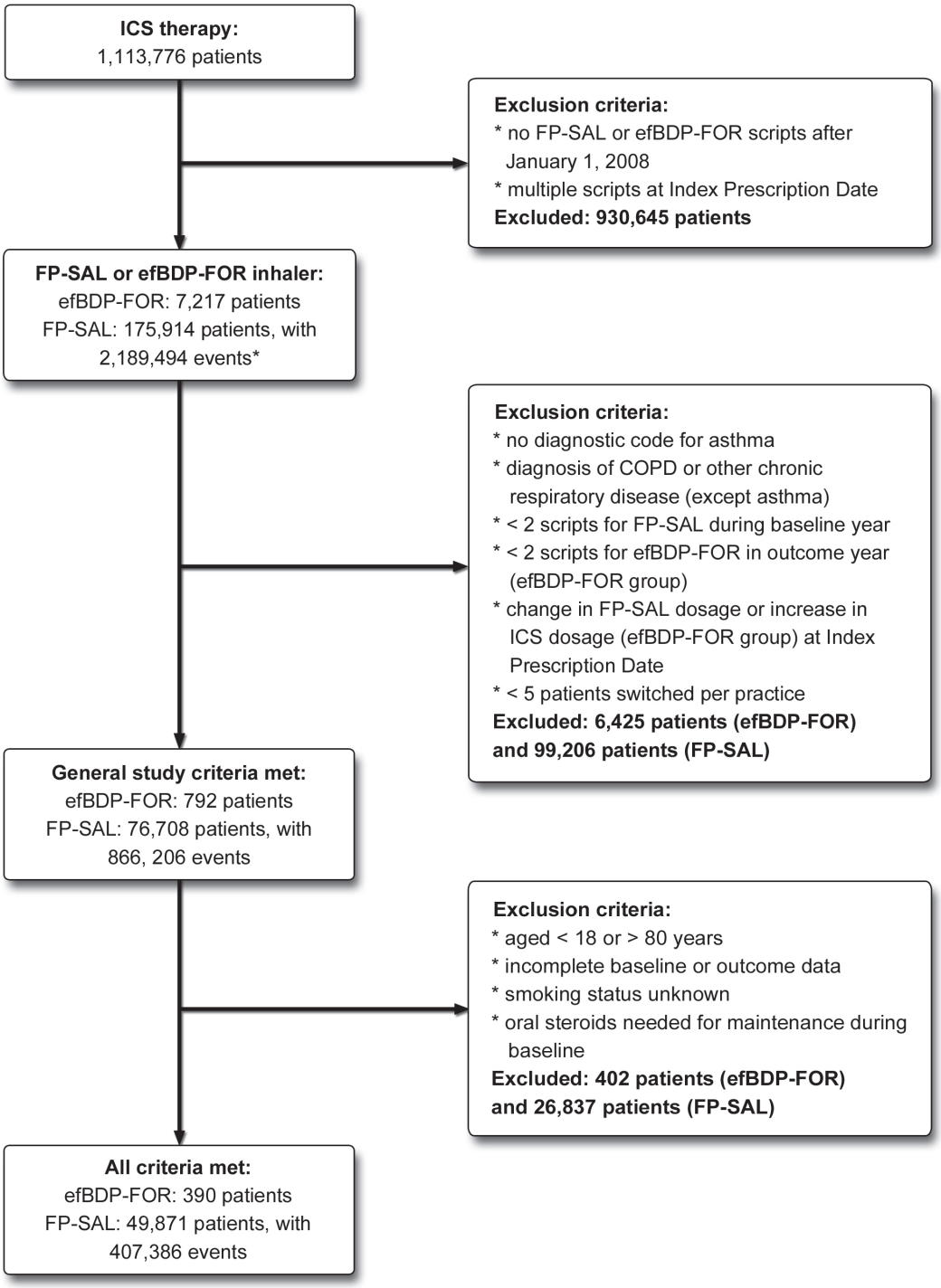
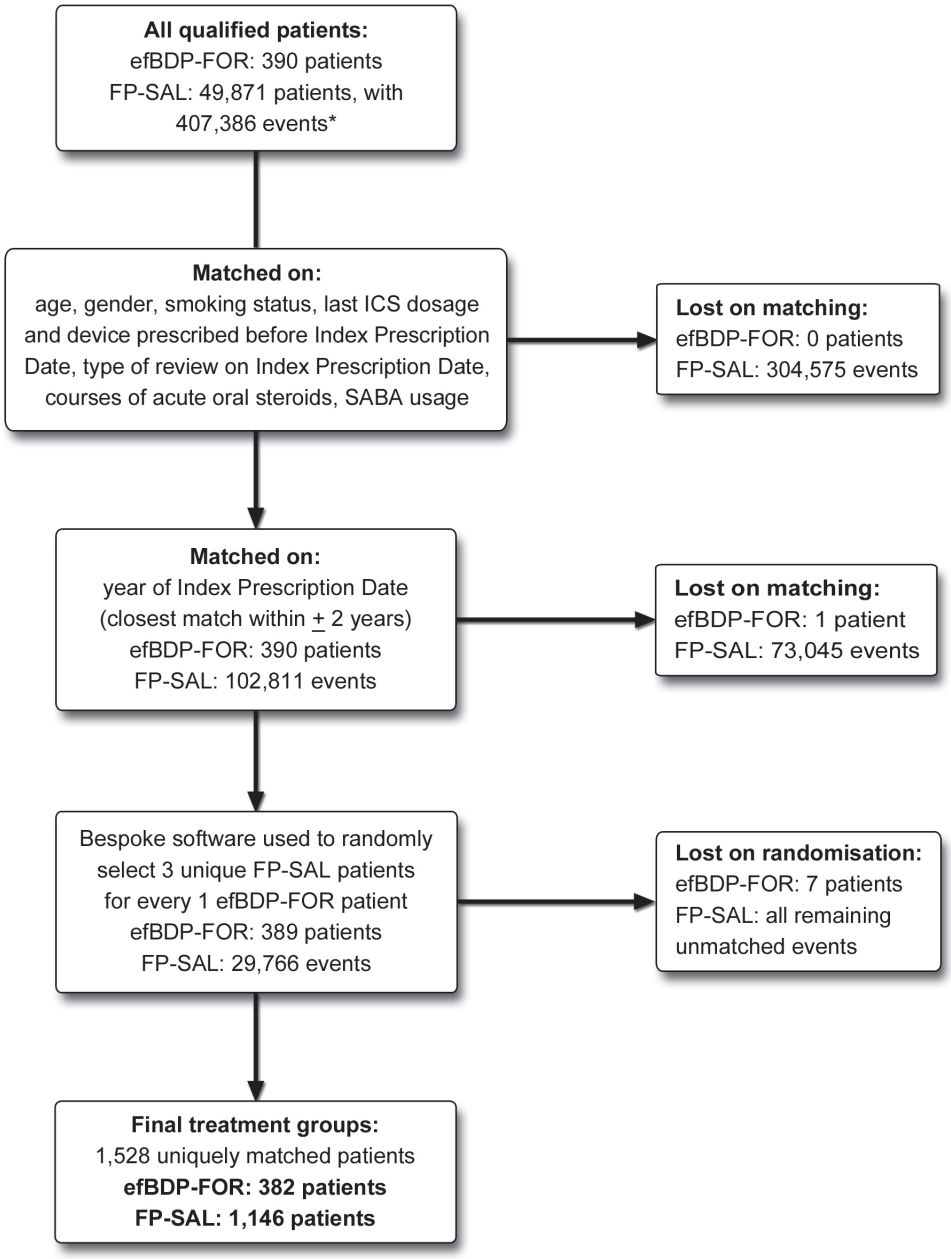
2. Homan K. Briefing paper: Primary care switch protocol—low and moderate dose ICS/LABA combination inhalers switch to Fostair 100/6 inhaler (bulletin on the internet). Cambridge: NHS East of England, June 2011. Available from http://www.see.nhs.uk/content/file/GP%20Zone/Medicine%20management/QOF/Inhalers/129-bulletin-5.pdf (accessed 4 May 2013).
3. Homan K. Primary care switch protocol—stepping down high dose ICS/LABA inhalers in asthma patients to moderate dose ICS/LABA inhalers including a switch to Fostair® 100/6 inhaler (bulletin on the internet). Cambridge: NHS East of England, July 2011. Available from http://www.clingov.eoe.nhs.uk/prescqipp/index.php/prescribing/prescqipp-bulletins (accessed 4 May 2013).

Figure S1. CONSORT diagram of patient selection for the Real-world Effectiveness in Asthma therapy of Combination inHalers (REACH) study. *An event comprised a repeat prescription for FP-SAL. Each repeat prescription was counted as a separate event, so patients may have had multiple events. This step was taken to ensure that enough eligible patients prescribed ongoing FP-SAL therapy were available so that each qualified efBDP-FOR patient could be closely matched with three unique FP-SAL patients (see Figure S2)



COPD=chronic obstructive pulmonary disease, efBDP-FOR=extra-fine particle beclometasone and formoterol as fixed-dose combination inhaler, FP-SAL=fluticasone and salmeterol as fixed-dose combination inhaler, ICS=inhaled corticosteroid.

Figure S2. CONSORT diagram of patient matching for the Real-world Effectiveness in Asthma therapy of Combination inHalers (REACH) study. *An event comprised a repeat prescription for FP-SAL (see explanation in Figure S1)



efBDP-FOR=extra-fine particle beclometasone and formoterol as fixed-dose combination inhaler, FP-SAL=fluticasone and salmeterol as fixed-dose combination inhaler, ICS=inhaled corticosteroid, SABA=short-acting β_2-receptor agonist.

Box 2. Potential confounders examined in the initial analysis

Potential confounders examined at (or closest to) the index prescription date (IPD):

- Age
- Gender
- Height
- Weight
- Body mass index (BMI) (where BMI can be evaluated)
- Lung function, as indicated by % predicted peak expiratory flow (calculated using age-specific equations for patients 18 years of age[1] and those over 18 years[2])
- Smoking status

Potential confounders examined regardless of when they occurred relative to the IPD:

- Date of first asthma diagnosis
- Other respiratory or confounding diagnoses, including:
  - o Rhinitis
  - o Gastroesophageal reflux disease (GERD)
  - o Cardiac disease
  - o Eczema

Potential confounders examined in the year before the IPD:

- Presence/absence of co-morbid rhinitis (diagnosis ever and/or prescriptions for rhinitis therapy in the prior/outcome year)
- Presence/absence of co-morbid eczema (diagnosis ever and/or prescriptions for eczema therapy in the prior/outcome year)
- Presence of GERD (diagnosis ever and/or prescriptions for GERD therapy in the prior/outcome year)
- Other important unrelated co-morbidities using a modified Charlson Comorbidity Index[3]
- Number of exacerbations in year prior to the IPD
- Number of acute courses of oral steroids in the year prior to the IPD
- Number of hospitalisations for asthma/lower respiratory reasons or possibly asthma/lower respiratory-related (a non-specific hospitalisation code and an asthma/lower respiratory code within one week)
- Number of hospital outpatient attendances in the prior year where asthma and/or lower respiratory illness was the reason for referral
- Number of prescriptions for any antibiotic in the prior year where the reason for the prescription was lower respiratory tract infection
- Number of prescriptions for any respiratory therapy (split by number of prescriptions for each) in the prior year
- Other medications, number of prescriptions for the following in the year prior to the IPD:
  - o Paracetamol
  - o Non-steroidal anti-inflammatory drugs (NSAIDs)
  - o Beta-blockers
  - o Theophylline
- Number of primary care consultations in the year prior
- Number of asthma consultations in the year prior
- Number of asthma consultations in the prior year that did not result in asthma exacerbation treatment
- Average short-acting β_2 agonist (SABA) daily dose (total combined dose of refilled prescriptions, averaged over 365 days)
- Number of SABA prescriptions received in the prior year
- Average inhaled corticosteroid (ICS) daily dose during the prior year (total combined dose of refilled prescriptions, averaged over 365 days)
- Adherence to ICS therapy (see Table 2 in main text)
- Spacer use/prescription
- Oral thrush

1. Rosenthal M, Cramer D, Bain SH, Denison D, Bush A, Warner JO. Lung function in white children aged 4 to 19 years. II. Single breath analysis and plethysmography. *Thorax* 1993;**48**(8):803-08.
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Table 3b. Clinically important baseline variables in matched treatment groups: primary and secondary outcome measures

Variable	FP-SAL (n=1,146)	efBDP-FOR* (n=382)	p Value†
Severe exacerbation rate (ATS/ERS definition)			
0	928 (81.0%)	312 (81.7%)	1.000
1	149 (13.0%)	46 (12.0%)	
2+	69 (6.0%)	24 (6.3%)	
Mean (SD)	0.29 (0.76)	0.34 (1.13)	0.112
Median (IQR)	0 (0, 0)	0 (0, 0)	
Risk domain asthma control			
Controlled	761 (66.4%)	260 (68.1%)	0.415
Overall asthma control			
Controlled	389 (33.9%)	135 (35.3%)	0.297
Severe exacerbation rate (clinical definition)			
0	782 (68.2%)	263 (68.8%)	0.816
1	237 (20.7%)	79 (20.7%)	
2+	127 (11.1%)	40 (10.5%)	
Mean (SD)	0.51 (0.94)	0.55 (1.26)	0.286
Median (IQR)	0 (0, 1)	0 (0, 1)	
Inpatient asthma-related hospitalisations			
0	1,138 (99.3%)	381 (99.7%)	0.355
1+	8 (0.7%)	1 (0.3%)	
Adherence to ICS therapy			
<50%	231 (20.2%)	70 (18.3%)	0.282
50–69%	237 (20.7%)	76 (19.9%)	
70–99%	415 (36.2%)	142 (37.2%)	
100+%	263 (22.9%)	94 (24.6%)	
Mean (SD)	82.0 (40.5)	82.6 (34.1)	0.783
Median (IQR)	80 (54, 99)	81 (57, 99)	
Incidence of oral thrush			
Diagnosis	5 (0.4%)	3 (0.8%)	0.421
Diagnosis or antifungal therapy	20 (1.7%)	10 (2.6%)	0.295

All values are n (%) unless otherwise stated.

*These patients were on FP-SAL during their baseline year but were switched to efBDP-FOR at the index prescription date.

†Conditional logistic regression.

ATS/ERS=American Thoracic Society and European Respiratory Society, efBDP-FOR=extra-fine particle beclometasone and formoterol as fixed-dose combination inhaler, FP-SAL=fluticasone and salmeterol as fixed-dose combination inhaler, ICS=inhaled corticosteroid, IQR=interquartile range, SD=standard deviation.

Table 3c. Clinically important baseline variables in matched treatment groups: other clinically relevant variables

Variable	FP-SAL (n=1,146)	efBDP-FOR* (n=382)	p Value†
Co-morbidities			
Rhinitis‡	495 (43.2%)	143 (37.4%)	0.047
Cardiac disease	178 (15.5%)	34 (8.9%)	0.001
Asthma consultations			
0	255 (22.3%)	53 (13.9%)	<0.001
1	500 (43.6%)	165 (43.2%)	
2+	391 (34.1%)	164 (42.9%)	
Mean (SD)	1.43 (1.38)	1.70 (1.44)	<0.001
Median (IQR)	1 (1, 2)	1 (1, 2)	
Respiratory prescriptions (all scripts)			
Mean (SD)	11.0 (7.4)	13.2 (8.6)	<0.001
Median (IQR)	9 (6, 14)	11 (7, 17)	
ICS scripts			
Mean (SD)	6.2 (3.4)	7.5 (3.3)	<0.001
Median (IQR)	5 (4, 8)	7 (5, 10)	
SABA scripts			
Mean (SD)	3.8 (3.7)	4.5 (4.6)	<0.001
Median (IQR)	3 (1, 5)	3 (1, 6)	
Average daily ICS dosage (µg/day)			
1–200	295 (25.7%)	70 (18.3%)	0.015
201–400	409 (35.7%)	150 (39.3%)	
401–600	285 (24.9%)	111 (29.1%)	
601+	157 (13.7%)	51 (13.3%)	
Mean (SD)	374.9 (255.2)	388.0 (241.0)	0.253
Median (IQR)	329 (197, 493)	329 (206, 493)	
LRTI consultations resulting in antibiotic prescription			
0	916 (79.9%)	312 (81.7%)	0.520
1	167 (14.6%)	50 (13.1%)	
2+	63 (5.5%)	20 (5.2%)	
Mean (SD)	0.28 (0.65)	0.27 (0.67)	0.729
Median (IQR)	0 (0, 0)	0 (0, 0)	
Controller-reliever ratio			
<0.5	193 (16.8%)	48 (12.6%)	0.017
≥0.5	953 (83.2%)	334 (87.4%)	

All values are n (%) unless otherwise stated.

*These patients were on FP-SAL during their baseline year but were switched to efBDP-FOR at the index prescription date.

†Conditional logistic regression.

‡Rhinitis diagnosis or nasal spray use.

efBDP-FOR=extra-fine particle beclometasone and formoterol as fixed-dose combination inhaler, FDC=fixed-dose combination inhaler, FP-SAL=fluticasone and salmeterol as fixed-dose combination inhaler, ICS=inhaled corticosteroid, IQR=interquartile range, LRTI=lower respiratory tract infection, SABA=short-acting β_2-receptor agonist, SD=standard deviation.

Table 5b. Comparison of secondary outcomes between matched treatment groups during the outcome year

Outcome	FP-SAL (n=1,146)	efBDP-FOR (n=382)
Risk domain asthma control		
Controlled	786 (68.6%)	277 (72.5%)
Adjusted odds ratio* (95% CI)	1.00	1.15 (0.88 to 1.52)
Overall asthma control (risk and impairment)		
Controlled	358 (31.2%)	149 (39.0%)
Adjusted odds ratio† (95% CI)	1.00	1.56 (1.14 to 2.14)
Also adjusted for BMI‡ (95% CI)	1.00	1.53 (1.10 to 2.11)
Severe exacerbation rate (clinical definition)		
0	812 (70.9%)	280 (73.3%)
1	211 (18.4%)	62 (16.2%)
2+	123 (10.7%)	40 (10.5%)
Adjusted rate ratio§ (95% CI)	1.00	1.01 (0.80 to 1.29)
Treatment success		
Successful	727 (63.4%)	263 (68.8%)
Adjusted odds ratio¶ (95% CI)	1.00	1.24 (0.95 to 1.62)
Average daily SABA usage (µg)		
0	173 (15.1%)	55 (14.4%)
1–100	325 (28.4%)	128 (33.5%)
101–200	320 (27.9%)	90 (23.6%)
201–400	252 (22.0%)	91 (23.8%)
401+	76 (6.6%)	18 (4.7%)
Adjusted odds ratio** (95% CI)	1.00	0.74 (0.60 to 0.91)
Adherence to ICS therapy (%)		
<50	314 (27.4%)	79 (20.7%)
50–69	174 (15.2%)	53 (13.9%)
70–99	377 (32.9%)	131 (34.3%)
100+	281 (24.5%)	119 (31.1%)
Odds ratio (95% CI)	1.00	1.40 (1.13 to 1.73)
Inpatient asthma-related hospitalisations		
1+	28 (2.4%)	7 (1.8%)
Adjusted rate ratio†† (95% CI)	1.00	0.67 (0.30 to 1.49)
Incidence of oral thrush		
1+	29 (2.5%)	16 (4.2%)
Adjusted rate ratio‡‡ (95% CI)	1.00	1.59 (0.77 to 3.27)

Values are n (%) unless otherwise stated.
*Adjusted for baseline confounders: (consultations for LRTIs resulting in a course of antibiotics (categorised), allergy prescriptions (categorised), and asthma-related Outpatient Department attendance (yes/no).
†Adjusted for: rhinitis diagnosis and/or therapy (yes/no), cardiac disease diagnosis (yes/no), asthma consults with no oral steroid script (categorised), SABA scripts (categorised), single inhaler ICS use (yes/no), and LRTI consults resulting in antibiotics (categorised).
‡BMI: body mass index (categorised).
§Adjusted for: acute oral steroids (categorised), LRTI consults resulting in antibiotics (categorised), allergy scripts (categorised), and asthma consults (categorised).
¶Adjusted for: asthma consults with no oral steroid script (categorised), SABA scripts (categorised), and allergy scripts (categorised).
**Adjusted for: asthma consults (categorised), scripts for separate ICS inhalers (yes/no), and SABA scripts (categorised).
††Adjusted for: primary care consults (categorised).
‡‡Adjusted for: asthma consults (categorised), non-asthma-related consults (categorised), and baseline incidence of oral thrush (yes/no).

CI=confidence intervals, efBDP-FOR=extra-fine particle beclometasone and formoterol as fixed-dose combination inhaler, FP-SAL=fluticasone and salmeterol as fixed-dose combination inhaler, ICS=inhaled corticosteroid, LRTI=lower respiratory tract infection, SABA=short-acting β_2-receptor agonist.