

# A Comparison of the Real-Life Clinical Effectiveness of the Leading Licensed ICS/LABA Combination Inhalers in the Treatment for COPD

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**Introduction:** The Fostair® 100/6 (BDP/FF) pressurized metered-dose inhaler, delivering an extrafine formulation, is licensed for asthma and COPD in the UK. However, its real-life effectiveness for COPD has not been evaluated. This study compared the clinical effectiveness of BDP/FF against other licensed ICS/LABA combination inhalers: the Seretide® Accuhaler® (FP/SAL) and the Symbicort® Turbohaler® (BUD/FF).

**Methods:** A matched historical cohort study was conducted using records of patients with diagnostic codes for COPD from the Optimum Patient Care Research Database (OPCRD). Patients who had received BDP/FF as their first ICS/LABA were matched 1:1 with patients who had received FP/SAL or BUD/FF, resulting in two matched comparisons. Additional analysis was conducted on patients who had never had diagnostic codes for asthma. Noninferiority in terms of the proportion of patients with moderate/severe COPD exacerbations on the different inhalers in the following year was assessed. Noninferiority was achieved if the upper CI limit were  $\leq 1.2$ .

**Results:** This study included 537 and 540 patient pairs in the BDP/FF vs FP/SAL cohort and the BDP/FF vs BUD/FF cohort, respectively. The proportion of patients with COPD exacerbations in the BDP/FF group was not significantly different from either the FP/SAL (68.7% vs 70.2%, AOR 0.89, 95% CI 0.67–1.19) or BUD/FF group (68.5% vs 69.4%, AOR 0.79, 95% CI 0.58–1.08). Noninferiority of BDP/FF in preventing COPD exacerbations was fulfilled in both comparisons. In patients without asthma, BDP/FF was also noninferior to BUD/FF (proportion with COPD exacerbations, 67.8% vs 64.7%, AOR 0.79, 95% CI 0.51–1.1997). Additionally, a significantly lower proportion of patients prescribed BDP/FF had COPD exacerbations than FP/SAL (64.8% vs 73.7%, AOR 0.64 95% CI 0.43–0.96).

**Conclusion:** Initiating ICS/LABA treatment of COPD with extrafine-formulation BDP/FF was noninferior in preventing moderate/severe exacerbations compared to FP/SAL and BUD/FF.

**Keywords:** metered-dose inhaler, dry-powder inhaler, chronic obstructive pulmonary disease, treatment efficacy, cost-effectiveness

## Plain-Language Summary

The Fostair® (BDP/FF) inhaler has been licensed for asthma and chronic obstructive pulmonary disease (COPD) treatment in the UK. The medicine is delivered as very small particles, which helps delivery to the lungs. However, how well BDP/FF works for COPD treatment has been studied only in controlled clinical trials, but not in real-life clinical practice settings. We aimed to assess how well BDP/FF prevents COPD exacerbations compared to other similar products licensed in the UK: Seretide® (FP/SAL) and

Symbicort® (BUD/FF). General practice records stored in the Optimum Patient Care Research Database (OPCRD) were used in this study. The proportion of patients with COPD exacerbations in the year the inhalers were started were compared across the different groups. In patients prescribed BDP/FF, 68.7% experienced exacerbations compared to 70.2% prescribed FP/SAL. In the other comparison, 68.5% and 69.4% of patients prescribed BDP/FF and BUD/FF, respectively, experienced exacerbations. Therefore, prescription of BDP/FF led to comparable prevention of COPD exacerbations compared to prescription of FP/SAL or BUD/FF. Furthermore, BDP/FF was associated with better outcomes than FP/SAL within the group of patients without a previous history of asthma (35.2% vs 26.3% without exacerbations).

## Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by declining lung function associated with high morbidity and health-care burden.<sup>1</sup> In the UK alone, an estimated 1.2 million people have COPD, with a much larger population remaining undiagnosed.<sup>2,3</sup> COPD accounts for 1.4 million general practice (GP) consultations yearly and one in eight emergency attendances.<sup>4</sup>

Inhaled corticosteroid (ICS) is administered to reduce the risk of subsequent COPD exacerbation.<sup>5</sup> Evidence from clinical trials has suggested efficacy of an ICS administered in combination with a long-acting  $\beta$ -agonist (LABA) for patients with moderate/severe COPD.<sup>6,7</sup> The Fostair® 100/6 (BDP/FF) pressurized metered-dose inhaler (pMDI) has been licensed for patients with severe COPD (Forced Expiratory Volume in 1 second [FEV<sub>1</sub>] <50% predicted normal) and a history of exacerbations who have significant symptoms, despite regular therapy with long-acting bronchodilators.<sup>8</sup> Other licensed ICS/LABA combination inhalers for COPD include the Seretide® Accuhaler® 500/50 (FP/SAL) dry-powder inhaler (DPI) and the Symbicort® Turbohaler® 200/6 and 400/12 (BUD/FF) DPI. BDP/FF, FP/SAL, and BUD/FF were the most commonly used ICS/LABA combination inhalers in the UK at the inception of this study.

The extrafine formulation of BDP/FF results in greater deposition to smaller airways, allowing for lower dosage for similar effects, thus subsequently reducing potential side effects compared to non-extrafine inhaler formulations.<sup>9–12</sup> The efficacy of BDP/FF has been previously demonstrated in randomized controlled trials (RCTs). The FUTURE trial showed BDP/FF to be equivalent to FP/SAL in improving breathlessness scores and superior at improving FEV<sub>1</sub> and St

George's Respiratory Questionnaire (SGRQ) scores, despite lower ICS dosage.<sup>13</sup> Another trial also showed BDP/FF to be noninferior to BUD/FF in improving predose morning FEV<sub>1</sub>.<sup>11</sup> Complementing the results from RCTs, a study in a real-life setting demonstrated BDP/FF to be noninferior to FP/SAL in preventing symptom exacerbation in patients with asthma at equal or lower dosage.<sup>14</sup> However, there is a lack of studies investigating the effectiveness of BDP/FF in COPD patients. Investigation of the clinical effectiveness of each ICS/LABA may be beneficial in guiding treatment of COPD patients requiring an ICS/LABA combination inhaler.

The current study aimed to assess the noninferiority of initiating BDP/FF compared to FP/SAL and BUD/FF in terms of proportion of patients free from moderate/severe COPD exacerbations.

## Methods

### Study Design

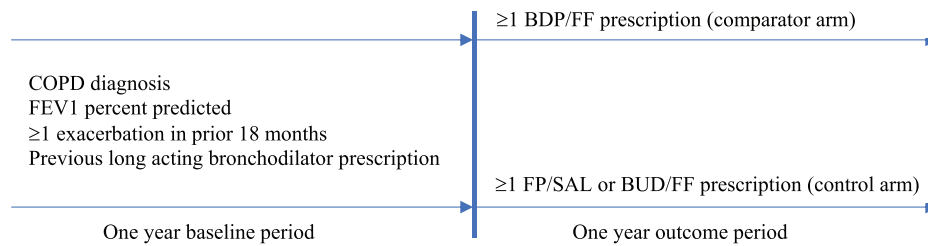
This was a historical matched cohort study encompassing a 1-year baseline period prior to the index date for characterization of patients for matching and a 1-year outcome period after the index date to identify outcomes (Figure 1). The index date was defined as the date of first prescription of a BDP/FF pMDI, FP/SAL DPI, or BUD/FF DPI.

### Data Source

Data for this study were obtained from the Optimum Patient Care Research Database (OPCRD; [www.opcrd.co.uk](http://www.opcrd.co.uk)), which comprises medical records of >7 million patients from over 700 GP practices across the UK.<sup>15</sup> The OPCRD is approved by the Health Research Authority of the UK National Health Service for clinical research use (Research Ethics Committee reference 15/EM/0150).

### Medication Studied

ICS/LABA combination inhalers with sufficient data in the OPCRD at the inception of this study — BDP/FF, FP/SAL, and BUD/FF — were chosen for this study. The BDP/FF investigated in this study was Fostair®, an ICS/LABA combination inhaler, containing 100  $\mu$ g beclometasone dipropionate and 6  $\mu$ g formoterol fumarate per inhalation in a pMDI device.<sup>16</sup> The FP/SAL investigated in this study was the Seretide® Accuhaler® 500 DPI, containing 500  $\mu$ g fluticasone propionate and 50  $\mu$ g salmeterol xinafoate per inhalation in a DPI device.<sup>17</sup> The BUD/FF investigated was the Symbicort® Turbohaler®, containing either 200  $\mu$ g budesonide and 6  $\mu$ g formoterol fumarate dihydrate (Symbicort 200/



**Figure 1** Study design.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; BDP/FF, beclomethasone and formoterol fixed-dose combination inhaler; FP/SAL, fluticasone propionate and salmeterol fixed-dosed combination inhaler; BUD/FF, budesonide and formoterol fixed-dose combination inhaler.

6) or 400 µg budesonide and 12 µg formoterol fumarate dihydrate (Symbicort 400/12) per inhalation in a DPI device.<sup>18,19</sup> As the recommended dosage for BUD/FF is two puffs twice daily of 200/6 or one puff of 400/12, we assumed equal BUD/FF dosage in both groups and thereby combined them.

## Inclusion Criteria

Inclusion and exclusion criteria and patient flow are presented in Table 1. Patients included were ≥35 years old with COPD diagnosis confirmed by spirometry reading (FEV<sub>1</sub>/Forced Vital Capacity [FVC] <0.7) and had at least one moderate to severe exacerbation within the 18 months prior to the index. They must also have had available data encompassing the entire baseline and outcome periods, had one or more prescriptions of LABA, LAMA, or unlicensed ICS/LABA combination inhaler in the 2 years prior to the index, and had received two or more prescriptions of the same licensed ICS/LABA combination inhaler during the outcome period (including initial prescription). Patients were excluded if they were recorded in the database to be nonsmoking or if there were no documentation of smoking status.

Patients were included if they had postbronchodilator FEV<sub>1</sub>% predicted <55% at any time prior to index. As a typical bronchodilator response is around 12%, patients with FEV<sub>1</sub>% predicted of 55% are expected to reflect patients with trough FEV<sub>1</sub> predicted of 50% (reflecting the indication for BDP/FF).

Alternative comparison groups were selected excluding patients who had ever had a diagnostic code for asthma. This alternative comparison group was selected to investigate patients who had been treated with ICS/LABA specifically for COPD and not for asthma.

## Outcome Assessments

The primary outcome of this study was the proportion of patients with moderate/severe COPD exacerbations,

defined as any of: 1) unscheduled respiratory related hospital admission or A&E attendance, 2) acute OCS prescriptions (definition provided in the [online supplementary material](#)), or 3) antibiotic prescriptions with a respiratory consultation in the 1-year outcome period.

## Matching

Patients on BDP/FF pMDI were matched 1:1 with patients on FP/SAL and patients on BUD/FF, resulting in two matched comparisons. Patients who had been prescribed more than one type of ICS/LABA combination inhalers on separate occasions were selected only once during the comparison. The selected index patient event was the prescription of BDP/FF to maximize the number of matched pairs. Variables for matching were selected based on the standardized difference and bias potential on the proportion of patients with an exacerbation between the treatment arms and clinical relevance. The final matching variables consisted of age, smoking status, FEV<sub>1</sub>% predicted, and number of exacerbations during the baseline year. Patients in the additional analysis, excluding patients with an asthma diagnosis, were matched in the same manner.

## Statistical Analysis

Based on a previous study,<sup>20</sup> if there is a true difference in AOR in favor of BDP/FF compared to the standard difference of 1.2, 552 patients in each group are required to be 80% sure that the upper limit of a one-sided 97.5% CI will exclude a difference in favor of the predefined noninferiority margin of 20%.

Analysis was performed with SPSS version 23, SAS version 9.3, Stata SE version 14 (StataCorp, College Station, TX, USA), and Microsoft Office Excel 2013, as appropriate. Forest plots were generated using DistillerSR, an online tool from Evidence Partners.

Standardized mean difference (SMD) was calculated to quantify differences in baseline characteristics between

**Table 1** Patient Flow and Inclusion and Exclusion Criteria

Patient Numbers	Inclusion/Exclusion Criteria	Number Excluded
3,460,270	All patients in the OPCR	NA
BDP/FF 30,933 FP/SAL 34,842 BUD/FF 97,997	Inclusion: initiated on licensed ICS/LABA combination inhaler	3,296,498
BDP/FF 6,744 FP/SAL 22,854 BUD/FF 30,819	Inclusion: COPD diagnosis, FEV <sub>1</sub> /FVC<0.7	BDP/FF 24,159 FP/SAL 11,988 BUD/FF 67,178
BDP/FF 3,586 FP/SAL 15,678 BUD/FF 22,275	Inclusion: 1 year of data prior to and after initiation of licensed ICS/LABA combination inhaler	BDP/FF 3,188 FP/SAL 7,176 BUD/FF 8,544
BDP/FF 3,573 FP/SAL 15,637 BUD/FF 22,150	Inclusion: aged 35 years or older	BDP/FF 13 FP/SAL 41 BUD/FF 125
BDP/FF 2,999 FP/SAL 13,645 BUD/FF 18,629	Inclusion: at least two prescriptions of licensed ICS/LABA combination inhaler in the outcome period (including index date)	BDP/FF 574 FP/SAL 1,992 BUD/FF 3,521
BDP/FF 2,405 FP/SAL 11,339 BUD/FF 15,805	Inclusion: no change of ICS/LABA combination inhaler in outcome period	BDP/FF 594 FP/SAL 2,306 BUD/FF 2,824
BDP/FF 1,550 FP/SAL 7,929 BUD/FF 8,577	Inclusion: At least one prescription of LABA and/or LAMA and/or unlicensed ICS/LABA combination inhaler prior to index date	BDP/FF 855 FP/SAL 3,410 BUD/FF 7,228
BDP/FF 1,065 FP/SAL 5,640 BUD/FF 5,969	Inclusion: At least one exacerbation in the prior 18 months	BDP/FF 485 FP/SAL 2,289 BUD/FF 2,608
BDP/FF 573 FP/SAL 3,628 BUD/FF 3,669	Inclusion: FEV <sub>1</sub> <55% predicted recorded ever	BDP/FF 492 FP/SAL 2,012 BUD/FF 2,300
BDP/FF 549 FP/SAL 3,416 BUD/FF 3,419	Exclusion: documented nonsmoker or no documented smoking status	BDP/FF 24 FP/SAL 212 BUD/FF 250
BDP/FF 549 FP/SAL 3,374 BUD/FF 3,001	Exclusion: duplicate patients <sup>a</sup>	BDP/FF 0 FP/SAL 42 BUD/FF 418

**Notes:** <sup>a</sup>Patients prescribed more than one ICS/LABA combination inhalers were assigned to the BDP/FF group.

compared treatment groups. An SMD  $\geq 10$  indicated sufficient imbalance between the groups. SMD was utilized over *p*-value, as it is unaffected by sample size and is thus a better way to judge imbalance.

### Primary Outcome Analysis

Adjusted proportions of patients within each treatment group recording any exacerbations in the outcome period

was calculated using a generalized linear model with binomial distribution and logit link (logistic regression). Conditional logistic regression analysis was performed on the matched data set, taking matching into account for matched pairs.

Selection of factors for adjustment started with a model with exposure as the only explanatory variable. Variables were added one by one from the highest individual bias

potential and kept in the model if there was a change in estimate of at least 2% relative to the prior model.

Noninferiority of BDP/FF pMDI was achieved if the upper bound of the 95% CI for odds of patients reporting COPD exacerbations was no more than 20% higher than the odds in the comparator groups (ie, the higher CI was <1.20). The noninferiority limit was predetermined based on a study assessing COPD as the outcome.<sup>21</sup> Superiority of BDP/FF was then claimed if the proportion was significantly lower at  $p=0.05$ .

## Ethics

This study complied with all local and international laws and regulations, including ICH E6 guidelines for Good Clinical Practices, and governed by the Anonymous Data Ethics Protocols and Transparency (ADEPT) committee. This study was registered on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) database (EUPAS9142), and the study protocol was approved by the ADEPT committee (ADEPT1016).

## Results

### Patient Demographics

After applying the inclusion and exclusion criteria, 549, 3374, and 3001 patients prescribed BDP/FF pMDI, FP/SAL DPI, and BUD/FF DPI respectively, were identified. Unmatched background demographics for these subjects are presented in [Table S1](#) of the [online supplementary material](#). Following matching, the final study population consisted of 537 pairs of patients in the BDP/FF pMDI vs FP/SAL DPI cohort and 540 pairs in the BDP/FF pMDI vs BUD/FF DPI cohort. Matched baseline characteristics of both cohorts are presented in [Table 2](#). Demographic characteristics were mostly balanced between groups in both pairs; however, fewer patients in the BDP/FF groups had been prescribed SABA compared to the FP/SAL (75.4% vs 83.2%) or BUD/FF (75.6% vs 82.2%) groups. The BDP/FF group also had more patients with modified Medical Research Council (mMRC) dyspnea scores of 3 or 4 (indicating severe breathlessness) than the FP/SAL group (25.2% vs 21.3%), but fewer than the BUD/FF group (24.7% vs 25.8%). Proportions of patients who had moderate/severe COPD exacerbations were 91.4% and 91.1% in each matched cohort, respectively. The exploratory analysis cohort (subjects without history of asthma diagnosis) consisted of 315 and 314 pairs of subjects in the respective matched cohorts. Baseline characteristics for patients in the exploratory

analysis cohort are presented in [Table S2](#) of the [online supplementary material](#).

### Prevention of COPD Exacerbations Patients with Asthma Diagnosis Included

In the BDP/FF vs FP/SAL matched pair, the proportions of patients who had at least 1 COPD exacerbation were 68.7% and 70.2% respectively (AOR 0.89; 95% CI 0.67–1.19). The proportions of patients in the BDP/FF vs BUD/FF pair were 68.5% and 69.4% respectively (AOR 0.79; 95% CI 0.58–1.08). As the upper limits of the 95% CI in both pairs were lower than the pre-defined noninferiority margin of 1.2, BDP/FF was noninferior to both FP/SAL and BUD/FF in preventing subsequent exacerbations ([Figure 2](#)). Unadjusted OR are provided in the [online supplementary material](#) ([Table S3](#)).

### Patients with Asthma Diagnosis Excluded

Among patients who never had an asthma diagnosis, proportions of those prescribed BDP/FF and BUD/FF who had at least one COPD exacerbation in the outcome period were 67.8% vs 64.7%, respectively (AOR 0.79, 95% CI 0.51–1.1997), thus also fulfilling the noninferiority criterion for prevention of COPD. However, in addition to being noninferior, BDP/FF was also superior to FP/SAL within this comparison group (64.8% vs 73.7%, AOR 0.64, 95% CI 0.43–0.96).

## Discussion

### Summary of Findings

In this real-life observational study, the Fostair® 100/6 (extrafine formulation BDP/FF) pMDI was found to be noninferior to both the Seretide® Accuhaler® 500/50 (FP/SAL) DPI and the Symbicort® Turbohaler® 200/6 (two puffs twice daily dose) and 400/12 (one puff twice daily dose) (BUD/FF) DPI in terms of the proportion of patients experiencing a COPD exacerbation within a year since treatment initiation.

To the best of our knowledge, this is the first study to evaluate the clinical effectiveness of BDP/FF pMDI compared with other ICS/LABA combination inhalers for management of COPD within a real-life setting. This study adds evidence to the current literature, which has established the efficacy of extrafine formulation BDP/FF for the management of COPD via RCTs.<sup>11, 13, 22,23</sup> The observed efficacy of BDP/FF may also be partly due to the extrafine formulation, which has been demonstrated to be advantageous over fine-particle ICS in both asthma<sup>24</sup> and COPD.<sup>25</sup>



**Table 2** Matched Baseline Patient Characteristics

		BDP/FF vs FP/SAL			BDP/FF vs BUD/FF		
		BDP/FF n=537	FP/SAL n=537	SMD	BDP/FF n=540	BUD/FF n=540	SMD
Sex	Male	292 (54.4)	313 (58.3)	7.9	295 (54.6)	293 (54.3)	0.7
Age (years) <sup>a</sup>	≥35-<45	7 (1.3)	7 (1.3)	0	10 (1.9)	10 (1.9)	0
	≥45-<55	39 (7.3)	39 (7.3)		41 (7.6)	41 (7.6)	
	≥55-<65	115 (21.4)	115 (21.4)		113 (20.9)	113 (20.9)	
	≥65	376 (70.0)	376 (70.0)		376 (69.6)	376 (69.6)	
BMI (kg/m <sup>2</sup> )	n (% not missing)	537 (100)	536 (99.8)	5.5	540 (100)	538 (99.6)	9.6
	<18.5	30 (5.6)	31 (5.8)		30 (5.6)	30 (5.6)	
	≥18.5-<25	180 (33.5)	191 (35.6)		179 (33.1)	200 (37.2)	
	≥25-<30	192 (35.8)	179 (33.4)		193 (35.7)	171 (31.8)	
	≥30	135 (25.1)	135 (25.2)		138 (25.6)	137 (25.5)	
Patient-reported smoking status <sup>a</sup>	Nonsmoker	19 (3.5)	19 (3.5)	0	17 (3.1)	17 (3.1)	0
	Current smoker	224 (41.7)	224 (41.7)		227 (42.0)	227 (42.0)	
	Ex-smoker	294 (54.7)	294 (54.7)		296 (54.8)	296 (54.8)	
Baseline SABA prescription(s)	0	132 (24.6)	90 (16.8)	<b>23.9</b>	132 (24.4)	96 (17.8)	<b>18.9</b>
	1	38 (7.1)	36 (6.7)		38 (7.0)	43 (8.0)	
	2-4	82 (15.3)	110 (20.5)		81 (15.0)	93 (17.2)	
	5-10	141 (26.3)	169 (31.5)		145 (26.9)	173 (32.0)	
	≥11	144 (26.8)	132 (24.6)		144 (26.7)	135 (25.0)	
	SAMA/SABA combination prescriptions	Yes	7 (1.3)	53 (9.9)	<b>38.0</b>	7 (1.3)	41 (7.6)
ICS combination-inhaler prescriptions	0	187 (34.8)	173 (32.2)	<b>10.9</b>	184 (34.1)	242 (44.8)	<b>27.7</b>
	1	26 (4.8)	23 (4.3)		26 (4.8)	29 (5.4)	
	2-4	51 (9.5)	59 (11.0)		53 (9.8)	65 (12.0)	
	5-10	146 (27.2)	135 (25.1)		147 (27.2)	110 (20.4)	
	≥11	127 (23.6)	147 (27.4)		130 (24.1)	94 (17.4)	
	Total ICS dosage (µg BDP equivalent)	0-249	235 (43.8)	221 (41.2)	7.1	235 (43.5)	275 (51.0)
250-499		148 (27.6)	145 (27.0)		149 (27.6)	158 (29.3)	
500+		154 (28.7)	171 (31.8)		156 (28.9)	106(19.7)	
LAMA prescriptions	Yes	340 (63.3)	323 (60.1)	6.5	342 (63.3)	285 (52.8)	<b>21.5</b>
LABA prescriptions	Yes	63 (11.7)	79 (14.7)	8.8	64 (11.9)	127 (23.5)	<b>30.9</b>
Maintenance OCS	Yes	36 (6.7)	25 (4.7)	8.9	37 (6.9)	22 (4.1)	<b>12.2</b>
Asthma diagnosis ever <sup>b</sup>	Yes	218 (40.6)	197 (36.7)	8.0	220 (40.7)	230 (42.6)	3.8
Active anxiety/depression diagnosis	Yes	134 (25.0)	123 (22.9)	4.8	135 (25.0)	105 (19.4)	<b>13.4</b>
Charlson Comorbidity Index	0-2	343 (63.9)	347 (64.6)	2.2	345 (63.9)	349 (64.6)	9.1
	3-4	134 (25.0)	129 (24.0)		135 (25.0)	145 (26.9)	
	5+	60 (11.2)	61 (11.4)		60 (11.1)	46 (8.5)	
Baseline moderate/severe COPD exacerbations <sup>a,c</sup>	0	46 (8.6)	46 (8.6)	0	48 (8.9)	48 (8.9)	0
	1	159 (29.6)	159 (29.6)		162 (30.0)	162 (30.0)	
	2	139 (25.9)	139 (25.9)		138 (25.6)	138 (25.6)	
	3	75 (14.0)	75 (14.0)		75 (13.9)	75 (13.9)	
	4+	118 (22.0)	118 (22.0)		117 (21.7)	117 (21.7)	
	Lowest percentage predicted FEV <sub>1</sub> <sup>a</sup>	<20%	24 (4.5)	24 (4.5)	0	24 (4.4)	24 (4.4)
20%-<30%		98 (18.2)	98 (18.2)		96 (17.8)	96 (17.8)	
30%-<40%		159 (29.6)	159 (29.6)		161 (29.8)	161 (29.8)	
40% -<55%		256 (47.7)	256 (47.7)		259 (48.0)	259 (48.0)	

(Continued)

**Table 2** (Continued).

		BDP/FF vs FP/SAL			BDP/FF vs BUD/FF		
		BDP/FF n=537	FP/SAL n=537	SMD	BDP/FF n=540	BUD/FF n=540	SMD
mMRC score	n (% not missing)	317 (59.0)	310 (57.7)	<b>19.9</b>	315 (58.3)	267 (49.4)	<b>17.2</b>
	mMRC 0	37 (11.7)	23 (7.4)		37 (11.7)	21 (7.9)	
	mMRC 1	105 (33.1)	121 (39.0)		106 (33.7)	101 (37.8)	
	mMRC 2	95 (30.0)	100 (32.3)		94 (29.8)	76 (28.5)	
	mMRC 3	66 (20.8)	52 (16.8)		64 (20.3)	61 (22.8)	
	mMRC 4	14 (4.4)	14 (4.5)		14 (4.4)	8 (3.0)	

**Notes:** Numbers presented as n (%). SMD values >10 (indicating sufficient imbalance between comparison groups) are emphasized in bold. <sup>a</sup>Matching variable. <sup>b</sup>Based on presence of QOF diagnosis code for asthma. <sup>c</sup>Occurrence of any one of: 1) COPD-related unscheduled hospital admission/A&E attendance, 2) an acute course of oral steroid, or 3) antibiotics prescribed with lower respiratory consultation.

**Abbreviations:** SMD, standardised mean difference; SABA, short-acting  $\beta$ -agonist; SAMA, short-acting muscarinic antagonist; LAMA, long-acting muscarinic antagonist; LABA, long-acting  $\beta$ -agonist; OCS, oral corticosteroid.

The National Institute for Health and Care Excellence (NICE) guidelines for COPD recommend consideration of ICS/LABA in patients with features of asthma or a higher blood-eosinophil count.<sup>26</sup> This study showed that in a real-life setting, BDP/FF has an advantage over FP/SAL in COPD patients without asthma.

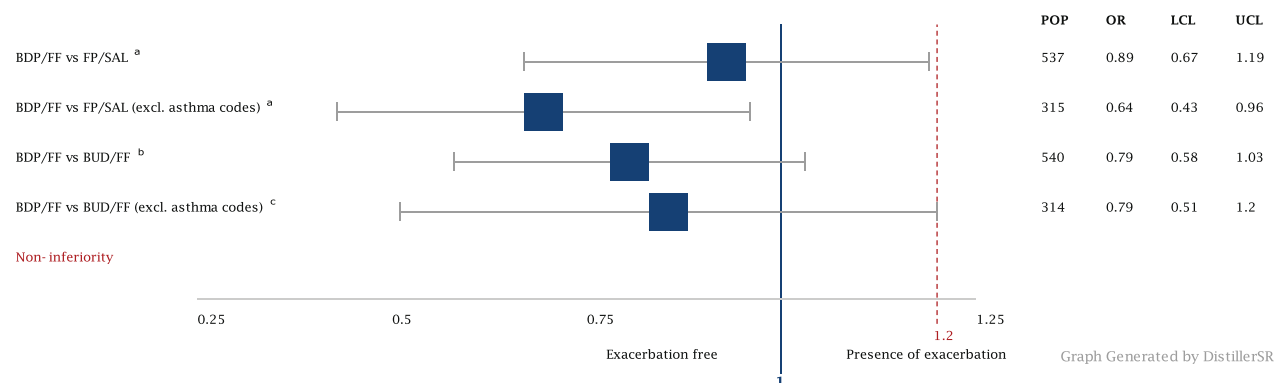
## Strengths and Weaknesses

The current study investigated the effectiveness of BDP/FF within a real-life observational setting. RCTs employ inclusion and exclusion criteria to ensure high internal validity for the investigation of the investigational products' efficacy at the cost of their external generalizability.<sup>27</sup> Real-life studies complement RCTs by enabling investigation on a wider range of subjects, including those typically excluded in RCTs. Therefore, our results may be more representative of patients managed in real-life health-care practice.<sup>28</sup>

Regardless, this study's inclusion criteria reflected the population of COPD patients indicated for BDP/FF, thus supporting the findings from previous RCTs with real-life evidence.<sup>7,11</sup>

Another strength of this study is the observation of outcomes of initiating ICS/LABA-combination inhalers over a 1-year outcome period. Therefore, any transient or seasonal changes that may have affected outcomes were minimized.

The limitation of this study is inherent to its nature as a historical study. Despite extensive quality control and validation, records collected in the OPCRCD were not initially collected for research, but for routine clinical purposes. As such, some degree of inaccuracy and incompleteness may be present. Also inherent to retrospective studies is the inability to control for potential confounders and variables not recorded in the database.



**Figure 2** Odds ratios for COPD exacerbation between BDP/FF and FP/SAL or BUD/FF.

**Notes:** <sup>a</sup>Adjusted for baseline ICS/LABA combination-inhaler prescriptions, baseline SABA prescriptions, baseline SAMA/SABA prescriptions, and active anxiety/depression. <sup>b</sup>Adjusted for theophylline prescription, ischemic heart disease diagnosis, and LTRA prescriptions. <sup>c</sup>Adjusted for SABA daily dose, ICS prescriptions, hypertension, and diabetes diagnosis.

**Abbreviations:** POP, population size; OR, odds ratio; LCL, lower confidence interval; UCL, upper confidence interval.

After applying all inclusion and exclusion criteria, the number of matched pairs in both comparison groups (n=537 and 540) fell short of the number required to be 80% sure that the upper limit of a one-sided 97.5% CI will exclude a difference in favor of the predefined noninferiority margin of 20%. However, the upper bound of the CIs of both comparison groups still fell under 1.20. We used different adjustment variables for each comparison pair in our analysis for the OR for COPD exacerbation. This was conducted as each matched comparison pair was drawn from different patient populations. However, this may have included a risk of overfitting to our statistical models.

As data on medication usage were not captured in the OPCR, the current study was unable to control completely for adherence to prescribed ICS/LABA in this study. It is well established that despite its impact on the outcome of inhaler treatment, poor adherence is common among asthma and COPD patients.<sup>30,31</sup> Therefore, future observational studies evaluating the effectiveness of inhalers might consider stratifying patients by their adherence to their prescribed ICS/LABA inhalers. A possible proxy for the measurement of adherence from clinical records includes medication possession ratio, defined as the ratio between the actual and expected number of medications prescribed.<sup>30–32</sup>

The current study was unable to account for proper use and handling of inhaler devices, which are vital for optimal delivery of drugs to the lungs.<sup>33</sup> Poor inhaler technique is known to be very common among patients with COPD, especially in a real-life setting.<sup>34–36</sup> Even though BDP/FF is now licensed with a DPI device, this study analyzed the real-world performance of an extrafine-formulation BDP/FF pMDI. Regardless, this study shows that in a real-life setting, where imperfect inhaler-handling techniques might exist, in addition to the potential imperfect adherence to therapy, the BDP/FF pMDI was not inferior to FP/SAL or BUD/FF DPI.

Lastly, despite the noninferiority and superiority observed when comparing BDP/FF against BUD/FF and FP/SAL in the exploratory analysis group of patients without asthma, further investigation is required, as this exploratory group was not sufficiently powered for a non-inferiority analysis.

## Future Studies

COPD is a complex disorder with multiple underlying phenotypes that may respond differently to therapy.<sup>37</sup> In this study, we observed differential responses to BDP/FF compared to FP/SAL among COPD patients without

asthma. Further investigation on the differential responses to FDC ICS/LABA by other phenotypic markers, such as peripheral blood eosinophil level is of interest.

The scope of our current study was limited to FDC ICS/LABA licensed for COPD in the UK at the time of this study's conception. Future studies may be conducted to repeat our analyses for comparison of BDP/FF with other licensed ICS/LABA combinations, such as FF/Vilanterol FDC (Relvar Ellipta). Our current study also focused on the comparative effectiveness of BDP/FF pMDI. Drug tolerability for BDP/FF pMDI may also be considered for the outcome of subsequent studies.

## Conclusion

This study showed that in a real-life practice setting, the extrafine-formulation BDP/FF pMDI was found to be non-inferior to both FP/SAL DPI and BDP/FF DPI in terms of the proportion of patients with COPD exacerbations within 1-year after ICS/LABA combination/inhaler prescription. Lastly, within patients without a history of asthma, our results suggested that initiation of BDP/FF may be associated with a lower proportion of patients with subsequent COPD exacerbations compared to initiation with FP/SAL.

## Abbreviations

BDP, beclometasone dipropionate; BUD, budesonide; COPD, chronic obstructive pulmonary disease; DPI, dry-powder inhaler; ENCePP, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; ERS, European Respiratory Society; FEV<sub>1</sub>, forced expiratory volume in 1 second; FF, formoterol; GOLD, Global Initiative for Chronic Obstructive Disease; GP, general practitioner; ICS, inhaled corticosteroid; LABA, long-acting  $\beta$ -agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; OPCR, Optimum Patient Care Research Database; pMDI, pressurized metered-dose inhaler; SABA, short-acting  $\beta$ -agonist; SAL, salbutamol; SAMA, short-acting muscarinic antagonist.

## Data-Sharing Statement

All relevant data are within the paper and its Supporting Information files. The data set supporting the conclusions of this article was derived from the UK Optimum Patient Care Research Database ([www.opcrd.co.uk](http://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 OPCR 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).

## Ethics Approval

This study was approved by the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee, the independent scientific advisory committee for the OPCRd commissioned by the Respiratory Effectiveness Group. The study was designed, implemented, and registered in accordance with the criteria of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (registration EUPAS9142).

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## Author Contributions

The overall conduct of this study was supervised by DBP. All authors made a significant contribution to the work reported, whether is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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## Disclosure

David Price has board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Napp, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, and Teva Pharmaceuticals, consultancy agreements with 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) from AKL Research and Development, AstraZeneca, Boehringer Ingelheim, British

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## References

- Price D, Chisholm A, Ryan D, Crockett A, Jones R. The use of roflumilast in COPD: a primary care perspective. *Primary Care Respiratory j.* 2010;19(4):342–351. doi:10.4104/pcrj.2010.0066
- Chronic obstructive pulmonary disease (COPD) statistics. Available from: <https://statistics.blf.org.uk/copd>. Accessed March 2018.
- Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Available from: <https://www.nice.org.uk/guidance/cg101>. Accessed March 2018.
- Stockton-on-tees Borough Council. *Joint Strategic Needs Assessment*. 2009.
- Price D, Yawn B, Brusselle G, Rossi A. Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. *Primary Care Respiratory j.* 2013;22(1):92–100. doi:10.4104/pcrj.2012.00092
- Price D, West D, Brusselle G, et al. Management of COPD in the UK primary-care setting: an analysis of real-life prescribing patterns. *Int J Chron Obstruct Pulmon Dis.* 2014;9:889–904. doi:10.2147/COPD.S62750
- Nannini LJ, Poole P, Milan SJ, Kesterton A. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease. *Cochrane Database Systematic Reviews.* 2013;8:Cd006826.
- EMC. Fostair 100/6 inhalation solution. Available from: <https://www.medicines.org.uk/emc/product/6318/smpc>. Accessed March 15, 2018.
- Scichilone N, Battaglia S, Sorino C, et al. Effects of extra-fine inhaled beclomethasone/formoterol on both large and small airways in asthma. *Allergy.* 2010;65(7):897–902. doi:10.1111/j.1398-9995.2009.02306.x
- Scichilone N, Benfante A, Morandi L, Bellini F, Papi A. Impact of extrafine formulations of inhaled corticosteroids/long-acting beta-2 agonist combinations on patient-related outcomes in asthma and COPD. *Patient Relat Outcome Meas.* 2014;5:153–162.
- Calverley PM, Kuna P, Monso E, et al. Beclomethasone/formoterol in the management of COPD: a randomised controlled trial. *Respir Med.* 2010;104(12):1858–1868. doi:10.1016/j.rmed.2010.09.008
- Vehring R, Lechuga-Ballesteros D, Joshi V, Noga B, Dwivedi SK. Cosuspensions of microcrystals and engineered microparticles for uniform and efficient delivery of respiratory therapeutics from pressurized metered dose inhalers. *ACS J Surfaces Colloids.* 2012;28(42):15015–15023. doi:10.1021/la302281n
- Singh D, Nicolini G, Bindi E, et al. Extrafine beclomethasone/formoterol compared to fluticasone/salmeterol combination therapy in COPD. *BMC Pulm Med.* 2014;14:43. doi:10.1186/1471-2466-14-43
- Price D, Small I, Haughney J, et al. Clinical and cost effectiveness of switching asthma patients from fluticasone-salmeterol to extra-fine particle beclomethasone-formoterol: a retrospective matched observational study of real-world patients. *Primary Care Respiratory j.* 2013;22(4):439–448. doi:10.4104/pcrj.2013.00088
- OPCRD. The Optimum Patient Care Research Database (OPCRD). Available from: <https://opcrd.co.uk/>. Accessed June 2018.
- EMC. Fostair 100/6 inhalation solution. Available from: <https://www.medicines.org.uk/emc/medicine/21006/SPC/Fostair+100+6+inhalation+solution/>. Accessed January 2016.
- EMC. Seretide 100, 250, 500 accuhaler. Available from: <https://www.medicines.org.uk/emc/medicine/2317>. Accessed January 2016.
- EMC. Symbicort turbohaler 200/6 inhalation powder. Available from: <https://www.medicines.org.uk/emc/medicine/4821>. Accessed January 2016.
- EMC. Symbicort turbohaler 400/12, inhalation powder. Available from: <https://www.medicines.org.uk/emc/medicine/11882>. Accessed January 2016.
- Hagedorn C, Kassner F, Banik N, Ntampakas P, Fielder K. Influence of salmeterol/fluticasone via single versus separate inhalers on exacerbations in severe/very severe COPD. *Respir Med.* 2013;107(4):542–549. doi:10.1016/j.rmed.2012.12.020
- Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med.* 2014;371(14):1285–1294. doi:10.1056/NEJMoa1407154
- Wedzicha JA, Singh D, Vestbo J, et al. Extrafine beclomethasone/formoterol in severe COPD patients with history of exacerbations. *Respir Med.* 2014;108(8):1153–1162. doi:10.1016/j.rmed.2014.05.013

23. Singh D, Vezzoli S, Petruzzelli S, Papi A. The efficacy of extrafine beclomethasone dipropionate-formoterol fumarate in COPD patients who are not “frequent exacerbators”: a post hoc analysis of the FORWARD study. *Int J Chron Obstruct Pulmon Dis*. 2017;12:3263–3271. doi:10.2147/COPD.S141416
24. van der Molen T, Postma DS, Martin RJ, et al. Effectiveness of initiating extrafine-particle versus fine-particle inhaled corticosteroids as asthma therapy in the Netherlands. *BMC Pulm Med*. 2016;16(1):80. doi:10.1186/s12890-016-0234-0
25. Sonnappa S, Martin R, Israel E, et al. Risk of pneumonia in obstructive lung disease: A real-life study comparing extra-fine and fine-particle inhaled corticosteroids. *PLoS One*. 2017;12(6):e0178112. doi:10.1371/journal.pone.0178112
26. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management; 2018. Available from: <https://www.nice.org.uk/guidance/ng115>. Accessed Feb 25, 2019.
27. Roche N, Reddel HK, Agusti A, et al. Integrating real-life studies in the global therapeutic research framework. *Lancet Respiratory Medicine*. 2013;1(10):e29–30.
28. Roche N, Reddel H, Martin R, et al. Quality standards for real-world research. Focus on observational database studies of comparative effectiveness. *Ann Am Thorac Soc*. 2014;11(Suppl 2):S99–104. doi:10.1513/AnnalsATS.201309-300RM
29. Dekhuijzen PNR, Batsiou M, Bjermer L, et al. Incidence of oral thrush in patients with COPD prescribed inhaled corticosteroids: effect of drug, dose, and device. *Respir Med*. 2016;120:54–63. doi:10.1016/j.rmed.2016.09.015
30. Covvey JR, Mullen AB, Ryan M, et al. A comparison of medication adherence/persistence for asthma and chronic obstructive pulmonary disease in the United Kingdom. *Int J Clin Pract*. 2014;68(10):1200–1208. doi:10.1111/ijcp.12451
31. Mueller S, Wilke T, Bechtel B, Punekar YS, Mitzner K, Virchow JC. Non-persistence and non-adherence to long-acting COPD medication therapy: A retrospective cohort study based on a large German claims dataset. *Respir Med*. 2017;122:1–11. doi:10.1016/j.rmed.2016.11.008
32. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol*. 1997;50(1):105–116. doi:10.1016/S0895-4356(96)00268-5
33. Wright J, Brocklebank D, Ram F. Inhaler devices for the treatment of asthma and chronic obstructive airways disease (COPD). *Qual Saf Health Care*. 2002;11(4):376–382. doi:10.1136/qhc.11.4.376
34. Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med*. 2011;105(6):930–938. doi:10.1016/j.rmed.2011.01.005
35. Molimard M, Raheison C, Lignot S, et al. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. *Eur Respir J*. 2017;49:2. doi:10.1183/13993003.01794-2016
36. Haughney J, Price D, Barnes NC, Virchow JC, Roche N, Chrystyn H. Choosing inhaler devices for people with asthma: current knowledge and outstanding research needs. *Respir Med*. 2010;104(9):1237–1245. doi:10.1016/j.rmed.2010.04.012
37. Montuschi P, Malerba M, Santini G, Miravittles M. Pharmacological treatment of chronic obstructive pulmonary disease: from evidence-based medicine to phenotyping. *Drug Discov Today*. 2014;19(12):1928–1935. doi:10.1016/j.drudis.2014.08.004

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