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Real-world effectiveness evaluation of budesonide/formoterol Spiromax® for the management of asthma and chronic obstructive pulmonary disease in the United Kingdom

Running title: Real-world effectiveness of BF Spiromax®

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ABSTRACT

Objectives: Budesonide/formoterol (BF) Spiromax® is an inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) fixed-dose combination inhaler, designed to minimise common inhaler errors and provide reliable and consistent dose delivery in asthma and chronic obstructive pulmonary disease (COPD). We evaluated non-inferiority of BF Spiromax after changing from another FDC inhaler, compared with continuing the original inhaler.

Methods: Patients with asthma and/or COPD who switched to BF Spiromax were matched (1:3) with non-switchers. Data were from Optimum Patient Care Research Database and Clinical Practice Research Datalink in the United Kingdom (UK). Primary endpoint was proportion of patients achieving disease control (using Risk Domain Control [RDC] algorithm); secondary endpoints were: exacerbation rate, short-acting β_2-agonists (SABA) use, and treatment stability (achieved RDC; no maintenance treatment change). Non-inferiority was defined as having 95% confidence interval (CI) lower bound above –10%, using conditional logistic regression and adjusted for relevant confounders.

Results: Comparing 385 matched patients (asthma 253; COPD 132) who switched to BF Spiromax with 1091 (asthma 743; COPD 348) non-switchers, non-inferiority of BF Spiromax in RDC was demonstrated (adjusted difference: +6.6%; 95% CI: –0.3-13.5). Among asthma patients, switchers to BF Spiromax versus BF Turbuhaler reported fewer exacerbations (adjusted rate ratio [RR] 0.76; [95% CI 0.60-0.99]; p=0.044); were less likely to use high SABA daily doses (adjusted odds ratio [OR] 0.71; [95% CI 0.52-0.98]; p=0.034); used fewer SABA inhalers (adjusted RR 0.92; [95% CI 0.86-0.99]; p=0.019), and were more likely to achieve treatment stability (adjusted OR 1.44; [95% CI 1.02-2.04]; p=0.037). No significant differences in these endpoints were seen among COPD patients.

Conclusions: Among UK asthma and COPD patients, real-world use of BF Spiromax was non-inferior to BF Turbuhaler in terms of disease control. Among asthma patients, switching to BF Spiromax was associated with reduced exacerbations, reduced SABA use, and improved treatment stability versus continuing on BF Turbuhaler.

Key words/terms (from MEDLINE MeSH): asthma, budesonide/formoterol, chronic obstructive pulmonary disease, comparative effectiveness research, disease control, inhalation devices, observational study

Strengths and limitations of this study

- Clearly defined *a priori* hypothesis, endpoints, and sample size.
- A non-selective patient population, obtained through the use of real-world data from validated databases of primary care patients, with sufficient follow-up period for observing relevant outcomes.
- Hospital admissions, A&E attendances, and outpatient visits are not systematically recorded in primary care databases, and the applied definition to identify asthma-related hospital admissions or A&E events may have given rise to false positive events.
- Potential effects of inhaler technique on the reported outcomes could not be taken into account, as this would require close observation and communication with each patient as they demonstrated their inhaler technique.
- Observed differences in secondary outcomes could have arisen as a consequence of factors unrelated to the inhalers that might not have been captured in the dataset.

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are common respiratory conditions.[1, 2] Cornerstone asthma/COPD treatment consists of inhaled therapy with proven efficacy in randomised clinical trials (RCTs).[3, 4] In real life, however, incorrect inhaler use is common in patients with asthma or COPD, resulting in poor symptom control and worse outcomes.[5, 6] Specifically, critical inhaler errors were reported in a review of 3660 patients;[7] insufficient respiratory effort in dry-powder inhaler (DPI) users and actuation before inhalation in metered-dose inhaler users were found to be associated with uncontrolled asthma.[7]

DuoResp® Spiromax® (Teva Pharmaceutical Industries, Petach Tikva, Israel) is an inhaler containing a fixed-dose combination (FDC) of the inhaled corticosteroid (ICS) budesonide and the long-acting β_2-agonist (LABA) formoterol (budesonide/formoterol [BF]). The Spiromax® inhaler was designed to maximise ease of use, reliability of dosing, and consistency of lung deposition[8, 9] in patients with asthma or COPD. It is similar in design and appearance to a metered dose inhaler, but uses different internal configuration. The Spiromax® requires only one preparation step (opening the cap) and provides consistent dose delivery across a broad range of inspiratory flow rates.[8, 9] Recent findings suggest that Spiromax is associated with a reduced number of errors related to dose preparation, undertaking the steps needed to correctly deliver the dose during inhalation, and handling the device after inhalation, as well as being easier for patients and healthcare professionals to use compared with other DPIs.[10, 11] BF Spiromax has demonstrated pharmacokinetic bioequivalence to BF Turbuhaler® (AstraZeneca UK Limited, UK) in healthy volunteers.[12, 13] A recent independent study in COPD found BF Spiromax to have a faster onset of bronchodilation than BF Turbuhaler, likely due to differences in drug deposition between the two devices.[14] However, evidence for the real-world effectiveness of BF Spiromax in comparison with other inhalers in asthma and/or COPD patients is lacking.

The current study was part of a multi-phase assessment of real-world outcomes over 1 year in patients with asthma and/or COPD who switched to BF Spiromax compared with patients who remained on another device, using data from two United Kingdom (UK) primary care administrative

databases. The primary objective of this phase of the study was to evaluate the non-inferiority of changing from another FDC inhaler to BF Spiromax versus continuing to use the original FDC inhaler, in terms of achieving disease control, based on the Risk Domain Control (RDC) algorithm; secondary objectives included the effects of the switch on the occurrence of moderate/severe exacerbations and respiratory-related hospitalisations, treatment stability, and short-acting β_2-agonist (SABA) use.

METHODS

Patients and study design

This was a matched, historic cohort study of patients with asthma and/or COPD using two validated primary care databases of patients in the UK, Optimum Patient Care Research Database (OPCRD) and Clinical Practice Research Datalink (CPRD).[15, 16] The OPCRD is governed by The Anonymous Data Ethics Protocols and Transparency committee, commissioned by the Respiratory Effectiveness Group.[17] The CPRD is a UK government research service, jointly supported by the National Institute for Health Research and the Medicines and Healthcare Products Regulatory Agency, that provides access to anonymised NHS data. It operates under a range of UK and European Laws as well as NHS and other guidelines.[16] This study is registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (Register Number EUPAS13238).[18]

The OPCRD and CPRD databases were searched onwards from 2010 to identify prescriptions of BF Spiromax, BF Turbuhaler, and fluticasone propionate/salmeterol (FS) Accuhaler®/Diskus® (GlaxoSmithKline, Uxbridge, UK) in patients ≥18 years of age with asthma and/or COPD (Figure 1). The OPCRD and CPRD datasets for this study were constructed separately and checked for overlap before pooling to exclude duplicate patients. Patients had to have at least 2 years of data, comprising a minimum of 1 baseline year and a 1-year outcome period. Patients were required to have at least three prescriptions for ICS/LABA FDC (BF Spiromax, BF Turbuhaler, or FS Accuhaler/Diskus) therapy during the baseline period. Switch patients must have evidence of an

initial BF Spiromax prescription in the outcome period as well as at least one supplementary prescription for BF Spiromax in the 1-year outcome period to ensure consistent usage. Likewise, patients remaining on their inhaler required at least one repeat prescription in the outcome period. In addition, to minimise the probability of patients included in the study having been switched to BF Spiromax for clinical reasons, BF Spiromax patients must have been registered at practices considered to have a policy of BF Spiromax adoption or wholesale change, identified as practices at which ≥5 patients change to BF Spiromax within a 3-month period. The current study includes only patients who stayed on BF Turbuhaler or switched from BF Turbuhaler to BF Spiromax, due to the low number of patients who switched from FS Accuhaler/Diskus to BF Spiromax. The date of the first prescription of BF Spiromax or the (matched) date of the repeat prescription for BF Turbuhaler in the control arm was the index date.

Asthma patients were required to have a diagnostic code (Read code)[19] for asthma and/or at least two prescriptions for asthma therapy during the baseline year, and to have no other chronic respiratory disease diagnosis. COPD patients were required to be ≥40 years of age at first prescription for BF Spiromax or the matching BF Turbuhaler prescription, and to have a diagnostic code for COPD and a post-bronchodilator FEV_1/FVC <0.70 consistent with the criteria for inclusion in the UK register of patients with COPD (Quality and Outcomes Framework). The subgroup of patients with only an asthma diagnosis is referred to henceforth as the asthma group. The patients with a COPD diagnosis (with or without an asthma diagnosis) are referred to henceforth as the COPD group.

Outcome measures

The primary outcome was disease control as assessed by RDC, a composite measure that has been used in several similar matched historical cohort studies to define absence of exacerbations.[20-23] To achieve RDC in this study, patients must not have an asthma/COPD-related hospital admission, asthma/COPD-related Accident and Emergency (A&E) attendance, or course of oral corticosteroids (OCS) during the outcome period. In addition, patients in the COPD group must not have received antibiotics for a lower respiratory tract infection (LRTI).

Secondary outcomes included the number of moderate/severe exacerbations and hospitalisations, and change in treatment stability. A moderate/severe exacerbation (for COPD) or severe exacerbation (for asthma) was defined following the American Thoracic Society/European Respiratory Society Task Force Position Statement.[24] Lower respiratory hospitalisations were identified and classified as follows: definite hospitalisations were those with a lower respiratory code, including asthma and LRTI codes; OR a generic hospitalisation Read code that has been recorded on the same day as a lower respiratory consultation; definite + probable hospitalisations were those occurring within a 7-day window (either side of the hospitalisation date) of a lower respiratory Read code. Adequate treatment stability was defined as achieving RDC and no increase in dose, change in delivery device, and change in type of ICS and/or use of LABAs, theophylline, long-acting muscarinic antagonists, or leukotriene receptor antagonists (LTRAs).[22] Additional outcomes were SABA usage, which was expressed as average daily SABA dosage during the outcome year and calculated from prescriptions as ([*Count of inhalers* x *doses in pack* x *µg strength*] / 365), and a pneumonia event which was defined as having a Read coded diagnosis (probable pneumonia), or a Read coded diagnosis with a hospital admission or chest x-ray within 1 month (definite pneumonia).

Statistical analyses

It was estimated that 349 patients would have 90% power to demonstrate non-inferiority of BF Spiromax and BF Turbuhaler for achieving RDC, at a one-sided significance level of 0.050. For the calculation, an expected difference in proportions of zero was used, assuming that the proportion of discordant pairs was 0.458. This assumption was based on previous studies showing that a weighted average of 71.6% of asthma and COPD patients prescribed FDC therapy have no exacerbations over a one-year period.[25, 26]

Descriptive statistics of all baseline demographic characteristics, co-morbidities, medication use, indicators of disease severity and other patient characteristics were computed separately for the patients in the BF Spiromax and BF Turbuhaler groups and for patients in the asthma and COPD groups. In cases where multiple observations existed for a patient, one was randomly selected.

Continuous variables were summarised using the number of non-missing observations, percentage of non-missing observations, mean, standard deviation (SD), median and interquartile range (difference between the 25th and 75th percentile), and a P-value for the Kruskal-Wallis equality-of-populations rank test. Binary and categorical variables were summarised using the percentage of non-missing observations, the frequency and percentages (based on the non-missing sample size) of observed levels, and a P-value for the Pearson's chi-square test of independent categories.

Patients switched to BF Spiromax were compared with matched controls who stayed on BF Turbuhaler. Mixed matching was performed 1:3 so that each BF Spiromax patient would be matched with up to three patients who remained on BF Turbuhaler (see Supplementary methods in Appendix for a full description of the mixed matching process). Mixed matching was performed to increase precision of the effect estimates. Because the analyses were conducted on all of the matched patients, which could introduce residual confounding due to imbalanced matching ratios, a sensitivity analysis was performed in which the outcome analyses were also performed in the subpopulation of patients in the BF Spiromax arm with exactly three matched patients in the BF Turbuhaler arm. Matching was performed using the most relevant confounders which were identified based on baseline imbalance and bias potential in relation to the primary outcome. For asthma, these confounders included age, gender, number of antibiotic courses, number of OCS courses, Global Initiative for Asthma (GINA) control categories, number of exacerbations, and RDC; matching confounders for COPD included age, gender, drug therapy, ICS average daily dose, number of antibiotic courses, number of exacerbations, and Global Initiative for Chronic Obstructive Lung Disease (GOLD) risk categories. Baseline imbalance was assessed using the Standardised Mean Difference (SMD), which, unlike a P-value, is not affected by the number of observations in a sample,[27, 28] and provides information on the size of the difference. An SMD of ≤10% was assumed to represent sufficient balance between the arms,[29] and the formula used is presented in the Supplementary methods of the Appendix. Bias potential is the degree to which the observed association between the exposures of interest and the outcome is affected by conditioning on another variable; the formula is presented in the Supplementary methods of the Appendix. A sensitive bias potential cut off of ≥2% was used for this study.

Baseline variables with highest bias potential that were also insufficiently balanced were presented to a panel of experts for final selection. Following matching, the process was repeated in the matched sample to identify any residual confounding.

After mixed matching, conditional logistic regression of the between-patient difference in the primary outcome was performed to provide a 95% confidence interval (CI) with which to assess non-inferiority. Analyses were undertaken for the patients in the asthma and COPD groups combined, as well as by disease group. The model was adjusted for baseline variables that remained with bias potential after matching. Non-inferiority was claimed if the lower bound of the 95% CI for the primary endpoint (RDC) was above –10%, a difference widely regarded as clinically important for many outcomes in respiratory studies,[30,31] and used previously in similar studies.[22, 23] If non-inferiority was achieved, superiority was tested.

Secondary outcomes were analysed in the matched sample and adjusted for baseline variables that remained with bias potential after matching, and reported as conditional rate ratios (RR) or odds ratios (OR) with their 95% CIs. Number of exacerbations and hospitalisations were analysed in the matched sample using conditional Poisson regression to obtain estimates of relative rates, treatment stability was analysed in the matched sample using conditional logistic regression, and SABA usage was analysed in the matched sample using conditional ordinal logistic regression, after the SABA average daily dose was categorised.

All statistical analyses were conducted using Stata MP6 version 12 and Stata SE version 14 (StataCorp, College Station, TX). A statistically significant result was defined as $p < 0.05$.

RESULTS

Study population

Overall, 420 patients switched to BF Spiromax (Figure 1). Of the patients who used BF Turbuhaler,

410 switched to BF Spiromax and 49,386 remained on BF Turbuhaler. Baseline characteristics of these unmatched patients are shown in Supplementary Table 1, where imbalanced covariates (SMD >10%) for asthma include mean age, drug therapy, ICS average daily dose, and number of exacerbations in baseline years; those for COPD include smoking status, drug therapy, and ICS average daily dose.

For the matched analysis, a total of 385 patients switching to BF Spiromax were analysed; a total of 1091 patients who stayed on BF Turbuhaler were matched to the switch patients (**Figure 1**). Twenty five patients who switched back to BF Turbuhaler or to another FDC ICS/LABA were not included in the analysis. In the baseline characteristics of the matched patients, covariates with SMD >10% in the asthma group were body mass index and ischaemic heart disease; for COPD they were smoking status, ischaemic heart disease, heart failure, number of exacerbations, and number of acute OCS courses (**Table 1**).

Table 1. Patient characteristics in matched analysis

Variable	Asthma patients				COPD patients			
	BF Spiromax (n=253)	BF Turbuhaler (n=743)	P-value	SMD (%)	BF Spiromax (n=132)	BF Turbuhaler (n=348)	P-value	SMD (%)
Mean (SD) age, years	55.9 (15.3)	55.8 (15.1)	0.9101	0.7	70.5 (8.8)	70.5 (8.5)	0.9512	0.2
Males, n (%)	112 (44.3)	331 (44.5)	0.9382	0.6	66 (50.0)	184 (52.9)	0.5736	5.7
Body mass index*, n (%)			0.4038	12.1				
<18.5 kg/m^2	3 (1.3)	9 (1.2)			6 (4.7)	11 (3.2)	0.6977	7.4
18.5 to <25 kg/m^2	65 (27.2)	163 (22.5)			46 (35.7)	112 (32.4)		
25 to <30 kg/m^2	88 (36.8)	265 (36.5)			39 (30.2)	120 (34.7)		
>30 kg/m^2	83 (34.7)	289 (39.8)			38 (29.5)	103 (29.8)		
Smoking status†, n (%)			0.7393	5.2			0.5696	10.8
Non-smoker	126 (50.8)	397 (53.6)			14 (10.6)	48 (13.9)		
Current smoker	44 (17.7)	123 (16.6)			36 (27.3)	98 (28.3)		
Ex-smoker	78 (31.5)	220 (29.7)			82 (62.1)	200 (57.8)		
Cardiovascular disease, n (%)								
Ischaemic heart disease	13 (5.1)	62 (8.3)	0.0951	12.8	22 (16.7)	78 (22.4)	0.1662	14.5
Heart failure	1 (0.4)	8 (1.1)	0.3225	8.0	4 (3.0)	23 (6.6)	0.1286	16.7
Exacerbations, n (%)			0.9869	3.6			0.7809	12.9
0	199 (78.7)	593 (79.8)			54 (40.9)	156 (44.8)		
1	42 (16.6)	120 (16.2)			38 (28.8)	106 (30.5)		
2	7 (2.8)	18 (2.4)			15 (11.4)	35 (10.1)		
3	4 (1.6)	9 (1.2)			13 (9.8)	28 (8.0)		
≥4	1 (0.4)	3 (0.4)			12 (9.1)	23 (6.6)		
No. of respiratory-related hospital admissions, n (%)			1.0000	0			0.1460	2.8
0	253 (100.0)	743 (100.0)			129 (97.7)	338 (97.1)		
1	0	0			1 (0.8)	9 (2.6)		
≥2	0	0			2 (1.5)	1 (0.3)		
Uncontrolled risk domain control, n (%)	70 (27.7)	194 (26.1)	0.6278	3.5	78 (59.1)	192 (55.2)	0.4397	7.9
No. of antibiotic courses, n (%)			0.8362	5.5			0.9478	6.4
0	212 (83.8)	630 (84.8)			74 (56.1)	198 (56.9)		
1	34 (13.4)	99 (13.3)			37 (28.0)	104 (29.9)		

Variable	Asthma patients				COPD patients			
	BF Spiromax (n=253)	BF Turbuhaler (n=743)	P-value	SMD (%)	BF Spiromax (n=132)	BF Turbuhaler (n=348)	P-value	SMD (%)
2	5 (2.0)	12 (1.6)			11 (8.3)	26 (7.5)		
3	1 (0.4)	1 (0.1)			4 (3.0)	8 (2.3)		
≥4	1 (0.4)	1 (0.1)			6 (4.5)	12 (3.4)		
No. of acute OCS courses, n (%)								
0	199 (78.7)	593 (79.8)			79 (59.8)	225 (64.7)		
1	42 (16.6)	120 (16.2)	0.9869	3.6	28 (21.2)	74 (21.3)	0.6813	14.4
2	7 (2.8)	18 (2.4)			9 (6.8)	20 (5.7)		
3	4 (1.6)	9 (1.2)			7 (5.3)	15 (4.3)		
≥4	1 (0.4)	3 (0.4)			9 (6.8)	14 (4.0)		
Average daily SABA dose, n (%)								
0	64 (25.3)	224 (30.1)			23 (17.4)	65 (18.7)		
>0 to ≤200 µg/day	70 (27.7)	196 (26.4)	0.4055	4.9	22 (16.7)	66 (19.0)	0.3524	8.4
>200 to ≤400 µg/day	56 (22.1)	139 (18.7)			32 (24.2)	78 (22.4)		
>400 to ≤600 µg/day	25 (9.9)	59 (7.9)			5 (3.8)	29 (8.3)		
>600 µg/day	38 (15.0)	125 (16.8)			50 (37.9)	110 (31.6)		

BF: Budesonide/formoterol; OCS: oral corticosteroids; SABA: short-acting β_2-agonist; SMD: standardised mean difference

*Some missing data for this parameter: n=239 for asthma on BF Spiromax, n=726 for asthma on BF Turbuhaler; n=129 for COPD on BF Spiromax, n=346 for COPD on BF Turbuhaler.

†Some missing data for this parameter: n=248 for asthma on BF Spiromax, n=740 for asthma on BF Turbuhaler, n=346 for COPD on BF Turbuhaler.

Outcomes analyses

Descriptive statistics of disease outcomes in the matched patients are shown in **Table 2**. The FDC average daily dose was numerically lower among patients using BF Spiromax among patients in the asthma group (382.1 vs 505.3µg) and mean percent RDC was higher among patients using BF Spiromax in both the asthma (73.1% vs 68.0%) and COPD (40.2% vs 37.1%) groups (**Table 2**).

Table 2. Descriptive statistics of disease outcomes in the matched cohorts of patients.

	Asthma patients		COPD patients	
Outcomes	BF Spiromax (n=253)	BF Turbuhaler (n=743)	BF Spiromax (n=132)	BF Turbuhaler (n=348)
% Risk domain control	73.1	68.0	40.2	37.1
No. of exacerbations (SD)	0.3 (0.7)	0.4 (0.7)	1.1 (1.4)	1.0 (1.4)
% Treatment stability	72.7	66.9	39.4	37.1
SABA average daily dose (SD)	1.4 (1.9)	1.5 (2.9)	2.6 (2.9)	2.4 (2.3)
No. of SABA inhalers (SD)	5.1 (6.8)	5.5 (10.7)	9.5 (11.0)	8.7 (8.5)
No. of antibiotics prescriptions (SD)	0.2 (0.7)	0.4 (0.8)	0.7 (1.1)	0.8 (1.1)
No. of acute OCS courses (SD)	0.3 (0.7)	0.3 (0.7)	1.0 (1.7)	0.9 (1.3)
FDC ICS average daily dose (SD)	382.1 (351.3)	505.3 (585.0)	555.3 (427.1)	561.8 (646.1)
No. of FDC inhalers (SD)	14.0 (8.9)	10.8 (5.6)	15.0 (6.7)	11.9 (5.4)
No. of respiratory A&E attendances (SD)	0.0 (0.1)	0.0 (0.1)	0.0 (0.2)	0.1 (0.4)
No. of probable respiratory inpatient hospitalisations (SD)	0.0 (0.1)	0.0 (0.1)	0.1 (0.4)	0.1 (0.5)
No. of definite respiratory inpatient hospitalisations (SD)	0.0 (0.1)	0.0 (0.1)	0.0 (0.3)	0.1 (0.4)
% Probably pneumonia*	0.0	0.0	3.0	2.3
% Definite pneumonia*	0.0	0.0	2.3	0.6

A&E, accident and emergency; BF: budesonide/formoterol; FDC: fixed dose combination; ICS, inhaled corticosteroid; OCS: oral corticosteroid; RDC: risk domain control; SABA, short acting beta agonist; SD: standard deviation.

*A pneumonia event was defined as having a Read coded diagnosis (probable pneumonia), or a Read coded diagnosis with a hospital admission or chest x-ray within 1 month (definite pneumonia).

The lower bound of the 95% CI of the adjusted percentage difference in the frequency of achieving RDC in the combined population was –0.3%, meeting the criterion for non-inferiority of switching to BF Spiromax compared with continuing on BF Turbuhaler (**Figure 2**). Although a higher proportion of patients achieved RDC in the group who switched to BF Spiromax compared with patients who stayed on BF Turbuhaler, the difference was not statistically significant, and the mean between-group difference was less than the 10% considered to be clinically relevant.[22, 23, 30, 31] In the

sensitivity analysis where only BF Spiromax switchers that had three matched controls were used, a significant difference was shown in the combined patients group (adjusted % difference 8.3; 95% CI 1.0-15.6; p=0.025) (data not shown). In the sensitivity analysis, the adjusted percentage difference was nearly 10% in the COPD group but there was a wide confidence interval (adjusted % difference 9.9; 95% CI -2.4-22.2; p=0.114). Similarly, in the asthma group, the adjusted percentage difference was 6.5% (95% CI -2.7-15.7; p=0.168). The conditional logistic regression model in all matched patients showed an adjusted OR of 1.31 (95% CI 0.99-1.73; p=0.061) for BF Spiromax versus BF Turbuhaler for RDC, which did not achieve statistical significance. However, in the sensitivity analysis, the OR of 1.41 was statistically significant (95% CI 1.05-1.90; p=0.022) (data not shown).

Secondary outcomes shown are expressed as adjusted conditional RRs (**Figure 3a**) and ORs (**Figure 3b**) separately for patients with asthma and those with COPD. Among asthma patients, switchers to BF Spiromax versus BF Turbuhaler reported fewer exacerbations, were less likely to use high amounts of SABA daily dose, used fewer SABA inhalers, and were more likely to achieve treatment stability. Among patients with COPD, no significant differences in these endpoints were seen between those who switched to BF Spiromax and those staying on BF Turbuhaler. Confidence intervals for patients who switched to BF Spiromax show a trend effect for lower risk of being on high-dose SABA therapy and reduction in use of SABA inhalers in the COPD group. In the combined patients group, significance among switchers to BF Spiromax was noted in SABA average daily dose (OR 0.70; [95% CI 0.53-0.94]; p=0.017), reduction in use of SABA inhalers (RR 0.94; [95% CI 0.89-0.99]; p=0.012), and improved treatment stability (OR 0.74; [95% CI 0.56-0.99]; p=0.041).

DISCUSSION

This study, the first to compare the real-world effectiveness of switching to the BF Spiromax inhaler from BF Turbuhaler found that, among N=253 patients with asthma and N=132 patients with COPD, BF Spiromax showed non-inferiority with respect to achievement of disease control to BF

Turbuhaler in matched patients with asthma and/or COPD. In the primary analysis in the combined population, patients who switched to BF Spiromax had 31% higher odds of achieving RDC compared with those who remained on BF Turbuhaler; however, this finding did not meet the threshold for statistical significance. Patients in the asthma group who switched to BF Spiromax had significantly reduced SABA use, fewer exacerbations, and greater treatment stability compared with matched patients who remained on BF Turbuhaler. No significant differences between patients who switched and those who did not were observed in the COPD group.

The results observed in this real-world study are consistent with previous evidence gained from RCTs where BF Spiromax was found to have similar efficacy to BF Turbuhaler.[32] The suggestion of potential superiority on secondary outcome measures in the current study, a result which was not seen in RCTs, might plausibly reflect differences in ease of use and/or adherence between the inhalers when prescribed in routine care. Patients participating in respiratory RCTs usually represent only between 1% and 5% of the true population of patients with asthma or COPD[33] and the proportion of COPD patients in primary care who would be eligible for inclusion in recent large pharmaceutically-sponsored COPD studies has ranged from 17% to 42%.[34] In addition, adherence to treatment in real-world observational studies is usually much lower than in RCTs.[35] Moreover, proper inhaler technique is often artificially high in clinical trials because of patient selection, extensive training, and close monitoring, which may explain why minimal differences in outcomes between devices have been observed in RCTs.[36] However, in daily practice, patients' differential ability to correctly use their inhaler may result in larger differences in health outcomes. Previous studies have shown that study participants and healthcare professionals find it easier to learn how to use the Spiromax inhaler correctly, compared with other DPIs.[10,11] Furthermore, patients are able to achieve slightly higher peak inspiratory flow rates with the Spiromax inhaler compared with the Turbuhaler.[37]

This study had clearly defined *a priori* hypothesis, endpoints, and sample size, as is recommended for this type of observational research.[38] A particular strength was the non-selective patient population obtained through the use of real-world data from validated databases of primary care

patients. The size and scope of these databases allowed for the collection of important clinical variables and a sufficient follow-up period for observing relevant outcomes. In addition, the study's time horizon of 1 year has minimised the impact of potential seasonal differences in disease activity.[39] Overall, the study was well-powered to investigate the primary outcome which was RDC of disease.

The inclusion of matched patients in our analysis of RDC risked introducing residual confounding due to imbalanced matching ratios. We therefore performed a sensitivity analysis in the subpopulation of patients in the BF Spiromax arm with exactly three matched patients in the BF Turbuhaler arm. Compared with patients who remained on BF Turbuhaler, patients who switched to BF Spiromax had 31% and 41% higher odds of achieving RDC in the primary analysis and sensitivity analysis, respectively, with the difference reaching statistical significance in the sensitivity analysis only. Regardless of whether significance was achieved, the difference in odds with BF Spiromax versus BF Turbuhaler is quite similar between the primary and sensitivity analyses, supporting the overall validity of our assumptions for the effect of BF Spiromax versus BF Turbuhaler on achieving disease control.

Limitations of the study are important to note. The use of databases to evaluate outcomes depends on the information registered, which is for clinical and routine use rather than research purposes. Possible issues include the fact that hospital admissions, A&E attendances, and outpatient visits are not systematically recorded in primary care databases and the applied definition to identify asthma-related hospital admissions or A&E events may give false positive events. However, this limitation would apply equally to both groups. In addition, inhaler technique could not be taken into account for this study as this would require close observation and communication with each patient as they demonstrated their inhaler technique. Regarding the secondary outcomes, we cannot rule out the possibility that the observed differences were caused by factors unrelated to the inhalers, as patients who switched to BF Spiromax may have differed from non-switchers in ways not captured in our data set. An important limitation in observational studies is the potential for confounding of the associations arising from systematic differences between the patients being

compared. In this study, confounding was minimised where possible using matching techniques to create cohorts that were comparable in terms of important demographic and clinical characteristics as recommended by the Respiratory Effectiveness Group.[38] Multivariate models were adjusted by those variables that continued to confound the associations of interest after matching. However, in the COPD group, due to a limited number of patients, only a restricted set of variables could be used for matching and model adjustment. Therefore, we cannot ensure confounding of the association of interest was sufficiently addressed in this group.

This real-world analysis showed that switching from BF Turbuhaler to BF Spiromax was associated with no loss of symptom control and may be beneficial in some patients. These data validate, in a real-world population of patients with asthma and COPD, similar efficacy to that previously demonstrated in an RCT.[32] Such validation is important for primary practitioners as it provides reassurance that BF Spiromax is effective in real-world primary care patients, and not just in the carefully selected and closely monitored cohorts of patients typical of RCTs. It should however be noted that periodical assessments of adherence, motivation and inhaler technique are still likely to be required to ensure that optimal inhaler use is maintained long-term.[40-43] Further research may be needed to assess the extent to which the results of this analysis are generalisable to patients outside of the UK.

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CONTRIBUTIONS

JV was involved in the design of the study, participated in the development of the analysis plan, performed the analysis of the data, participated in the interpretation of the data, and was involved in development of the manuscript and completed critical reviews. He is guarantor.

NR was involved in the design of the study, participated in the development of the analysis plan, participated in the interpretation of the data, and was involved in development of the manuscript and completed critical reviews.

HB was involved in the design of the study, participated in the development of the analysis plan, participated in the interpretation of the data, and was involved in development of the manuscript and completed critical reviews.

MvdT was involved in the design of the study, participated in the development of the analysis plan, participated in the interpretation of the data, and was involved in development of the manuscript and completed critical reviews.

VC was involved in the design of the study, participated in the development of the analysis plan, participated in the interpretation of the data, and was involved in development of the manuscript and completed critical reviews.

JvB was involved in the design of the study, participated in the development of the analysis plan, participated in the interpretation of the data, and was involved in development of the manuscript and completed critical reviews.

LB was involved in the design of the study, participated in the development of the analysis plan, participated in the interpretation of the data, and was involved in development of the manuscript and completed critical reviews.

MM was involved in the design of the study, participated in the development of the analysis plan, participated in the interpretation of the data, and was involved in development of the manuscript and completed critical reviews.

DP was involved in the design of the study, participated in the development of the analysis plan, participated in the interpretation of the data, and was involved in development of the manuscript and completed critical reviews.

DATA SHARING

All relevant data are within the paper and its Supporting Information files. The dataset supporting the conclusions of this article was derived from the Clinical Practice Research Datalink (www.cprd.com) and the UK Optimum Patient Care Research Database (www.opcrd.co.uk). We do not have permission to give public access to these databases; however, researchers may request access for their own purposes. The CPRD has broad National Research Ethics Service Committee (NRES) ethics approval for purely observational research using the primary care data and established data linkages. The OPCRD has ethical approval from the National Health Service (NHS) Research Authority to hold and process anonymized research data (Research Ethics Committee reference: 15/EM/0150). This study was approved by the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee (reference ADEPT0816) – the independent scientific advisory committee for the OPCRD, commissioned by the Respiratory Effectiveness Group, and the Independent Scientific Advisory Committee (ISAC) for the CPRD (registration number, 16_086), The study was designed, implemented, and registered in accordance with the criteria of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP/SDPP/13238).

COMPETING INTERESTS

JV and **VC** are employees of OPRI, which has conducted paid research in respiratory disease on behalf of the following organizations in the past 5 years: Aerocrine, AKL Research and Development Ltd, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, Zentiva (a Sanofi company).

NR reports grants and personal fees from BoehringerIngelheim, Novartis, and personal fees from Teva, GSK, AstraZeneca, Chiesi, Mundipharma, Cipla, Sanofi, Sandoz, 3M, Pfizer, Zambon, outside the presented work.

HB is an employee of Teva Pharmaceuticals

MvdT was an employee of Teva Pharmaceuticals Europe BV at the time the study was conducted.

JvB has received consultancy fees from AstraZeneca, speaker fees from Menarini, research support from GSK, Boehringer Ingelheim, Astrazeneca and Chiesi and travel support from the European COPD Coalition and the Respiratory Effectiveness Group.

LB has during the last three years received honoraria for to participate or to give lectures for the following companies: ALK, AstraZeneca, Boehringer, Chiesi, GlaxoSmithklein, Novartis and Teva.

MM declares no relevant competing interests.

DP has board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, and Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp, Novartis, Pfizer, Respiratory Effectiveness Group, Teva Pharmaceuticals, Theravance, UK National Health Service, Zentiva; payment for lectures/speaking engagements from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, and Teva Pharmaceuticals; payment for manuscript preparation from Mundipharma and Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma and Novartis; payment for travel/accommodation/meeting

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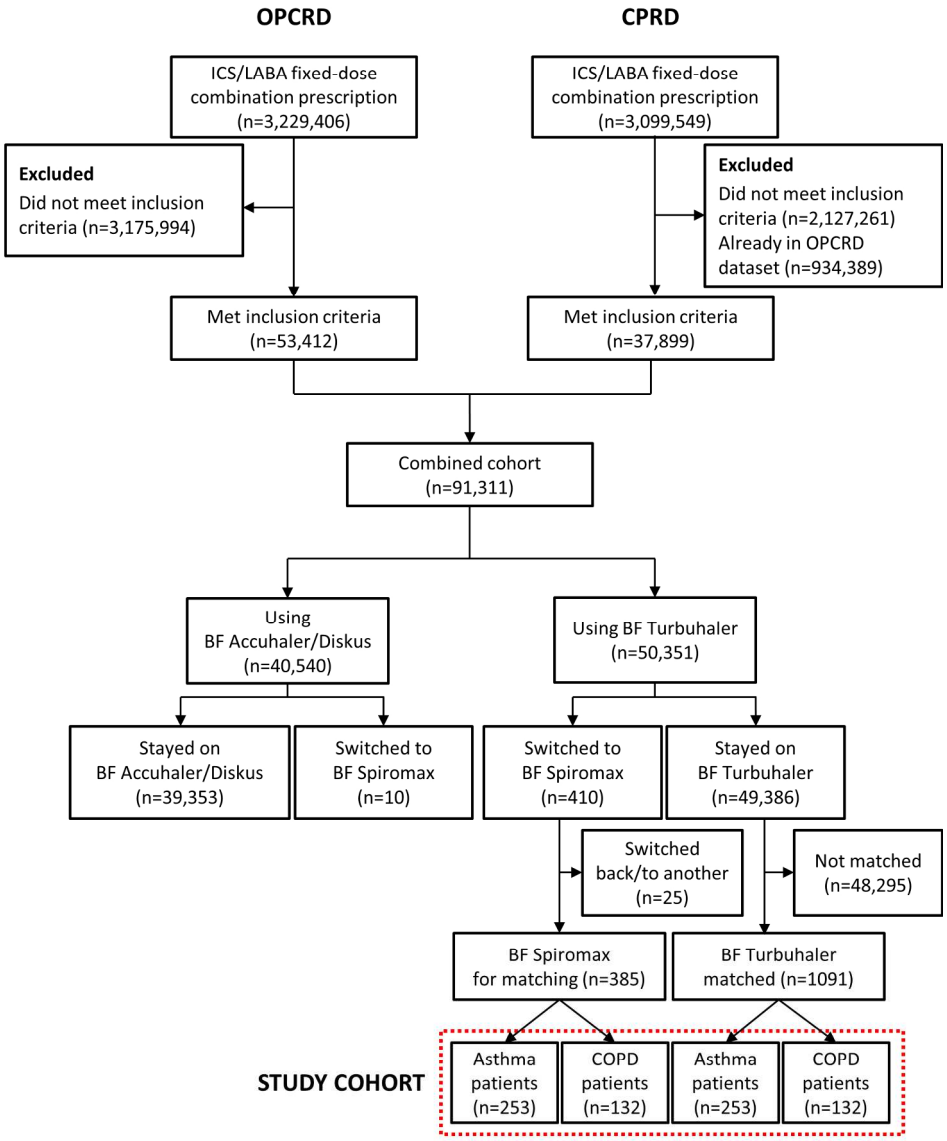
Figure legends:

Figure 1. Patient flow diagram (prior to matching)

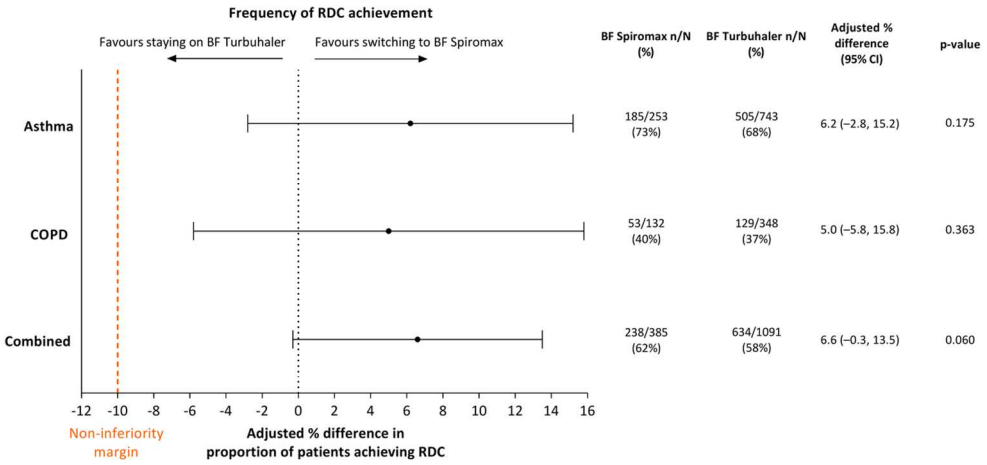
Figure 2. Frequency of achievement of RDC in patients switching to BF Spiromax and those continuing on BF Turbuhaler

Figure 3. Clinical outcomes expressed as adjusted conditional (A) rate ratios (95% CI) and (B) odds ratios (95% CI), among patients switching to BF Spiromax versus continuing on BF Turbuhaler in the matched analysis. *Model did not converge in the asthma group.



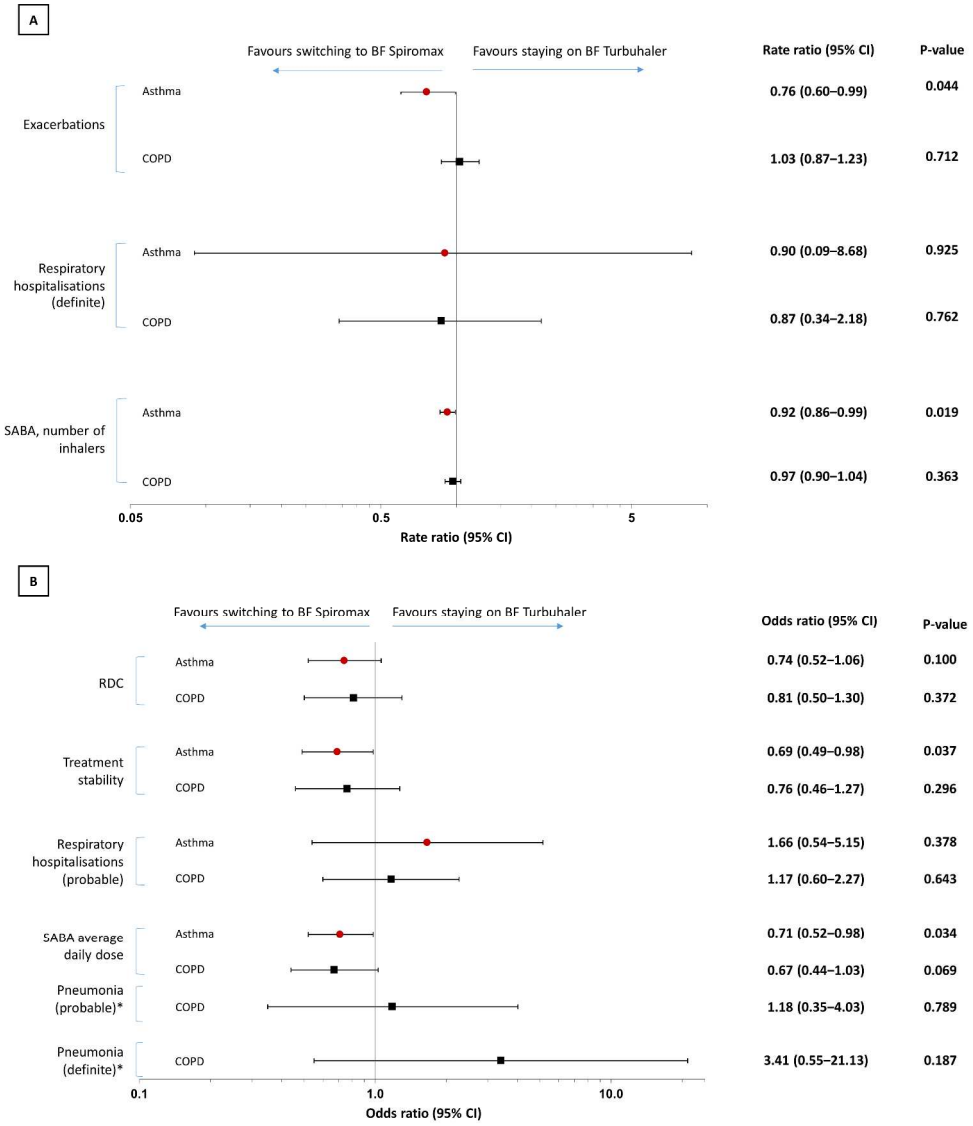
Patient flow diagram (prior to matching)

180x230mm (300 x 300 DPI)



Frequency of achievement of RDC in patients switching to BF Spiromax and those continuing on BF Turbuhaler

120x58mm (300 x 300 DPI)



Clinical outcomes expressed as adjusted conditional (A) rate ratios (95% CI) and (B) odds ratios (95% CI), among patients switching to BF Spiromax versus continuing on BF Turbuhaler in the matched analysis.
*Model did not converge in the asthma group.

338x399mm (300 x 300 DPI)

Supplementary Methods

Matching

Matching was done using the most relevant confounders of the association between the treatment (BF Spiromax vs. BF Turbuhaler) and the primary outcome (achieving risk domain control [RDC]).

Confounders that are unbalanced between the treatment arms can bias associations of interest between the treatment arms and the outcomes. Potential confounders were identified based on a combination of baseline imbalance, bias potential in relation to the primary outcome, as well as expert judgement. Through this, the most relevant confounders were used for direct matching. As it is necessary to limit the number of variables used for direct matching to avoid overly restricting the patient population, variables that do not relevantly affect the association of interest were excluded.

After matching, this approach was repeated in the matched sample to identify any residual confounding, selecting confounders for direct adjustment in the outcome analyses.

Baseline balance

Together with the baseline characterisation, the difference between the arms was quantified using the standardized mean difference (SMD). This measure is not affected by the number of observations in a sample, gives the size of the difference, and, thus, is a better way to judge imbalance than a P-value of a hypothesis test of difference. The SMD was calculated as described below. A SMD of ≤10% was taken as sufficient balance between the arms.

Formulae for standardised difference

Continuous covariate:

$$SDD = \frac{(\overline{x_t} - \overline{x_r})}{\sqrt{\frac{s_t^2 + s_r^2}{2}}},$$

where $\overline{x_t}$, $\overline{x_r}$ denote the sample means and s_t, s_r the standard deviations

Binary Covariate:

$$SDD = \frac{(\widehat{p_t} - \widehat{p_r})}{\sqrt{\frac{\hat{p}_t(1-\hat{p}_t) + \hat{p}_r(1-\hat{p}_r)}{2}}},$$

where $\widehat{p_t}$, $\widehat{p_r}$ denote the proportion of patients in each category

Categorical (>2 categories) Covariate:

$$SDD = \sqrt{(T-C)'S^{-1}(T-C)}$$

where S is a $(k-1) \times (k-1)$ covariance matrix:

$$S = [S_{kl}] = \begin{cases} \frac{\hat{p}_{1k}\,(1-\hat{p}_{1k}) + \hat{p}_{2k}\,(1-\hat{p}_{2k})}{2}, & k = l \\ \frac{\hat{p}_{1k}\,\hat{p}_{1l} + \hat{p}_{2k}\,\hat{p}_{2l}}{2}, & k \neq l \end{cases}$$

, $= (\hat{p}_{12}, \ldots, \hat{p}_{1k})'$, $C = (\hat{p}_{22}, \ldots, \hat{p}_{2k})'$ and $\hat{p}_{jk} = P\,(category\ k | treatment\ arm\ j)$, $j = 1,2$, $k = 2,3, \ldots, k$

Bias potential

Bias potential assesses the degree to which the observed association between the exposure of interest and the outcome is affected by conditioning on another variable. It is also called change-in-estimate. In the case of the primary outcome, a binary indicator for achieving RDC, the definition of bias potential was:

$$Bias\ potential = abs(1 - e^{(\beta_{crude} - \beta_{adjusted})})$$

where β_{crude} = ln(OR) (=natural log of the odds ratio) of exposure from the model without the covariate and β_{crude} = ln(OR) of exposure after adding the covariate to the model. It is called *bias potential* since the bias was estimated without other covariates in the model. To what extent a variable introduces bias into a model will depend on the total model.

A bias potential of ≥2% was considered to indicate a relevant change in the association between the outcome and exposure. Often a cut-off of 5% or even 10% is used to select confounders during model building [44], but a more sensitive cut-off was applied for this study.

The baseline variables with the highest bias potential, that were also insufficiently balanced (SMD >10%), were presented to a panel of clinical experts for the final selection of variables to use for matching.

Matching process

Exact matching for categorical variables and matching within a maximum calliper (maximum distance allowed between a case and a control) for continuous variables was used to match patients, using nearest neighbour variable mixed matching with a match maximum of 3:1 without replacement. Patients in the asthma and COPD groups were matched separately with disease-specific matching criteria.

Mixed matching is a process that utilises more of the data by matching varying numbers of control arm patients to a treatment arm patient. In other words, there will be a cohort of unique patients matched 1:1, another cohort of unique patients matched 2:1, and a third cohort of unique patients matched 3:1. The analyses were conducted using all the matched patients even though some patients had 1 matched control while other patients had 3 matched controls. This imbalance in number of controls matched to cases could introduce residual confounding. Therefore, we verified our assumption that this would not affect the study outcomes through a sensitivity analysis, in which the outcome analyses were also undertaken in the subpopulation of patients in the BF Spiromax arm with exactly 3 matched patients in the BF Turbuhaler arm.

Although the patients in the BF Turbuhaler arm could have multiple records per patient to optimise

the matching process, only one record per patient contributed to the matching.

Matching was repeated 20 times with a different random patient sequence to select the run that resulted in the highest number of matched patients.

Missing data were treated as random and were not imputed. If a selected confounder had more than 20% of missing data, it was not considered as a potential matching variable. If the proportion of missing data was below 20%, the variable was encoded into a categorical variable, adding a category for the observations with missing values, enabling this variable to be used for matching.

Post-matching evaluation

The quality of the matching was evaluated using the same methods used to identify the confounders: standardised difference in combination with bias potential.

To minimise the number of covariates used to adjust the outcome model, a forward assessment of bias potential was used. The identified confounders were entered one-by-one, and the relative change in the effect size of exposure was assessed against the effect size before introducing the variable. If the relative change in effect size was ≥0.02, the variables remained in the model, and the next one was evaluated.

Supplementary Table 1. Patient characteristics in unmatched analysis

Variable	Asthma				COPD			
	BF Spiromax (n=265)	BF Turbuhaler (n=32,071)	P-Value	SMD	BF Spiromax (n=155)	BF Turbuhaler (n=17,315)	P-Value	SMD
Mean (SD) age, years	56.3 (15.5)	50.4 (17.4)	<0.0001	12.1	70.2 (9.1)	69.9 (11.0)	0.0109	3.5
Males, n (%)	121 (45.7)	13,520 (42.2)	<0.0001	5.5	77 (49.7)	9,198 (53.1)	0.5883	0.6
Body mass index, n (%)								
<18.5 kg/m^2	4 (1.6)	395 (1.3)			7 (4.6)	725 (4.2)		
≥18.5 to <25 kg/m^2	68 (27.2)	8,604 (27.8)	<0.0001	5.2	48 (31.8)	5,480 (32.0)	0.0001	5.3
≥25 to <30 kg/m^2	89 (35.6)	10,614 (34.3)			50 (33.1)	5,685 (33.2)		
≥30 kg/m^2	89 (35.6)	11,325 (36.6)			46 (30.5)	5,239 (30.6)		
Smoking status, n (%)								
Non-smoker	129 (49.6)	17,291 (54.2)	0.1366	2.0	18 (11.6)	2,518 (14.6)	<0.0001	10.7
Current smoker	47 (18.1)	5,736 (18.0)			42 (27.1)	4,948 (28.7)		
Ex-smoker	84 (32.3)	8,857 (27.8)			95 (61.3)	9,800 (56.8)		
Comorbidities, n (%)								
Ischaemic heart disease	15 (5.7)	1,945 (6.1)	<0.0001	8.5	29 (18.7)	3,771 (21.8)	0.0021	3.4
Heart failure	1 (0.4)	338 (1.1)	<0.0001	5.7	5 (3.2)	1,115 (6.4)	0.0228	2.2
Diabetes	21 (7.9)	2,297 (7.2)	<0.0001	8.5	20 (12.9)	2,533 (14.6)	0.0273	2.6
Probable pneumonia	1 (0.4)	136 (0.4)	0.6341	0.9	2 (1.3)	298 (1.7)	0.0023	3.5
GERD	41 (15.5)	3,896 (12.1)	0.0001	3.8	25 (16.1)	2,709 (15.6)	0.0030	3.5
Rhinitis	63 (23.8)	6,341 (19.8)	0.2007	0.8	17 (11.0)	1,544 (8.9)	<0.0001	7.2
Charlson Comorbidity Index, n (%)								
0	74 (27.9)	10,394 (32.4)	<0.0001	8.1	102 (65.8)	10,018 (57.9)	0.0002	4.3
1–4	164 (61.9)	19,749 (61.6)			37 (23.9)	5,220 (30.1)		
≥5	27 (10.2)	1,928 (6.0)			16 (10.3)	2,077 (12.0)		
Drug therapy, n (%)								
ICS+LABA	225 (84.9)	26,879 (83.8)			38 (24.5)	6,987 (40.4)		
ICS+LABA+LAMA	11 (4.2)	615 (1.9)	<0.0001	13.0	108 (69.7)	9,244 (53.4)	<0.0001	21.7
ICS+LABA+LAMA+LTRA	4 (1.5)	298 (0.9)			8 (5.2)	625 (3.6)		
ICS+LABA+LTRA	25 (9.4)	4,278 (13.3)			1 (0.6)	459 (2.7)		
Other	0 (0.0)	1 (0.0)			0 (0.0)	0 (0.0)		

SABA average daily dose, n (%)								
0	65 (27.2)	9,929 (34.2)	<0.0001	1.4	27 (18.4)	3,927 (25.7)	0.0003	4.8
>0 to ≤200 µg*	74 (31.0)	8,268 (28.4)			23 (15.6)	3,109 (20.4)		
>200 to ≤400 µg*	57 (23.8)	6,576 (22.6)			37 (25.2)	3,487 (22.8)		
>400 to ≤600 µg*	27 (11.3)	2,237 (7.7)			32 (21.8)	2,524 (16.5)		
>600 µg*	16 (6.7)	2,058 (7.1)			28 (19.0)	2,215 (14.5)		
ICS average daily dose, n (%)								
≤400 µg†	113 (42.6)	17,184 (53.6)	<0.0001	77.9	33 (21.3)	5,886 (34.0)	<0.0001	150.1
>400 to ≤800 µg†	103 (38.9)	10,701 (33.4)			77 (49.7)	7,369 (42.6)		
>800 to ≤1600 µg†	44 (16.6)	3,772 (11.8)			41 (26.5)	3,497 (20.2)		
>1600 µg†	5 (1.9)	414 (1.3)			4 (2.6)	563 (3.3)		
No. of exacerbations in baseline year, n (%)								
0	203 (76.6)	23,095 (72.0)	<0.0001	16.4	59 (38.1)	6,477 (37.4)	<0.0001	9.9
1	45 (17.0)	5,503 (17.2)			46 (29.7)	4,381 (25.3)		
2	12 (4.5)	2,108 (6.6)			16 (10.3)	2,772 (16.0)		
≥3	5 (1.9)	1365 (4.3)			34 (21.9)	3,685 (21.3)		
Disease control using RDC, n (%)	184 (69.4)	19,082 (59.5)	<0.0001	8.7	59 (38.1)	6,477 (37.4)	<0.0001	7.6

*Salbutamol equivalents; †Beclomethasone equivalents.

P-value = p-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate

BF, budesonide/formoterol; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; RDC, risk domain control; SABA, short-acting β_2-agonist; SD, standard deviation; SMD, standardized mean difference

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Real-world effectiveness evaluation of budesonide/formoterol Spiromax® for the management of asthma and chronic obstructive pulmonary disease in the United Kingdom

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Real-world effectiveness evaluation of budesonide/formoterol Spiromax® for the management of asthma and chronic obstructive pulmonary disease in the United Kingdom

Running title: Real-world effectiveness of BF Spiromax®

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ABSTRACT (300 words of 300 allowed)

Objectives: Budesonide/formoterol (BF) Spiromax® is an inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) fixed-dose combination inhaler, designed to minimise common inhaler errors and provide reliable and consistent dose delivery in asthma and chronic obstructive pulmonary disease (COPD). We evaluated non-inferiority of BF Spiromax after changing from another FDC inhaler, compared with continuing the original inhaler.

Methods: Patients with asthma and/or COPD who switched to BF Spiromax were matched (1:3) with non-switchers. Data were from Optimum Patient Care Research Database and Clinical Practice Research Datalink in the United Kingdom (UK). Primary endpoint was proportion of patients achieving disease control (using Risk Domain Control [RDC] algorithm); secondary endpoints were: exacerbation rate, short-acting β_2-agonists (SABA) use, and treatment stability (achieved RDC; no maintenance treatment change). Non-inferiority was defined as having 95% confidence interval (CI) lower bound above –10%, using conditional logistic regression and adjusted for relevant confounders.

Results: Comparing 385 matched patients (asthma 253; COPD 132) who switched to BF Spiromax with 1091 (asthma 743; COPD 348) non-switchers, non-inferiority of BF Spiromax in RDC was demonstrated (adjusted difference: +6.6%; 95% CI: –0.3-13.5). Among asthma patients, switchers to BF Spiromax versus BF Turbuhaler reported fewer exacerbations (adjusted rate ratio [RR] 0.76 [95% CI 0.60-0.99]; p=0.044); were less likely to use high SABA daily doses (adjusted odds ratio [OR] 0.71 [95% CI 0.52-0.98]; p=0.034); used fewer SABA inhalers (adjusted RR 0.92 [95% CI 0.86-0.99]; p=0.019); and were more likely to achieve treatment stability (adjusted OR 1.44 [95% CI 1.02-2.04]; p=0.037). No significant differences in these endpoints were seen among COPD patients.

Conclusions: Among UK asthma and COPD patients, real-world use of BF Spiromax was non-inferior to BF Turbuhaler in terms of disease control. Among asthma patients, switching to BF Spiromax was associated with reduced exacerbations, reduced SABA use, and improved treatment stability versus continuing on BF Turbuhaler.

Key words/terms (from MEDLINE MeSH): asthma, budesonide/formoterol, chronic obstructive pulmonary disease, comparative effectiveness research, disease control, inhalation devices, observational study

Strengths and limitations of this study

- Clearly defined *a priori* hypothesis, endpoints, and sample size.
- A non-selective patient population, obtained through the use of real-world data from validated databases of primary care patients, with sufficient follow-up period for observing relevant outcomes.
- Hospital admissions, A&E attendances, and outpatient visits are not systematically recorded in primary care databases, and the applied definition to identify asthma-related hospital admissions or A&E events may have given rise to false positive events.
- Potential effects of inhaler technique on the reported outcomes could not be taken into account, as this would require close observation and communication with each patient as they demonstrated their inhaler technique.
- Observed differences in secondary outcomes could have arisen as a consequence of factors unrelated to the inhalers that might not have been captured in the dataset.

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are common respiratory conditions.[1, 2] Cornerstone asthma/COPD treatment consists of inhaled therapy with proven efficacy in randomised clinical trials (RCTs).[3, 4] In real life, however, incorrect inhaler use is common in patients with asthma or COPD, resulting in poor symptom control and worse outcomes.[5, 6] Specifically, critical inhaler errors were reported in a review of 3660 patients;[7] insufficient respiratory effort in dry-powder inhaler (DPI) users and actuation before inhalation in metered-dose inhaler (MDI) users were found to be associated with uncontrolled asthma.[7]

In April 2014, marketing authorisation was granted for DuoResp® Spiromax® (Teva Pharmaceutical Industries, Petach Tikva, Israel), an inhaler containing a fixed-dose combination (FDC) of the inhaled corticosteroid (ICS) budesonide and the long-acting β_2-agonist (LABA) formoterol (budesonide/formoterol [BF]). The Spiromax® inhaler was designed to maximise ease of use, reliability of dosing, and consistency of lung deposition[8, 9] in patients with asthma or COPD. Spiromax® is a breath-actuated, multi-dose DPI that is similar in design and appearance to a MDI, but uses different internal configuration. Drug delivery is via the X-ACT® system, consisting of active metering (upon opening the cap, an air pump transfers the drug from the drug reservoir to the dose cup) and cyclone separator technology (turbulent airflow), which breaks up the dry-powder blend and separates fine drug particles from larger lactose particles.[8] Spiromax® requires only one preparation step (opening the cap) and provides consistent dose delivery across a broad range of inspiratory flow rates.[8, 9] Recent findings suggest that Spiromax is associated with a reduced number of errors related to dose preparation, undertaking the steps needed to correctly deliver the dose during inhalation, and handling the device after inhalation, as well as being easier for patients and healthcare professionals to use compared with other DPIs.[10, 11] BF Spiromax has demonstrated pharmacokinetic bioequivalence to BF Turbuhaler® (AstraZeneca UK Limited, UK) in healthy volunteers.[12, 13] A recent independent study in COPD found BF Spiromax to have a faster onset of bronchodilation than BF Turbuhaler, likely due to differences in drug deposition between the two devices.[14] However, evidence for the real-world effectiveness of BF Spiromax in comparison with other inhalers in asthma and/or COPD patients is lacking.

The current study was part of a multi-phase assessment of real-world outcomes over 1 year in patients with asthma and/or COPD who switched to BF Spiromax compared with patients who remained on another device, using data from two United Kingdom (UK) primary care administrative databases. The primary objective of this phase of the study was to evaluate the non-inferiority of changing from another FDC inhaler to BF Spiromax versus continuing to use the original FDC inhaler, in terms of achieving disease control, based on the Risk Domain Control (RDC) algorithm; secondary objectives included the effects of the switch on the occurrence of moderate/severe exacerbations and respiratory-related hospitalisations, treatment stability, and short-acting β_2-agonist (SABA) use.

METHODS

Patients and study design

This was a matched, historic cohort study of patients with asthma and/or COPD using two validated primary care databases of patients in the UK, Optimum Patient Care Research Database (OPCRD) and Clinical Practice Research Datalink (CPRD).[15, 16] The OPCRD is governed by The Anonymous Data Ethics Protocols and Transparency committee, commissioned by the Respiratory Effectiveness Group.[17] The CPRD is a UK government research service, jointly supported by the National Institute for Health Research and the Medicines and Healthcare Products Regulatory Agency, that provides access to anonymised NHS data. It operates under a range of UK and European Laws as well as NHS and other guidelines.[16] This study is registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (Register Number EUPAS13238).[18]

The OPCRD and CPRD databases were searched onwards from 2010 to identify prescriptions of BF Spiromax, BF Turbuhaler, and fluticasone propionate/salmeterol (FS) Accuhaler®/Diskus® (GlaxoSmithKline, Uxbridge, UK) in patients ≥18 years of age with asthma and/or COPD (Figure 1). The OPCRD and CPRD datasets for this study were constructed separately and checked for

overlap before pooling to exclude duplicate patients. Patients had to have at least 2 years of data, comprising a minimum of 1 baseline year and a 1-year outcome period. Patients were required to have at least three prescriptions for ICS/LABA FDC (BF Spiromax, BF Turbuhaler, or FS Accuhaler/Diskus) therapy during the baseline period. Switch patients must have evidence of an initial BF Spiromax prescription in the outcome period as well as at least one supplementary prescription for BF Spiromax in the 1-year outcome period to ensure consistent usage. Likewise, patients remaining on their inhaler required at least one repeat prescription in the outcome period. We only included patients switching to BF Spiromax who were registered at practices considered to have a policy of BF Spiromax adoption or wholesale change (i.e., the decision to switch inhaler was based on cost savings instead of clinical reasons). Such practices were identified as those at which ≥5 patients changed to BF Spiromax within a 3-month period. The current study includes only patients who stayed on BF Turbuhaler or switched from BF Turbuhaler to BF Spiromax, due to the low number of patients who switched from FS Accuhaler/Diskus to BF Spiromax. The date of the first prescription of BF Spiromax or the (matched) date of the repeat prescription for BF Turbuhaler in the control arm was the index date. The recommended dosing instructions of BF Turbuhaler and BF Spiromax in adults are the same (asthma: 1–2 inhalations twice daily; COPD: 2 inhalations twice daily), and we observed no significant differences in prescribed dose between BF Spiromax and BF Turbuhaler in the disease groups.

Asthma patients were required to have a diagnostic code (Read code)[19] for asthma and/or at least two prescriptions for asthma therapy during the baseline year, and to have no other chronic respiratory disease diagnosis. COPD patients were required to be ≥40 years of age at first prescription for BF Spiromax or the matching BF Turbuhaler prescription, and to have a diagnostic code for COPD and a post-bronchodilator FEV_1/FVC <0.70 consistent with the criteria for inclusion in the UK register of patients with COPD (Quality and Outcomes Framework). The subgroup of patients with only an asthma diagnosis is referred to henceforth as the asthma group. The patients with a COPD diagnosis (with or without an asthma diagnosis) are referred to henceforth as the COPD group.

Outcome measures

The primary outcome was disease control as assessed by RDC, a composite measure that has been used in several similar matched historical cohort studies to define absence of exacerbations.[20-23] To achieve RDC in this study, patients must not have an asthma/COPD-related hospital admission, asthma/COPD-related Accident and Emergency (A&E) attendance, or course of oral corticosteroids (OCS) during the outcome period. In addition, patients in the COPD group must not have received antibiotics for a lower respiratory tract infection (LRTI).

Secondary outcomes included the number of moderate/severe exacerbations and hospitalisations, and change in treatment stability. A moderate/severe exacerbation (for COPD) or severe exacerbation (for asthma) was defined following the American Thoracic Society/European Respiratory Society Task Force Position Statement.[24] Lower respiratory hospitalisations were identified and classified as follows: definite hospitalisations were those with a lower respiratory code, including asthma and LRTI codes; OR a generic hospitalisation Read code that has been recorded on the same day as a lower respiratory consultation; definite + probable hospitalisations were those occurring within a 7-day window (either side of the hospitalisation date) of a lower respiratory Read code. Adequate treatment stability was defined as achieving RDC and no increase in dose, change in delivery device, and change in type of ICS and/or use of LABAs, theophylline, long-acting muscarinic antagonists, or leukotriene receptor antagonists (LTRAs).[22] Additional outcomes were SABA usage, which was expressed as average daily SABA dosage during the outcome year and calculated from prescriptions as ([*Count of inhalers* x *doses in pack* x *µg strength*] / 365), and a pneumonia event which was defined as having a Read coded diagnosis (probable pneumonia), or a Read coded diagnosis with a hospital admission or chest x-ray within 1 month (definite pneumonia).

Statistical analyses

It was estimated that 349 patients would have 90% power to demonstrate non-inferiority of BF Spiromax and BF Turbuhaler for achieving RDC, at a one-sided significance level of 0.050. For the

calculation, an expected difference in proportions of zero was used, assuming that the proportion of discordant pairs was 0.458. This assumption was based on previous studies showing that a weighted average of 71.6% of asthma and COPD patients prescribed FDC therapy have no exacerbations over a 1-year period.[25, 26]

Descriptive statistics of all baseline demographic characteristics, co-morbidities, medication use, indicators of disease severity and other patient characteristics were computed separately for the patients in the BF Spiromax and BF Turbuhaler groups and for patients in the asthma and COPD groups. In cases where multiple observations existed for a patient, one was randomly selected. Continuous variables were summarised using the number of non-missing observations, percentage of non-missing observations, mean, standard deviation (SD), median and interquartile range (difference between the 25th and 75th percentile), and a P-value for the Kruskal-Wallis equality-of-populations rank test. Binary and categorical variables were summarised using the percentage of non-missing observations, the frequency and percentages (based on the non-missing sample size) of observed levels, and a P-value for the Pearson's chi-square test of independent categories.

Patients who switched to BF Spiromax were compared with matched controls who stayed on BF Turbuhaler. Mixed matching was performed 1:3 so that each BF Spiromax patient would be matched with up to three patients who remained on BF Turbuhaler (see Supplementary methods in Appendix for a full description of the mixed matching process). Mixed matching was performed to increase precision of the effect estimates. Because the analyses were conducted on all of the matched patients, which could introduce residual confounding due to imbalanced matching ratios, a sensitivity analysis was performed in which the outcome analyses were also performed in the subpopulation of patients in the BF Spiromax arm with exactly three matched patients in the BF Turbuhaler arm. Matching was performed using the most relevant confounders which were identified based on baseline imbalance and bias potential in relation to the primary outcome. For asthma, these confounders included age, gender, number of antibiotic courses, number of OCS courses, Global Initiative for Asthma (GINA) control categories, number of exacerbations, and RDC; matching confounders for COPD included age, gender, drug therapy, ICS average daily

dose, number of antibiotic courses, number of exacerbations, and Global Initiative for Chronic Obstructive Lung Disease (GOLD) risk categories. Baseline imbalance was assessed using the Standardised Mean Difference (SMD), which, unlike a P-value, is not affected by the number of observations in a sample,[27, 28] and provides information on the size of the difference. An SMD of ≤10% was assumed to represent sufficient balance between the arms,[29] and the formula used is presented in the Supplementary methods of the Appendix. Bias potential is the degree to which the observed association between the exposures of interest and the outcome is affected by conditioning on another variable; the formula is presented in the Supplementary methods of the Appendix. A sensitive bias potential cut off of ≥2% was used for this study.

Baseline variables with highest bias potential that were also insufficiently balanced were presented to a panel of experts for final selection. Following matching, the process was repeated in the matched sample to identify any residual confounding.

After mixed matching, conditional logistic regression of the between-patient difference in the primary outcome was performed to provide a 95% confidence interval (CI) with which to assess non-inferiority. Analyses were undertaken for the patients in the asthma and COPD groups combined, as well as by disease group. The model was adjusted for baseline variables that remained with bias potential after matching. Non-inferiority was claimed if the lower bound of the 95% CI for the primary endpoint (RDC) was above –10%, a difference widely regarded as clinically important for many outcomes in respiratory studies,[30,31] and used previously in similar real-life studies of patients in primary care settings.[22, 23] If non-inferiority was achieved, superiority was tested.

Secondary outcomes were analysed in the matched sample and adjusted for baseline variables that remained with bias potential after matching, and reported as conditional rate ratios (RR) or odds ratios (OR) with their 95% CIs. Number of exacerbations and hospitalisations were analysed in the matched sample using conditional Poisson regression to obtain estimates of relative rates, treatment stability was analysed in the matched sample using conditional logistic regression, and

SABA usage was analysed in the matched sample using conditional ordinal logistic regression, after the SABA average daily dose was categorised.

All statistical analyses were conducted using Stata MP6 version 12 and Stata SE version 14 (StataCorp, College Station, TX). A statistically significant result was defined as $p < 0.05$.

Patient and Public Involvement

No patients or public were involved in the design or conduct of this retrospective database study.

RESULTS

Study population

Overall, 420 patients switched to BF Spiromax (Figure 1). Of the patients who used BF Turbuhaler, 410 switched to BF Spiromax and 49,386 remained on BF Turbuhaler. Baseline characteristics of these unmatched patients are shown in Supplementary Table 1, where imbalanced covariates (SMD >10%) for asthma include mean age, drug therapy, ICS average daily dose, and number of exacerbations in baseline years; those for COPD include smoking status, drug therapy, and ICS average daily dose.

For the matched analysis, a total of 385 patients switching to BF Spiromax were analysed; a total of 1091 patients who stayed on BF Turbuhaler were matched to the switch patients (**Figure 1**). Twenty-five patients who switched back to BF Turbuhaler or to another FDC ICS/LABA were not included in the analysis. In the baseline characteristics of the matched patients, covariates with SMD >10% in the asthma group were body mass index and ischaemic heart disease; for COPD they were smoking status, ischaemic heart disease, heart failure, number of exacerbations, and number of acute OCS courses (**Table 1**).

Table 1. Patient characteristics in matched analysis

Variable	Asthma patients				COPD patients			
	BF Spiromax (n=253)	BF Turbuhaler (n=743)	P-value	SMD (%)	BF Spiromax (n=132)	BF Turbuhaler (n=348)	P-value	SMD (%)
Mean (SD) age, years	55.9 (15.3)	55.8 (15.1)	0.9101	0.7	70.5 (8.8)	70.5 (8.5)	0.9512	0.2
Males, n (%)	112 (44.3)	331 (44.5)	0.9382	0.6	66 (50.0)	184 (52.9)	0.5736	5.7
Body mass index*, n (%)			0.4038	12.1				
<18.5 kg/m^2	3 (1.3)	9 (1.2)			6 (4.7)	11 (3.2)	0.6977	7.4
18.5 to <25 kg/m^2	65 (27.2)	163 (22.5)			46 (35.7)	112 (32.4)		
25 to <30 kg/m^2	88 (36.8)	265 (36.5)			39 (30.2)	120 (34.7)		
>30 kg/m^2	83 (34.7)	289 (39.8)			38 (29.5)	103 (29.8)		
Smoking status†, n (%)			0.7393	5.2			0.5696	10.8
Non-smoker	126 (50.8)	397 (53.6)			14 (10.6)	48 (13.9)		
Current smoker	44 (17.7)	123 (16.6)			36 (27.3)	98 (28.3)		
Ex-smoker	78 (31.5)	220 (29.7)			82 (62.1)	200 (57.8)		
Cardiovascular disease, n (%)								
Ischaemic heart disease	13 (5.1)	62 (8.3)	0.0951	12.8	22 (16.7)	78 (22.4)	0.1662	14.5
Heart failure	1 (0.4)	8 (1.1)	0.3225	8.0	4 (3.0)	23 (6.6)	0.1286	16.7
Exacerbations, n (%)			0.9869	3.6			0.7809	12.9
0	199 (78.7)	593 (79.8)			54 (40.9)	156 (44.8)		
1	42 (16.6)	120 (16.2)			38 (28.8)	106 (30.5)		
2	7 (2.8)	18 (2.4)			15 (11.4)	35 (10.1)		
3	4 (1.6)	9 (1.2)			13 (9.8)	28 (8.0)		
≥4	1 (0.4)	3 (0.4)			12 (9.1)	23 (6.6)		
No. of respiratory-related hospital admissions, n (%)			1.0000	0			0.1460	2.8
0	253 (100.0)	743 (100.0)			129 (97.7)	338 (97.1)		
1	0	0			1 (0.8)	9 (2.6)		
≥2	0	0			2 (1.5)	1 (0.3)		
Uncontrolled risk domain control, n (%)	70 (27.7)	194 (26.1)	0.6278	3.5	78 (59.1)	192 (55.2)	0.4397	7.9
No. of antibiotic courses, n (%)			0.8362	5.5			0.9478	6.4
0	212 (83.8)	630 (84.8)			74 (56.1)	198 (56.9)		
1	34 (13.4)	99 (13.3)			37 (28.0)	104 (29.9)		

Variable	Asthma patients				COPD patients			
	BF Spiromax (n=253)	BF Turbuhaler (n=743)	P-value	SMD (%)	BF Spiromax (n=132)	BF Turbuhaler (n=348)	P-value	SMD (%)
2	5 (2.0)	12 (1.6)			11 (8.3)	26 (7.5)		
3	1 (0.4)	1 (0.1)			4 (3.0)	8 (2.3)		
≥4	1 (0.4)	1 (0.1)			6 (4.5)	12 (3.4)		
No. of acute OCS courses, n (%)								
0	199 (78.7)	593 (79.8)			79 (59.8)	225 (64.7)		
1	42 (16.6)	120 (16.2)	0.9869	3.6	28 (21.2)	74 (21.3)	0.6813	14.4
2	7 (2.8)	18 (2.4)			9 (6.8)	20 (5.7)		
3	4 (1.6)	9 (1.2)			7 (5.3)	15 (4.3)		
≥4	1 (0.4)	3 (0.4)			9 (6.8)	14 (4.0)		
Average daily SABA dose, n (%)								
0	64 (25.3)	224 (30.1)			23 (17.4)	65 (18.7)		
>0 to ≤200 µg/day	70 (27.7)	196 (26.4)	0.4055	4.9	22 (16.7)	66 (19.0)	0.3524	8.4
>200 to ≤400 µg/day	56 (22.1)	139 (18.7)			32 (24.2)	78 (22.4)		
>400 to ≤600 µg/day	25 (9.9)	59 (7.9)			5 (3.8)	29 (8.3)		
>600 µg/day	38 (15.0)	125 (16.8)			50 (37.9)	110 (31.6)		

BF: Budesonide/formoterol; OCS: oral corticosteroids; SABA: short acting β_2-agonist; SD, standard deviation; SMD: standardised mean difference

*Some missing data for this parameter: n=239 for asthma on BF Spiromax, n=726 for asthma on BF Turbuhaler; n=129 for COPD on BF Spiromax, n=346 for COPD on BF Turbuhaler.

†Some missing data for this parameter: n=248 for asthma on BF Spiromax, n=740 for asthma on BF Turbuhaler, n=346 for COPD on BF Turbuhaler.

Outcomes analyses

Descriptive statistics of disease outcomes in the matched patients are shown in **Table 2**. The FDC average daily dose was numerically lower among patients using BF Spiromax in the asthma group (382.1 vs 505.3 µg) and mean percent RDC was higher among patients using BF Spiromax in both the asthma (73.1% vs 68.0%) and COPD (40.2% vs 37.1%) groups (**Table 2**).

Table 2. Descriptive statistics of disease outcomes in the matched cohorts of patients.

	Asthma patients		COPD patients	
Outcomes	BF Spiromax (n=253)	BF Turbuhaler (n=743)	BF Spiromax (n=132)	BF Turbuhaler (n=348)
% Risk domain control	73.1	68.0	40.2	37.1
No. of exacerbations (SD)	0.3 (0.7)	0.4 (0.7)	1.1 (1.4)	1.0 (1.4)
% Treatment stability	72.7	66.9	39.4	37.1
SABA average daily dose (SD)	1.4 (1.9)	1.5 (2.9)	2.6 (2.9)	2.4 (2.3)
No. of SABA inhalers (SD)	5.1 (6.8)	5.5 (10.7)	9.5 (11.0)	8.7 (8.5)
No. of antibiotics prescriptions (SD)	0.2 (0.7)	0.4 (0.8)	0.7 (1.1)	0.8 (1.1)
No. of acute OCS courses (SD)	0.3 (0.7)	0.3 (0.7)	1.0 (1.7)	0.9 (1.3)
FDC ICS average daily dose (SD)	382.1 (351.3)	505.3 (585.0)	555.3 (427.1)	561.8 (646.1)
No. of FDC inhalers (SD)	14.0 (8.9)	10.8 (5.6)	15.0 (6.7)	11.9 (5.4)
No. of respiratory A&E attendances (SD)	0.0 (0.1)	0.0 (0.1)	0.0 (0.2)	0.1 (0.4)
No. of probable respiratory inpatient hospitalisations (SD)	0.0 (0.1)	0.0 (0.1)	0.1 (0.4)	0.1 (0.5)
No. of definite respiratory inpatient hospitalisations (SD)	0.0 (0.1)	0.0 (0.1)	0.0 (0.3)	0.1 (0.4)
% Probably pneumonia*	0.0	0.0	3.0	2.3
% Definite pneumonia*	0.0	0.0	2.3	0.6

A&E, accident and emergency; BF: budesonide/formoterol; FDC: fixed dose combination; ICS, inhaled corticosteroid; OCS: oral corticosteroid; RDC: risk domain control; SABA, short acting beta agonist; SD: standard deviation.

*A pneumonia event was defined as having a Read coded diagnosis (probable pneumonia), or a Read coded diagnosis with a hospital admission or chest x-ray within 1 month (definite pneumonia).

The lower bound of the 95% CI of the adjusted percentage difference in the frequency of achieving RDC in the combined population was –0.3%, meeting the criterion for non-inferiority of switching to BF Spiromax compared with continuing on BF Turbuhaler (**Figure 2**). Although a higher proportion of patients achieved RDC in the group who switched to BF Spiromax compared with patients who stayed on BF Turbuhaler, the difference was not statistically significant, and the mean between-group difference was less than the 10% considered to be clinically relevant.[22, 23, 30, 31] In the

sensitivity analysis where only BF Spiromax switchers that had three matched controls were used, a significant difference was shown in the combined patients group (adjusted % difference 8.3; 95% CI 1.0-15.6; p=0.025) (data not shown). In the sensitivity analysis, the adjusted percentage difference was nearly 10% in the COPD group but there was a wide confidence interval (adjusted % difference 9.9; 95% CI -2.4-22.2; p=0.114). Similarly, in the asthma group, the adjusted percentage difference was 6.5% (95% CI -2.7-15.7; p=0.168). The conditional logistic regression model in all matched patients showed an adjusted OR of 1.31 (95% CI 0.99-1.73; p=0.061) for BF Spiromax versus BF Turbuhaler for RDC, which did not achieve statistical significance. However, in the sensitivity analysis, the OR of 1.41 was statistically significant (95% CI 1.05-1.90; p=0.022) (data not shown).

Secondary outcomes shown are expressed as adjusted conditional RRs (**Figure 3a**) and ORs (**Figure 3b**) separately for patients with asthma and those with COPD. Among asthma patients, switchers to BF Spiromax versus BF Turbuhaler reported fewer exacerbations, were less likely to use high amounts of SABA daily dose, used fewer SABA inhalers, and were more likely to achieve treatment stability. Among patients with COPD, no significant differences in these endpoints were seen between those who switched to BF Spiromax and those staying on BF Turbuhaler. Confidence intervals for patients who switched to BF Spiromax show a trend effect for lower risk of being on high-dose SABA therapy and reduction in use of SABA inhalers in the COPD group. In the combined patients group, significance among switchers to BF Spiromax was noted in SABA average daily dose (OR 0.70 [95% CI 0.53-0.94]; p=0.017), reduction in use of SABA inhalers (RR 0.94 [95% CI 0.89-0.99]; p=0.012), and improved treatment stability (OR 0.74 [95% CI 0.56-0.99]; p=0.041).

DISCUSSION

This study, the first to compare the real-world effectiveness of switching to the BF Spiromax inhaler from BF Turbuhaler found that, among 253 patients with asthma and 132 patients with COPD, BF Spiromax showed non-inferiority with respect to achievement of disease control to BF Turbuhaler

in matched patients with asthma and/or COPD. In the primary analysis in the combined population, patients who switched to BF Spiromax had 31% higher odds of achieving RDC compared with those who remained on BF Turbuhaler; however, this finding did not meet the threshold for statistical significance.

Patients in the asthma group who switched to BF Spiromax had significantly reduced SABA use, fewer exacerbations, and greater treatment stability compared with matched patients who remained on BF Turbuhaler. Some of the observed reduction in SABA use associated with BF Spiromax may have arisen as a result of patients using their new device as a reliever medication in addition to its use as maintenance therapy. The use of BF in a single-inhaler maintenance and quick-relief therapy (SMART) regimen has been recommended as an improved method of administering ICS/LABA therapy [32,33]. However, the recommendations are not device-specific; as such, SABA use was not expected to differ between switchers to Spiromax and those who remained on Turbuhaler. The difference may be partially explained by the greater resemblance to an MDI device of Spiromax compared with Turbuhaler. No significant differences between patients who switched and those who did not were observed in the COPD group. This might be partly caused by lower statistical power in the COPD group, which included approximately half of the number of patients as in the asthma group, and by the general notion that the reduction in exacerbation frequency with ICS is less in COPD compared with asthma [34]. Another factor that could have contributed is the much older age (~15 years) of patients in the COPD group. Age is a proxy for many health-related characteristics, and there is evidence of a negative correlation between advancing age and correct inhaler technique across MDI and varying DPI devices [35].

Switching asthma medications is often necessary for several reasons, including regaining or achieving asthma control or to constrain healthcare costs. Due to the retrospective design of our study, reasons for switching inhaler were not captured. However, we selected BF Spiromax patients registered at practices considered to have a policy of BF Spiromax adoption or wholesale change. While we cannot exclude some inhaler switches being induced by clinical reasons, the requirement for practices to have ≥5 patients switch to BF Spiromax within a 3-month period

means that in our view it is probable that many of the switches to BF Spiromax at these centres were driven by economic rationales. Thus, it is expected that any differences between treatments in our study result from the switch in inhalers rather than improvement in poor disease control. A switch to a different inhaler may potentially increase patient-practice contact, in terms of additional evaluation and teaching of inhaler technique, which may confound the results. However, in a pilot study which has been published only in abstract form [36], 76% of 114 patients were switched to BF Spiromax without consultation, suggesting that any confounding created by additional physician teaching for those who switched versus those remaining on original therapy was limited in the overall patient population. Indeed, previous findings have shown that most asthma patients who have had their inhaler device switched without their consent believed that cost issues were a factor [37]. As such, it is likely that many of the switches experienced by our patient cohort took place at least in part for economic reasons.

The results observed in this real-world study are consistent with previous evidence gained from RCTs where BF Spiromax was found to have similar efficacy to BF Turbuhaler.[38] The suggestion of potential superiority on secondary outcome measures in the current study, a result which was not seen in RCTs, might plausibly reflect differences in ease of use and/or adherence between the inhalers when prescribed in routine care. Patients participating in respiratory RCTs usually represent only between 1% and 5% of the true population of patients with asthma or COPD[39] and the proportion of COPD patients in primary care who would be eligible for inclusion in recent large pharmaceutically-sponsored COPD studies has ranged from 17% to 42%.[40] In addition, adherence to treatment in real-world observational studies is usually much lower than in RCTs.[41] Moreover, proper inhaler technique is often artificially high in clinical trials because of patient selection, extensive training, and close monitoring, which may explain why minimal differences in outcomes between devices have been observed in RCTs.[42] However, in daily practice, patients' differential ability to correctly use their inhaler may result in larger differences in health outcomes. Previous studies have shown that study participants and healthcare professionals find it easier to learn how to use the Spiromax inhaler correctly, compared with other DPIs.[10,11] Furthermore,

patients are able to achieve slightly higher peak inspiratory flow rates with the Spiromax inhaler compared with the Turbuhaler.[43]

This study had clearly defined *a priori* hypothesis, endpoints, and sample size, as is recommended for this type of observational research.[44] A particular strength was the non-selective patient population obtained through the use of real-world data from validated databases of primary care patients. The size and scope of these databases allowed for the collection of important clinical variables and a sufficient follow-up period for observing relevant outcomes. In addition, the study's time horizon of 1 year has minimised the impact of potential seasonal differences in disease activity.[45] Overall, the study was well powered to investigate the primary outcome which was RDC of disease.

The inclusion of matched patients in our analysis of RDC risked introducing residual confounding due to imbalanced matching ratios. We therefore performed a sensitivity analysis in the subpopulation of patients in the BF Spiromax arm with exactly three matched patients in the BF Turbuhaler arm. Compared with patients who remained on BF Turbuhaler, patients who switched to BF Spiromax had 31% and 41% higher odds of achieving RDC in the primary analysis and sensitivity analysis, respectively, with the difference reaching statistical significance in the sensitivity analysis only. Regardless of whether significance was achieved, the difference in odds with BF Spiromax versus BF Turbuhaler is quite similar between the primary and sensitivity analyses, supporting the overall validity of our assumptions for the effect of BF Spiromax versus BF Turbuhaler on achieving disease control.

Limitations of the study are important to note. The use of databases to evaluate outcomes depends on the information registered, which is for clinical and routine use rather than research purposes. Possible issues include the fact that hospital admissions, A&E attendances, and outpatient visits are not systematically recorded in primary care databases and the applied definition to identify asthma-related hospital admissions or A&E events may give false positive events. However, this limitation would apply equally to both groups. In addition, inhaler technique could not be taken into

account for this study as this would require close observation and communication with each patient as they demonstrated their inhaler technique. Regarding the secondary outcomes, we cannot rule out the possibility that the observed differences were caused by factors unrelated to the inhalers, as patients who switched to BF Spiromax may have differed from non-switchers in ways not captured in our data set. Comparison with other ICS/LABA FDCs would have been useful to determine any differences attributable to pharmacological effect; however, there were insufficient patient numbers for such comparisons. An important limitation in observational studies is the potential for confounding of the associations arising from systematic differences between the patients being compared. In this study, confounding was minimised where possible using matching techniques to create cohorts that were comparable in terms of important demographic and clinical characteristics as recommended by the Respiratory Effectiveness Group.[44] Multivariate models were adjusted by those variables that continued to confound the associations of interest after matching. However, in the COPD group, due to a limited number of patients, only a restricted set of variables could be used for matching and model adjustment. Therefore, we cannot ensure confounding of the association of interest was sufficiently addressed in this group. Furthermore, as previously discussed, the selection of patients from practices which were required to have ≥5 switchers to BF Spiromax in a 3-month period could potentially have introduced a bias in favour of practices with greater than average asthma/COPD expertise and involvement in asthma/COPD patient care.

This real-world analysis showed that switching from BF Turbuhaler to BF Spiromax was associated with no loss of symptom control and may be beneficial in some patients. These data validate, in a real-world population of patients with asthma and COPD and clinical setting, similar efficacy to that previously demonstrated in an RCT.[38] Such validation is important for primary practitioners as it provides reassurance that BF Spiromax is effective in real-world primary care patients, and not just in the carefully selected and closely monitored cohorts of patients typical of RCTs. It should however be noted that periodical assessments of adherence, motivation and inhaler technique are still likely to be required to ensure that optimal inhaler use is maintained long-term.[46-51] Further research may be needed to assess the extent to which the results of this analysis are

generalisable to patients outside of the UK.

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CONTRIBUTIONS

All authors (JV, NR, HB, MvdT, VC, JvB, LB, MM, DP) were involved in the conception and design of the study. JV was responsible for the analysis of the data. All authors (JV, NR, HB, MvdT, VC, JvB, LB, MM, DP) interpreted the data, were involved in development of the manuscript and completed critical reviews. All authors (JV, NR, HB, MvdT, VC, JvB, LB, MM, DP) meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. JV is guarantor of the study.

COMPETING INTERESTS

JV and **VC** are employees of OPRI, which has conducted paid research in respiratory disease on behalf of the following organizations in the past 5 years: Aerocrine, AKL Research and Development Ltd, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, Zentiva (a Sanofi company).

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HB is an employee of Teva Pharmaceuticals

MvdT was an employee of Teva Pharmaceuticals Europe BV at the time the study was conducted.

JvB has received consultancy fees from AstraZeneca, speaker fees from Menarini, research support from GSK, Boehringer Ingelheim, Astrazeneca and Chiesi and travel support from the European COPD Coalition and the Respiratory Effectiveness Group.

LB has during the last three years received honoraria for to participate or to give lectures for the following companies: ALK, AstraZeneca, Boehringer, Chiesi, GlaxoSmithklein, Novartis and Teva.

MM declares no relevant competing interests.

DP has board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals, and Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp, Novartis, Pfizer, Respiratory Effectiveness Group, Teva Pharmaceuticals, Theravance, UK National Health Service, Zentiva; payment for lectures/speaking engagements from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, and Teva Pharmaceuticals; payment for manuscript preparation from Mundipharma and Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma and Novartis; payment for travel/accommodation/meeting

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DATA SHARING STATEMENT

All relevant data are within the paper and its Supporting Information files. The dataset supporting the conclusions of this article was derived from the Clinical Practice Research Datalink (www.cprd.com) and the UK Optimum Patient Care Research Database (www.opcrd.co.uk). We do not have permission to give public access to these databases; however, researchers may request access for their own purposes. The CPRD has broad National Research Ethics Service Committee (NRES) ethics approval for purely observational research using the primary care data and established data linkages. The OPCRD has ethical approval from the National Health Service (NHS) Research Authority to hold and process anonymized research data (Research Ethics Committee reference: 15/EM/0150). This study was approved by the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee (reference ADEPT0816) – the independent scientific advisory committee for the OPCRD, commissioned by the Respiratory Effectiveness Group, and the Independent Scientific Advisory Committee (ISAC) for the CPRD (registration number, 16_086), The study was designed, implemented, and registered in accordance with the criteria of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP/SDPP/13238).

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Figure legends

Figure 1. Patient flow diagram (prior to matching)

Figure 2. Frequency of achievement of RDC in patients switching to BF Spiromax and those continuing on BF Turbuhaler

Figure 3. Clinical outcomes expressed as adjusted conditional (A) rate ratios (95% CI) and (B) odds ratios (95% CI), among patients switching to BF Spiromax versus continuing on BF Turbuhaler in the matched analysis. *Model did not converge in the asthma group.

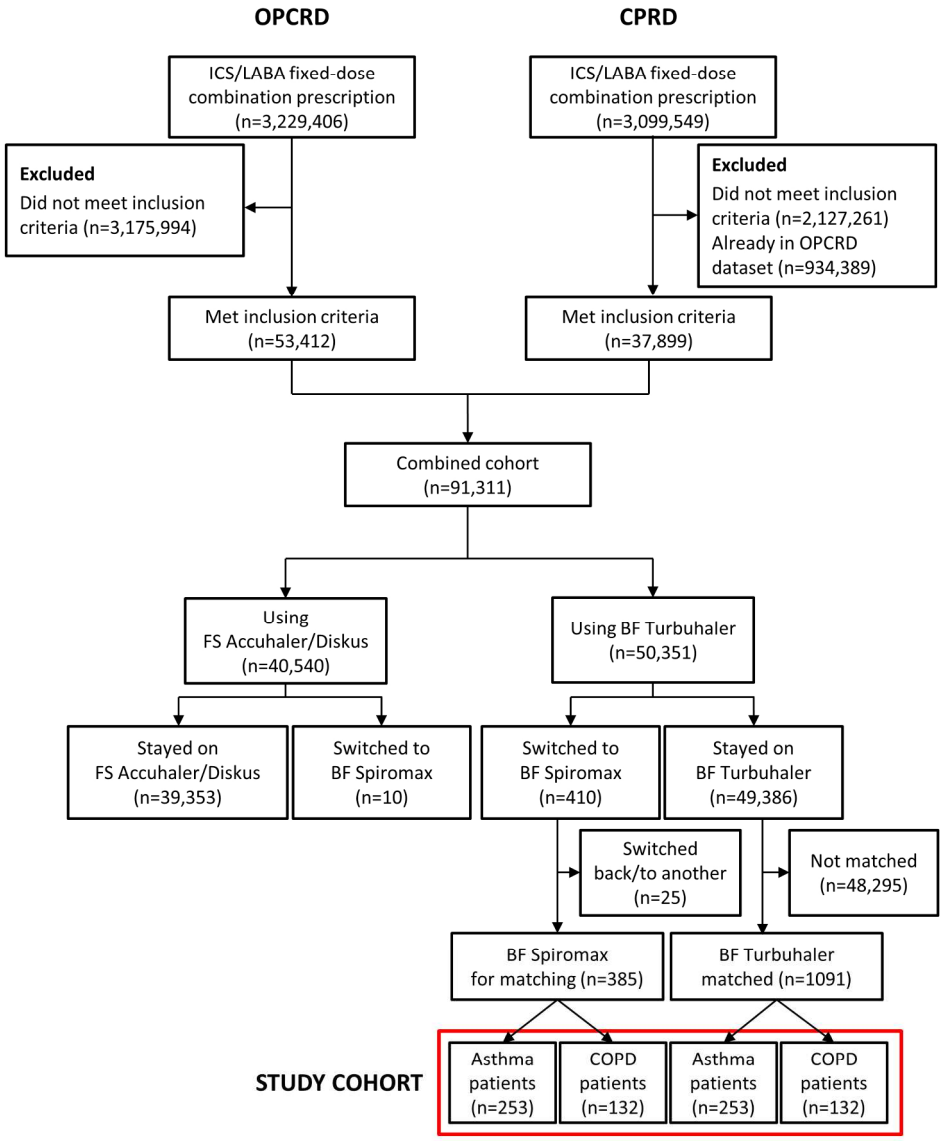
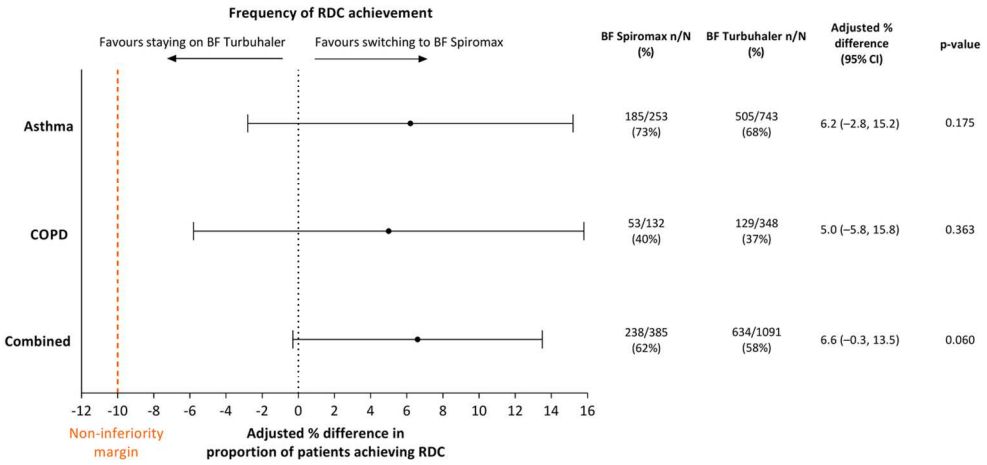


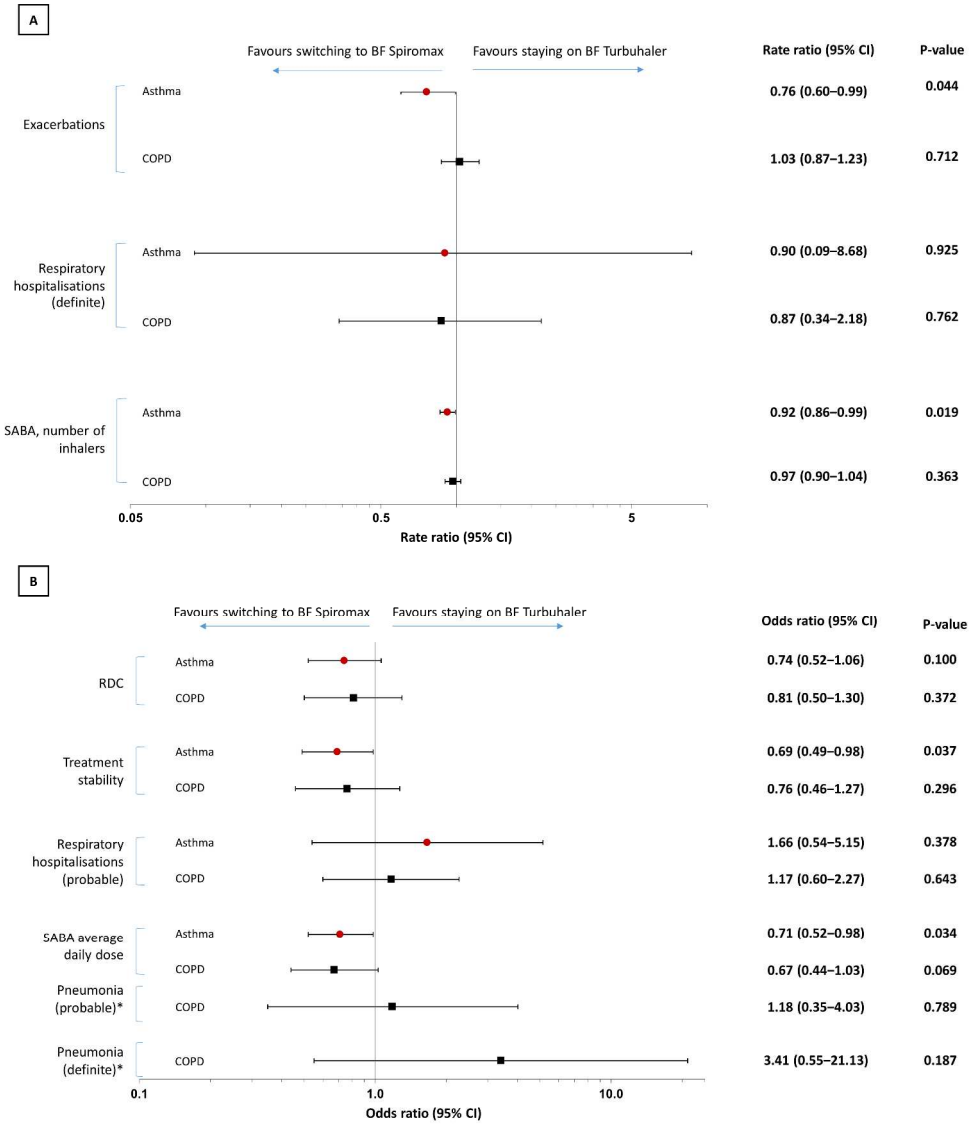
Figure 1. Patient flow diagram (prior to matching)

180x230mm (300 x 300 DPI)



Frequency of achievement of RDC in patients switching to BF Spiromax and those continuing on BF Turbuhaler

120x58mm (300 x 300 DPI)



Clinical outcomes expressed as adjusted conditional (A) rate ratios (95% CI) and (B) odds ratios (95% CI), among patients switching to BF Spiromax versus continuing on BF Turbuhaler in the matched analysis.
*Model did not converge in the asthma group.

338x399mm (300 x 300 DPI)

Supplementary Methods

Matching

Matching was done using the most relevant confounders of the association between the treatment (BF Spiromax vs. BF Turbuhaler) and the primary outcome (achieving risk domain control [RDC]).

Confounders that are unbalanced between the treatment arms can bias associations of interest between the treatment arms and the outcomes. Potential confounders were identified based on a combination of baseline imbalance, bias potential in relation to the primary outcome, as well as expert judgement. Through this, the most relevant confounders were used for direct matching. As it is necessary to limit the number of variables used for direct matching to avoid overly restricting the patient population, variables that do not relevantly affect the association of interest were excluded.

After matching, this approach was repeated in the matched sample to identify any residual confounding, selecting confounders for direct adjustment in the outcome analyses.

Baseline balance

Together with the baseline characterisation, the difference between the arms was quantified using the standardized mean difference (SMD). This measure is not affected by the number of observations in a sample, gives the size of the difference, and, thus, is a better way to judge imbalance than a P-value of a hypothesis test of difference. The SMD was calculated as described below. A SMD of ≤10% was taken as sufficient balance between the arms.

Formulae for standardised difference

Continuous covariate:

$$SDD = \frac{(\overline{x_t} - \overline{x_r})}{\sqrt{\frac{s_t^2 + s_r^2}{2}}},$$

where $\overline{x_t}$, $\overline{x_r}$ denote the sample means and s_t, s_r the standard deviations

Binary Covariate:

$$SDD = \frac{(\widehat{p_t} - \widehat{p_r})}{\sqrt{\frac{\hat{p}_t(1-\hat{p}_t) + \hat{p}_r(1-\hat{p}_r)}{2}}},$$

where $\widehat{p_t}$, $\widehat{p_r}$ denote the proportion of patients in each category

Categorical (>2 categories) Covariate:

$$SDD = \sqrt{(T-C)'S^{-1}(T-C)}$$

where S is a $(k-1) \times (k-1)$ covariance matrix:

$$S = [S_{kl}] = \begin{cases} \frac{\hat{p}_{1k}\,(1-\hat{p}_{1k}) + \hat{p}_{2k\,(1-\hat{p}_{2k})}}{2}, & k = l \\ \frac{\hat{p}_{1k}\,\hat{p}_{1l} + \hat{p}_{2k}\,\hat{p}_{2l}}{2}, & k \neq l \end{cases}$$

$, = (\hat{p}_{12}, \dots, \hat{p}_{1k})'$, $C = (\hat{p}_{22}, \dots, \hat{p}_{2k})'$ and $\hat{p}_{jk} = P\,(category\ k | treatment\ arm\ j)$, $j = 1,2$, $k = 2,3, \dots, k$

Bias potential

Bias potential assesses the degree to which the observed association between the exposure of interest and the outcome is affected by conditioning on another variable. It is also called change-in-estimate. In the case of the primary outcome, a binary indicator for achieving RDC, the definition of bias potential was:

$$Bias\ potential = abs(1 - e^{(\beta_{crude} - \beta_{adjusted})})$$

where β_{crude} = ln(OR) (=natural log of the odds ratio) of exposure from the model without the covariate and β_{crude} = ln(OR) of exposure after adding the covariate to the model. It is called *bias potential* since the bias was estimated without other covariates in the model. To what extent a variable introduces bias into a model will depend on the total model.

A bias potential of ≥2% was considered to indicate a relevant change in the association between the outcome and exposure. Often a cut-off of 5% or even 10% is used to select confounders during model building [44], but a more sensitive cut-off was applied for this study.

The baseline variables with the highest bias potential, that were also insufficiently balanced (SMD >10%), were presented to a panel of clinical experts for the final selection of variables to use for matching.

Matching process

Exact matching for categorical variables and matching within a maximum calliper (maximum distance allowed between a case and a control) for continuous variables was used to match patients, using nearest neighbour variable mixed matching with a match maximum of 3:1 without replacement. Patients in the asthma and COPD groups were matched separately with disease-specific matching criteria.

Mixed matching is a process that utilises more of the data by matching varying numbers of control arm patients to a treatment arm patient. In other words, there will be a cohort of unique patients matched 1:1, another cohort of unique patients matched 2:1, and a third cohort of unique patients matched 3:1. The analyses were conducted using all the matched patients even though some patients had 1 matched control while other patients had 3 matched controls. This imbalance in number of controls matched to cases could introduce residual confounding. Therefore, we verified our assumption that this would not affect the study outcomes through a sensitivity analysis, in which the outcome analyses were also undertaken in the subpopulation of patients in the BF Spiromax arm with exactly 3 matched patients in the BF Turbuhaler arm.

Although the patients in the BF Turbuhaler arm could have multiple records per patient to optimise

the matching process, only one record per patient contributed to the matching.

Matching was repeated 20 times with a different random patient sequence to select the run that resulted in the highest number of matched patients.

Missing data were treated as random and were not imputed. If a selected confounder had more than 20% of missing data, it was not considered as a potential matching variable. If the proportion of missing data was below 20%, the variable was encoded into a categorical variable, adding a category for the observations with missing values, enabling this variable to be used for matching.

Post-matching evaluation

The quality of the matching was evaluated using the same methods used to identify the confounders: standardised difference in combination with bias potential.

To minimise the number of covariates used to adjust the outcome model, a forward assessment of bias potential was used. The identified confounders were entered one-by-one, and the relative change in the effect size of exposure was assessed against the effect size before introducing the variable. If the relative change in effect size was ≥0.02, the variables remained in the model, and the next one was evaluated.

Supplementary Table 1. Patient characteristics in unmatched analysis

Variable	Asthma				COPD			
	BF Spiromax (n=265)	BF Turbuhaler (n=32,071)	P-Value	SMD	BF Spiromax (n=155)	BF Turbuhaler (n=17,315)	P-Value	SMD
Mean (SD) age, years	56.3 (15.5)	50.4 (17.4)	<0.0001	12.1	70.2 (9.1)	69.9 (11.0)	0.0109	3.5
Males, n (%)	121 (45.7)	13,520 (42.2)	<0.0001	5.5	77 (49.7)	9,198 (53.1)	0.5883	0.6
Body mass index, n (%)								
<18.5 kg/m^2	4 (1.6)	395 (1.3)			7 (4.6)	725 (4.2)		
≥18.5 to <25 kg/m^2	68 (27.2)	8,604 (27.8)	<0.0001	5.2	48 (31.8)	5,480 (32.0)	0.0001	5.3
≥25 to <30 kg/m^2	89 (35.6)	10,614 (34.3)			50 (33.1)	5,685 (33.2)		
≥30 kg/m^2	89 (35.6)	11,325 (36.6)			46 (30.5)	5,239 (30.6)		
Smoking status, n (%)								
Non-smoker	129 (49.6)	17,291 (54.2)	0.1366	2.0	18 (11.6)	2,518 (14.6)	<0.0001	10.7
Current smoker	47 (18.1)	5,736 (18.0)			42 (27.1)	4,948 (28.7)		
Ex-smoker	84 (32.3)	8,857 (27.8)			95 (61.3)	9,800 (56.8)		
Comorbidities, n (%)								
Ischaemic heart disease	15 (5.7)	1,945 (6.1)	<0.0001	8.5	29 (18.7)	3,771 (21.8)	0.0021	3.4
Heart failure	1 (0.4)	338 (1.1)	<0.0001	5.7	5 (3.2)	1,115 (6.4)	0.0228	2.2
Diabetes	21 (7.9)	2,297 (7.2)	<0.0001	8.5	20 (12.9)	2,533 (14.6)	0.0273	2.6
Probable pneumonia	1 (0.4)	136 (0.4)	0.6341	0.9	2 (1.3)	298 (1.7)	0.0023	3.5
GERD	41 (15.5)	3,896 (12.1)	0.0001	3.8	25 (16.1)	2,709 (15.6)	0.0030	3.5
Rhinitis	63 (23.8)	6,341 (19.8)	0.2007	0.8	17 (11.0)	1,544 (8.9)	<0.0001	7.2
Charlson Comorbidity Index, n (%)								
0	74 (27.9)	10,394 (32.4)	<0.0001	8.1	102 (65.8)	10,018 (57.9)	0.0002	4.3
1–4	164 (61.9)	19,749 (61.6)			37 (23.9)	5,220 (30.1)		
≥5	27 (10.2)	1,928 (6.0)			16 (10.3)	2,077 (12.0)		
Drug therapy, n (%)								
ICS+LABA	225 (84.9)	26,879 (83.8)			38 (24.5)	6,987 (40.4)		
ICS+LABA+LAMA	11 (4.2)	615 (1.9)	<0.0001	13.0	108 (69.7)	9,244 (53.4)	<0.0001	21.7
ICS+LABA+LAMA+LTRA	4 (1.5)	298 (0.9)			8 (5.2)	625 (3.6)		
ICS+LABA+LTRA	25 (9.4)	4,278 (13.3)			1 (0.6)	459 (2.7)		
Other	0 (0.0)	1 (0.0)			0 (0.0)	0 (0.0)		

SABA average daily dose, n (%)								
0	65 (27.2)	9,929 (34.2)	<0.0001	1.4	27 (18.4)	3,927 (25.7)	0.0003	4.8
>0 to ≤200 µg*	74 (31.0)	8,268 (28.4)			23 (15.6)	3,109 (20.4)		
>200 to ≤400 µg*	57 (23.8)	6,576 (22.6)			37 (25.2)	3,487 (22.8)		
>400 to ≤600 µg*	27 (11.3)	2,237 (7.7)			32 (21.8)	2,524 (16.5)		
>600 µg*	16 (6.7)	2,058 (7.1)			28 (19.0)	2,215 (14.5)		
ICS average daily dose, n (%)								
≤400 µg†	113 (42.6)	17,184 (53.6)	<0.0001	77.9	33 (21.3)	5,886 (34.0)	<0.0001	150.1
>400 to ≤800 µg†	103 (38.9)	10,701 (33.4)			77 (49.7)	7,369 (42.6)		
>800 to ≤1600 µg†	44 (16.6)	3,772 (11.8)			41 (26.5)	3,497 (20.2)		
>1600 µg†	5 (1.9)	414 (1.3)			4 (2.6)	563 (3.3)		
No. of exacerbations in baseline year, n (%)								
0	203 (76.6)	23,095 (72.0)	<0.0001	16.4	59 (38.1)	6,477 (37.4)	<0.0001	9.9
1	45 (17.0)	5,503 (17.2)			46 (29.7)	4,381 (25.3)		
2	12 (4.5)	2,108 (6.6)			16 (10.3)	2,772 (16.0)		
≥3	5 (1.9)	1365 (4.3)			34 (21.9)	3,685 (21.3)		
Disease control using RDC, n (%)	184 (69.4)	19,082 (59.5)	<0.0001	8.7	59 (38.1)	6,477 (37.4)	<0.0001	7.6

*Salbutamol equivalents; †Beclomethasone equivalents.

P-value = p-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate

BF, budesonide/formoterol; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; RDC, risk domain control; SABA, short-acting β_2-agonist; SD, standard deviation; SMD, standardized mean difference

Voorham J, et al. bmjopen-2018-022051: Real-world effectiveness evaluation of budesonide/formoterol Spiromax® for the management of asthma and chronic obstructive pulmonary disease in the United Kingdom

STROBE checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **– The title states that the study is a real-world effectiveness evaluation (Page 1)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **– Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **– Pages 4 and 5**
Objectives	3	State specific objectives, including any prespecified hypotheses **– Page 5**
Methods		
Study design	4	Present key elements of study design early in the paper **– Pages 5 and 6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **– Pages 5 and 6**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **– Pages 5–7** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **– Pages 8–10** *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **– Page 7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **– Page 7**
Bias	9	Describe any efforts to address potential sources of bias **– Pages 8–10**
Study size	10	Explain how the study size was arrived at **– Page 8**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **– Pages 8–10**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **– Pages 8–10**
		(*b*) Describe any methods used to examine subgroups and interactions **– Pages 8–10**
		(*c*) Explain how missing data were addressed **– Online supplement**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **– N/A as this was an observational study based on validated databases that included**

		patients with data for defined time points (Pages 5 and 6) *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **– Page 8**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **– Page 10 and Figure 1**
		(b) Give reasons for non-participation at each stage **– Page 10 and Figure 1**
		(c) Consider use of a flow diagram **– Figure 1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **– Page 10, Table 1, Supplementary Table 1**
		(b) Indicate number of participants with missing data for each variable of interest **– Table 1**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **– A fixed outcome period of 1 year was used (Page 6)**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **– Pages 13 and 14, Table 2**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **– Pages 13 and 14, Figures 2 and 3**
		(*b*) Report category boundaries when continuous variables were categorized **– Pages 13 and 14**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **– N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **– Page 14**
Discussion		
Key results	18	Summarise key results with reference to study objectives **– Pages 14 and 15**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **– Pages 15–17**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **– Page 18**
Generalisability	21	Discuss the generalisability (external validity) of the study results **– Page 18**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **– Page 19**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.