

Extrafine Beclometasone Dipropionate/ Formoterol Fumarate vs Double Bronchodilation Therapy in Patients with COPD: A Historical Real-World Non-Inferiority Study

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Purpose: This study aimed to evaluate the non-inferiority of initiating extrafine beclometasone dipropionate/formoterol fumarate (BDP/FF) versus double bronchodilation (long-acting beta-agonists [LABA]/long-acting muscarinic antagonists [LAMA]) among patients with a history of chronic obstructive pulmonary disease (COPD) exacerbations.

Patients and Methods: A historical cohort study was conducted using data from the UK's Optimum Patient Care Research Database. Patients with COPD ≥ 40 years at diagnosis were included if they initiated extrafine BDP/FF or any LABA/LAMA double therapy as a step-up from no maintenance therapy or monotherapy with inhaled corticosteroids (ICS), LAMA, or LABA and a history of ≥ 2 moderate/severe exacerbations in the previous two years. The primary outcome was exacerbation rate from therapy initiation until a relevant therapy change or end of follow-up. Secondary outcomes included rate of acute respiratory events, acute oral corticosteroids (OCS) courses, and antibiotic prescriptions with lower respiratory indication, modified Medical Research Council score (mMRC) ≥ 2 , and time to first pneumonia diagnosis. The non-inferiority boundary was set at a relative difference of 15% on the ratio scale. Five potential treatment effect modifiers were investigated.

Results: A total of 1735 patients initiated extrafine BDP/FF and 2450 patients initiated LABA/LAMA. The mean age was 70 years, 51% were male, 41% current smokers, and 85% had FEV₁ <80% predicted. Extrafine BDP/FF showed non-inferiority to LABA/LAMA for rate of exacerbations (incidence rate ratio [IRR] = 1.01 [95% CI 0.94–1.09]), acute respiratory events (IRR = 0.98 [0.92–1.04]), acute OCS courses (IRR = 1.01 [0.91–1.11]), and antibiotic prescriptions (IRR = 0.99 [0.90–1.09]), but not for mMRC (OR = 0.93 [0.69–1.27]) or risk of pneumonia (HR = 0.50 [0.14–1.73]). None of the a priori defined effect modifier candidates affected the comparative effectiveness.

Conclusion: This study found that stepping up to extrafine BDP/FF from no maintenance or monotherapy was not inferior to stepping up to double bronchodilation therapy in patients with a history of exacerbations.

Keywords: real-world, electronic health records, observational, comparative effectiveness, heterogeneity, chronic obstructive pulmonary disease

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Introduction

The aim of chronic obstructive pulmonary disease (COPD) treatment is to reduce symptoms and the frequency and severity of exacerbations, and to improve health status and exercise tolerance. Long-acting bronchodilators (long-acting muscarinic

antagonists [LAMAs] and long-acting beta-agonists [LABAs]) are the mainstay of therapeutic management for COPD; their combined use can result in greater benefits than from either therapy alone.^{1–5} Inhaled corticosteroids (ICS)/LABA combinations are also more effective than each component alone, especially for exacerbation prevention.⁶ Furthermore, higher blood eosinophil counts is a biomarker associated with an increased benefit from ICS.⁷ Therefore, in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 recommendations, ICS/LABA is indicated as a step-up from bronchodilator monotherapy for exacerbating patients (at least two moderate or one severe exacerbation in the previous year) with a blood eosinophil count above 100 cells/ μ L.⁸ However, these recommendations are solely based on insights obtained from randomized clinical trials. The real-world evidence on the effectiveness of ICS/LABA in such patients compared with other treatment combinations remains limited. Since patients in randomized trials are not necessarily representative of the patients with COPD in real life, we need real-world evidence added to the trial insights to ensure optimal disease management recommendations.

The FLAME study showed that indacaterol/glycopyrronium (LABA/LAMA) was more effective than fluticasone/salmeterol in exacerbation prevention in patients with a history of exacerbations.⁹ Only 19.3% of patients in the FLAME study however, had a history of two or more moderate to severe exacerbations in the previous year. In another trial (IMPACT), different results were reported regarding the respective efficacy of these two therapeutic options.¹⁰ This discrepancy could relate to variations in study populations (over 50% of the patients included in the IMPACT study had two or more exacerbations) and/or previous treatment history. The abrupt withdrawal of steroids in patients assigned to the LABA/LAMA arm, in addition to the inclusion of patients with asthma in the IMPACT trial, likely contributed to the rapid increase in exacerbations seen in the LABA/LAMA arm.¹¹

Extrafine formulations of inhaled treatments increase drug delivery to the small airways,¹² which may improve the benefit of ICS for exacerbation prevention in COPD, where small airway inflammation is prominent. A unique feature of extrafine beclometasone dipropionate/formoterol fumarate (BDP/FF) combination in a single inhaler is that it may be associated with increased effectiveness¹³ and lower risk of pneumonia.¹⁴ There are no real-world evidence studies on the comparative effectiveness of initiating

a fixed-dose combination of extrafine BDP/FF in a single inhaler versus LABA/LAMA.

We aimed to determine whether initiating treatment with an extrafine BDP/FF combination in a single inhaler was at least as effective as double bronchodilator therapy (LABA/LAMA) in terms of reducing COPD exacerbations in patients with COPD and a history of exacerbations in a historical cohort extracted from 2002 to 2019. Several patient characteristics have been identified before as risk factors for disease severity.^{15–17} Therefore, we also aimed to determine how the comparative effectiveness was modified by the exacerbation burden in the baseline year, most recent blood eosinophil count, degree of airflow limitation, COPD GOLD group, and number of concomitant drugs prescribed in the baseline year.

Materials and Methods

Study Design and Data Source

This was a historical cohort study comparing patients with COPD and a history of exacerbations who initiated extrafine BDP/FF (ICS/LABA) to those who initiated LABA/LAMA double therapy in the United Kingdom (UK; Figure 1). The index date, which was the date of therapy initiation, separated a one-year baseline period and the outcome period. Data were extracted for patients who stepped up to extrafine BDP/FF or LABA/LAMA from either no maintenance therapy, or monotherapy with ICS, LAMA, or LABA between 2002 and 2019. The study used primary care data from the Optimum Patient Care Research Database (OPCRD; <https://opcrd.co.uk/>). OPCRD contains anonymized, longitudinal medical record data for over eight million patients from over 700 primary care practices. The median follow-up duration of medical records is 13 years. These data contain information on demographic and lifestyle parameters, clinical events, referrals to and feedback from specialists, and prescriptions. It is a high-quality data source used regularly in clinical, epidemiological, and pharmaceutical research.^{18,19} OPCRD is approved by the Health Research Authority for clinical research use and governed by the Anonymised Data Ethics & Protocol Transparency (ADEPT) Committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG, <http://www.effectivenessevaluation.org/>). This study was approved by the ADEPT committee (approval reference ADEPT0419).

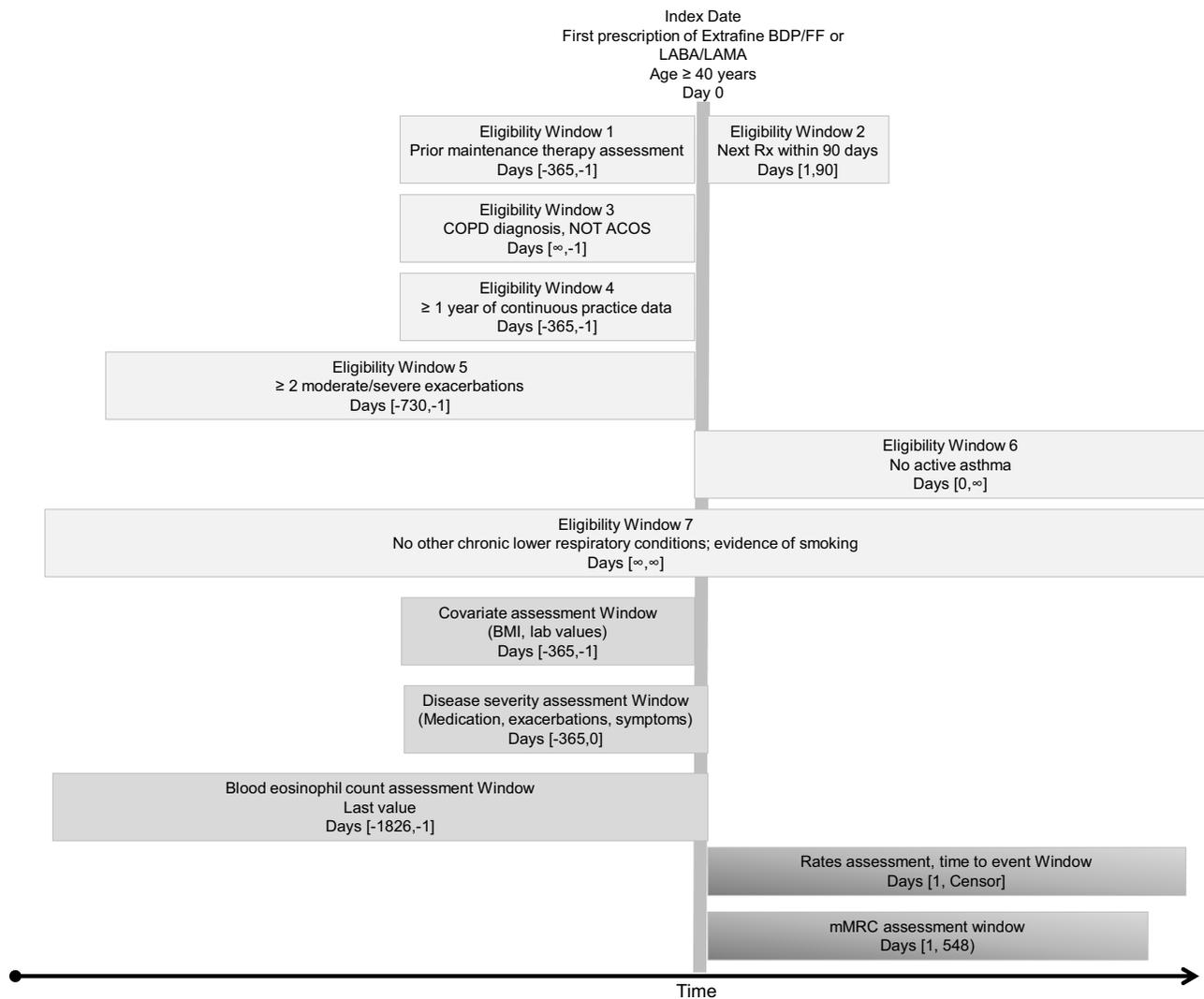


Figure 1 Study design.

Abbreviations: COPD, chronic obstructive pulmonary disease; extrafine BDP/FF, extrafine beclometasone dipropionate/formoterol fumarate; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; ACOS, asthma-COPD overlap syndrome; mMRC, Modified Medical Research Council Dyspnea Scale.

Study Population

Patients were included in the study if they met the following criteria: 1) initiated extrafine fixed dose combination ICS/LABA (extrafine BDP/FF) or any LABA/LAMA double therapy, either as a fixed-dose combination or two separate inhalers, as a step-up from no maintenance therapy or monotherapy with ICS, LAMA, or LABA; 2) received the initiated therapy for at least 90 days (to avoid the inclusion of artefacts, temporary medical records, and temporary interruption of one medication class); 3) had a diagnostic Read code for COPD, not followed by a COPD “resolved” code; 4) were aged ≥ 40 years at index date; 5) had at least one year of continuous practice data prior to the index date (baseline year); and 6) had two or more moderate/severe exacerbations (see Table 1 for definition) in the two years

prior to and including the index date. With this 2-year period we optimize the use of available longitudinal data, resulting in greater ability to assess effect modification by exacerbation burden.

Patients who had active asthma at or after the index date (defined as ≥ 1 diagnostic Read code for asthma or ≥ 1 asthma monitoring or review Read code recorded), a Read code for Asthma-COPD overlap syndrome as the COPD diagnostic code, a diagnostic code for other chronic lower respiratory conditions ever recorded, or no evidence of smoking ever were excluded from the analyses. All code lists are available from the authors upon request. Code lists for COPD and asthma were based on version 38 of the Quality and Outcomes Framework business rules, a pay-for-performance scheme active in the UK since 2004,

which has resulted in highly accurate recording of diagnoses.²⁰ In line with a recently suggested framework of graphical representation of studies done in health care databases,²¹ we provide such detailed information in Figure 1.

Patients were divided into two exposure groups: those who initiated extrafine BDP/FF in a single inhaler and those who initiated LABA/LAMA. Where a patient was eligible for both groups, the LABA/LAMA initiation date was used, to avoid a patient being used twice in the analyses. Where multiple initiation dates of the same drug group occurred, the first date was used as the index date in the analyses.

Study Outcomes

The primary outcome was the annualized rate of moderate/severe COPD exacerbations (see Table 1 for definition) during follow-up. Follow-up began on the index date (ie therapy initiation) and continued until the patient left the practice, had a relevant therapy change, or until the last date of the practice’s data collection. In the extrafine BDP/FF group, a relevant therapy change comprised a switch to triple therapy (ICS/LABA/LAMA), a switch to another ICS/LABA, or a switch to no maintenance therapy, LAMA or LABA monotherapy, or LABA/LAMA double therapy when extrafine BDP/FF was not switched back to within six months. This tolerance period of six months was used to avoid exposure misclassification due to apparent small changes in therapy which could be the result of artefacts in the data. In the LABA/LAMA group, a relevant therapy change comprised a switch to an ICS-containing therapy or a switch to no maintenance therapy or LAMA or LABA monotherapy when LABA/LAMA was not switched back to within six months. The secondary outcomes were rate of acute respiratory events, acute oral corticosteroids courses, and antibiotic prescriptions with lower respiratory indication, modified Medical Research Council score (mMRC) within 18 months after index date, and time to first pneumonia diagnosis. Details on the primary and secondary outcomes are presented in Table 1.

Data Analyses

Analyses were performed using Stata MP/6 version 15.1 (StataCorp, College Station, TX). The type and duration of prior maintenance therapies were assessed for all patients included.

Table 1 Study Outcomes and Definitions

Outcome	Definitions
Primary	Rate of moderate/severe COPD exacerbations during the entire follow-up (ie until end of data availability or censoring due to a relevant therapy change) defined as: <ul style="list-style-type: none"> • Respiratory-related hospital attendance/admission (based on GP medical record data) AND/OR, • Respiratory-related A&E attendance (based on GP medical record data) AND/OR, • Acute OCS course prescription AND/OR, • Antibiotics prescribed with evidence of a lower respiratory consultation on the same day. Events occurring within 14 days of a previous event were considered part of the same episode. A relevant therapy change was either discontinuation of the index therapy or additional medication.
Secondary	Rate of occurrences during the entire follow-up of: <ol style="list-style-type: none"> 1. Acute respiratory events (defined as a moderate/severe exacerbation or an unplanned respiratory-related consultation, not for annual monitoring/review). 2. Acute OCS courses. 3. Antibiotic prescriptions with evidence of lower respiratory consultation. 4. mMRC score within 18 months after index date (≥ 2 vs ≤ 2). 5. Time to first pneumonia diagnosis (diagnostic code with a code for a chest X-ray within 30 days around the date). 6. Treatment failure (defined as the occurrence of a moderate/severe exacerbation, prescription of additional chronic COPD therapy, or a step-up to triple therapy after the index date). This was an a priori secondary outcome, but not included for the purpose of this paper as the reasons for treatment failure were very different between the study arms, and we therefore judged it to be a poor indicator of treatment effectiveness. Events occurring within 14 days of a previous event were considered part of the same episode.

Abbreviations: COPD, chronic obstructive pulmonary disease; GP, general practice; mMRC, Modified Medical Research Council Dyspnea Scale; OCS, oral corticosteroid.

Continuous variables were summarized using descriptive statistics of central tendency (mean and median) and dispersion (standard deviation [SD] and interquartile range [IQR]). Categorical variables were described with frequencies and percentages. The standardized mean difference (SMD) was used to quantify differences in both continuous and categorical variables between the groups at baseline. We considered an SMD $\leq 10\%$ to indicate sufficient balance between the groups.

Inverse probability of treatment (IPT) weighting was used to account for potential biases such as indication bias, as attempts to match the study groups resulted in 29–50% loss in patient numbers and selection of less severely ill patients. A propensity score was generated with a logistic regression model using all available baseline characteristics which had shown an association to the outcome of interest. The propensity score was used to weight the data with the inverse of the treatment probability. Weights above the 99th percentile and below the 1st percentile were truncated at these values. Weighted SMDs were calculated to verify the balancing effect of the IPT weighting approach.

The number of patients who improved (ie, fewer number of exacerbations in the one-year follow-up period compared to the baseline period), remained stable (same number), and worsened (more in the one-year follow-up period than the baseline period) was calculated in those patients with at least one year of follow-up. Unadjusted and IPT weighted changes are reported.

Non-inferiority of initiating extrafine BDP/FF versus double bronchodilators was tested in per protocol analyses. The upper boundary of non-inferiority was set at a relative difference of 15% (corresponding to a hazard ratio [HR], incidence rate ratio [IRR], or odds ratio [OR] for outcomes with extrafine BDP/FF versus LABA/LAMA of 1.15) based on clinical and statistical considerations. The margin was defined on the limit of the 95% confidence interval that is closest to the null effect.²² Clinical judgement was applied to choose the fraction of the null effect that must be preserved by the active drug, in this case 50%. Event rates over the entire follow-up period were analyzed using conditional negative binomial regression, weighted by the logarithm of the duration of follow-up to account for differences in length of follow-up between patients and adjusted for covariates that caused a change in estimate of >2% in the IPT weighted analyses. Given the number of extrafine BDP/FF and LABA/LAMA initiators in this study, there was 90% power, using 5% significance, to detect a minimal difference in exacerbation rate of 10%. Time-to-event analyses were used to analyze the association between treatment and time to first pneumonia diagnosis with right censoring at the time of loss to follow-up or treatment change, adjusted for residual confounders following IPT weighting. To account for multiple testing, Holm's method²³ was used to adjust significance levels for the six primary and secondary outcomes. Patients with a history of asthma and/or a diagnosis of allergic rhinitis

were excluded in sensitivity analyses to assess the robustness of the findings with regards to incomplete exclusion of patients with concomitant asthma.

Effect modification was assessed for the following five candidates: exacerbation burden in the baseline year, most recent blood eosinophil count (within five years), degree of airflow limitation (FEV₁% predicted), COPD GOLD group (A-D), and number of distinct drugs (apart from COPD drugs) prescribed in the baseline year. Effect modification was tested by introducing an interaction term between exposure and the candidate modifier into the regression models. Significance levels for the interaction terms were adjusted using Holm's method.

The study population was created in 2018, and thus a large majority of patients had their index date before the changes in COPD treatment recommendations after 2018. More specifically, the 2019 GOLD Report version recommended incorporating the use of peripheral blood eosinophil counts to predict the efficacy of ICS for exacerbation prevention.⁸ Therefore, we further assessed the effect of blood eosinophil count on the comparative effectiveness, as post hoc analyses, in the following COPD subgroups: a) patients with ≥ 1 severe or ≥ 2 moderate exacerbations in the one-year baseline period (1597 LABA/LAMA and 1244 extrafineBDP/FF initiators), b) patients with ≥ 3 moderate/severe exacerbations in the one-year baseline period (734 LABA/LAMA and 681 extrafine BDP/FF initiators), and c) patients who stepped up from either LAMA or LABA monotherapy (669 LABA/LAMA and 283 extrafine BDP/FF initiators). Please refer to the online [Supplementary Materials](#) for further details regarding methodology.

Role of the Funding Source

The funder of the study participated in the study design. All authors, including those employed by the funder of the study, participated in the data interpretation, and writing of the manuscript. All authors had full access to study results and had final responsibility for the decision to submit for publication.

Results

A total of 1735 eligible patients initiated extrafine BDP/FF and 2450 patients initiated LABA/LAMA. A patient flow chart is displayed in [Figure 2](#). Weighted summary statistics of demographic and clinical characteristics of patients who initiated extrafine BDP/FF and those who initiated LABA/LAMA are presented in [Table 2](#) (and [Table e1](#) in the

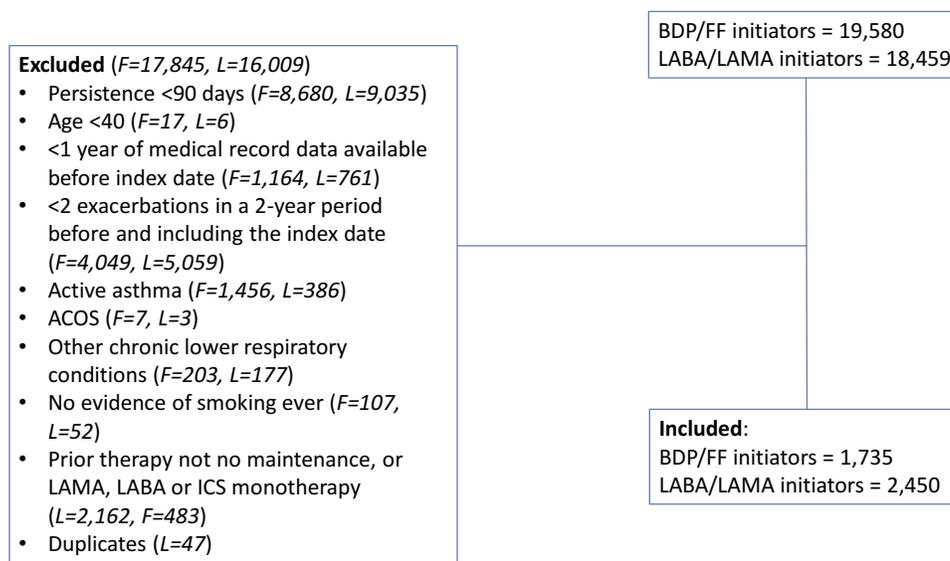


Figure 2 Patient flowchart.

Abbreviations: ACOS, asthma-COPD overlap syndrome; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta-agonist; ICS, inhaled corticosteroids; Extrafine BDP/FF, extrafine Beclometasone dipropionate/formoterol fumarate.

[Online Supplementary Materials](#)). Ninety-four percent (73/78) of characteristics were well balanced ($SMD \leq 10\%$) between treatment groups following weighting. The mean age in both groups was 70 years and around half of patients were male. Over 30% of patients in both groups belonged to GOLD group D at baseline. Unweighted baseline characteristics are presented in [supplementary Table e2](#). Notably, in the baseline year a higher percentage of extrafine BDP/FF initiators experienced from 3 to >5 exacerbations (43.6%) in comparison to LABA/LAMA initiators (33.9%). In the meantime, a higher percentage of LABA/LAMA initiators experienced from 0 to 2 exacerbations (66.1%) in comparison to extrafine BDP/FF initiators (56.6%). This imbalance was confirmed by the standardized mean difference of 23.8.

The duration of therapies prior to the index date and the time patients stayed on the index therapy was similar between patients who initiated extrafine BDP/FF and those who initiated LABA/LAMA. Approximately 38% of patients in each group received refill prescriptions for their index therapy for at least one year. The duration of follow-up was 1.5 years for both groups.

The number of patients who improved, remained stable, or worsened from the baseline year to the first follow-up year for each outcome variable is displayed in [Table 3](#). Both treatment groups showed a reduction in the number of exacerbations from the baseline to the outcome year (61% of extrafine BDP/FF and 58% of

LABA/LAMA initiators). The percentage of extrafine BDP/FF initiators who worsened was 21.5% compared to 23.5% of LABA/LAMA initiators ([Table 3](#)).

Multivariable Outcome Models

Extrafine BDP/FF was non-inferior to LABA/LAMA for the primary outcome in the weighted model; the upper confidence limit for exacerbation rate of 1.09 was below the prespecified non-inferiority margin of 1.15 (IRR = 1.01 [95% CI 0.94–1.09]; [Figure 3](#)). Extrafine BDP/FF was also non-inferior to LABA/LAMA for secondary outcomes including rate of acute respiratory events (IRR = 0.98 [0.92–1.04]), acute OCS courses (IRR = 1.01 [0.91–1.11]), and antibiotic prescriptions with evidence of lower respiratory indication (IRR = 0.99 [0.90–1.09]; [Figure 3](#)). However, non-inferiority was not achieved for the secondary outcomes of having an mMRC score ≥ 2 (HR = 0.96 [0.74–1.23]) and risk of a pneumonia infection (HR = 0.50 [0.14–1.73]). See [Table e3](#) in the [Online Supplementary Materials](#) for unadjusted data on follow-up and outcomes. Results were similar when patients with a history of asthma and/or rhinitis were excluded in sensitivity analyses (see [Figure e1](#) in the [Online Supplementary Materials](#)).

Effect Modification

There was no evidence that any of the a priori candidate modifiers (blood eosinophil count, exacerbations, GOLD group, FEV_{1%} predicted, other medication burden) significantly changed the comparative effectiveness between

Table 2 Baseline Characterization of IPT Weighted Population

Variable		LABA/LAMA (N=2450)	Extrafine BDP/FF (N=1735)	SMD
Age (years)	Mean (SD)	70.4 (10.0)	69.8 (10.5)	1.9
Male gender	n (%)	1299 (53.0)	822 (47.4)	2.7
Smoking status	Current, n (%) Former, n (%) Missing, n (%)	1044 (42.6) 1389 (56.7) 17 (0.7)	677 (39.0) 1052 (60.6) 6 (0.3)	0.8
BMI (kg/m ²)	<18.5, n (%) ≥18.5 <25, n (%) ≥25 <30, n (%) ≥30, n (%) Missing, n (%)	115 (4.7) 750 (30.6) 764 (31.2) 713 (29.1) 108 (4.4)	78 (4.5) 525 (30.3) 555 (32.0) 510 (29.4) 67 (3.9)	1.2
Asthma diagnosis ever	n (%)	481 (19.6)	496 (28.6)	0.7
Eosinophil count (10 ⁹ /L)	<0.05, n (%) 0.05 <0.15, n (%) 0.15 <0.25, n (%) 0.25 <0.35, n (%) 0.35 <0.45, n (%) 0.45 <0.55, n (%) 0.55 <0.65, n (%) ≥0.65, n (%) Missing, n (%)	80 (3.3) 593 (24.2) 682 (27.8) 396 (16.2) 180 (7.3) 95 (3.9) 50 (2.0) 63 (2.6) 311 (12.7)	67 (3.9) 407 (23.5) 455 (26.2) 288 (16.6) 147 (8.5) 84 (4.8) 31 (1.8) 62 (3.6) 194 (11.2)	1.9
Exacerbations [§]	0, n (%) 1, n (%) 2, n (%) 3, n (%) 4, n (%) ≥5, n (%)	216 (8.8) 608 (24.8) 796 (32.5) 364 (14.9) 204 (8.3) 262 (10.7)	114 (6.6) 306 (17.6) 560 (32.3) 296 (17.1) 175 (10.1) 284 (16.4)	3.2
Acute OCS courses [§]	0, n (%) 1, n (%) 2, n (%) 3, n (%) 4, n (%) ≥5, n (%)	1051 (42.9) 554 (22.6) 379 (15.5) 170 (6.9) 111 (4.5) 185 (7.6)	700 (40.3) 346 (19.9) 272 (15.7) 145 (8.4) 80 (4.6) 192 (11.1)	1.4
Antibiotics courses [§]	0, n (%) 1, n (%) 2, n (%) 3, n (%) 4, n (%) ≥5, n (%)	717 (29.3) 825 (33.7) 541 (22.1) 215 (8.8) 87 (3.6) 65 (2.7)	505 (29.1) 557 (32.1) 386 (22.2) 171 (9.9) 65 (3.7) 51 (2.9)	0.9
GOLD group	A, n (%) B, n (%) C, n (%) D, n (%) Missing, n (%)	358 (14.6) 348 (14.2) 689 (28.1) 781 (31.9) 274 (11.2)	175 (10.1) 170 (9.8) 575 (33.1) 601 (34.6) 214 (12.3)	1.7
FEV ₁ % predicted in 2-year period	<30, n (%) 30 <50, n (%) 50 <80, n (%) ≥80, n (%) Missing, n (%)	84 (3.4) 513 (20.9) 1164 (47.5) 319 (13.0) 370 (15.1)	92 (5.3) 385 (22.2) 676 (39.0) 205 (11.8) 377 (21.7)	0.4

Note: §: Counts in a 1-year baseline period.

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; IPT, inverse probability of treatment; LABA/LAMA, long-acting beta-agonist plus long-acting muscarinic antagonist; OCS, oral corticosteroids; SD, standard deviation; SMD, IPT weighted standardized mean difference.

Table 3 Number of Patients Who Improved, Remained Stable, or Worsened from 1-Year Baseline to the First Outcome Year

Unadjusted	LABA/LAMA, N (%)			Extrafine BDP/FF, N (%)		
Outcome	Improved	Stable	Worsened	Improved	Stable	Worsened
Exacerbations	1425 (58.1)	450 (18.4)	575 (23.5)	1058 (61.0)	304 (17.5)	373 (21.5)
Acute OCS courses	928 (37.9)	868 (35.4)	654 (26.7)	693 (39.9)	529 (30.5)	513 (29.6)
Antibiotics courses	1221 (49.8)	765 (31.2)	464 (19.0)	858 (49.4)	591 (34.1)	286 (16.5)
Acute respiratory events	1430 (58.4)	374 (15.2)	646 (26.4)	1071 (61.7)	255 (14.7)	409 (23.6)
Hospitalizations	230 (9.4)	2092 (85.4)	128 (5.2)	186 (10.7)	1436 (82.8)	113 (6.5)
A&E attendances	92 (3.8)	2311 (94.3)	47 (1.9)	97 (5.6)	1585 (91.3)	53 (3.1)

IPT Weighted	LABA/LAMA, N (%)			Extrafine BDP/FF, N (%)		
Outcome	Improved	Stable	Worsened	Improved	Stable	Worsened
Exacerbations	1278 (58.9)	378 (17.4)	514 (23.7)	1205 (59.8)	376 (18.7)	434 (21.5)
Acute OCS courses	829 (38.1)	736 (33.9)	604 (27.8)	792 (39.3)	661 (32.8)	563 (27.9)
Antibiotics	1088 (50.2)	671 (30.9)	411 (18.9)	991 (49.2)	685 (34.0)	339 (16.8)
Acute respiratory events	1264 (58.3)	326 (15.0)	579 (26.7)	1237 (61.4)	303 (15.0)	476 (23.6)
Hospitalizations	211 (9.7)	1840 (84.9)	118 (5.4)	205 (10.2)	1688 (83.7)	123 (6.1)
A&E attendances	81 (3.7)	2049 (94.5)	39 (1.8)	108 (5.4)	1847 (91.6)	61 (3.0)

Abbreviations: A&E, accident and emergency; LABA/LAMA, long-acting beta-agonist plus long-acting muscarinic antagonist; OCS, oral corticosteroids.

extrafine BDP/FF and LABA/LAMA. The results from assessment of effect modification of the modifier candidates using the primary and secondary outcomes is shown in [Table e4](#) as p-values of the interaction term in the adjusted outcome models corrected for multiple testing.

In subgroup analyses, no indication that blood eosinophil count was predictive of the rate of exacerbations during follow-up in the extrafine BDP/FF group was found. However, LABA/LAMA tended to lose efficacy in reducing exacerbations with increasing eosinophil count. In the

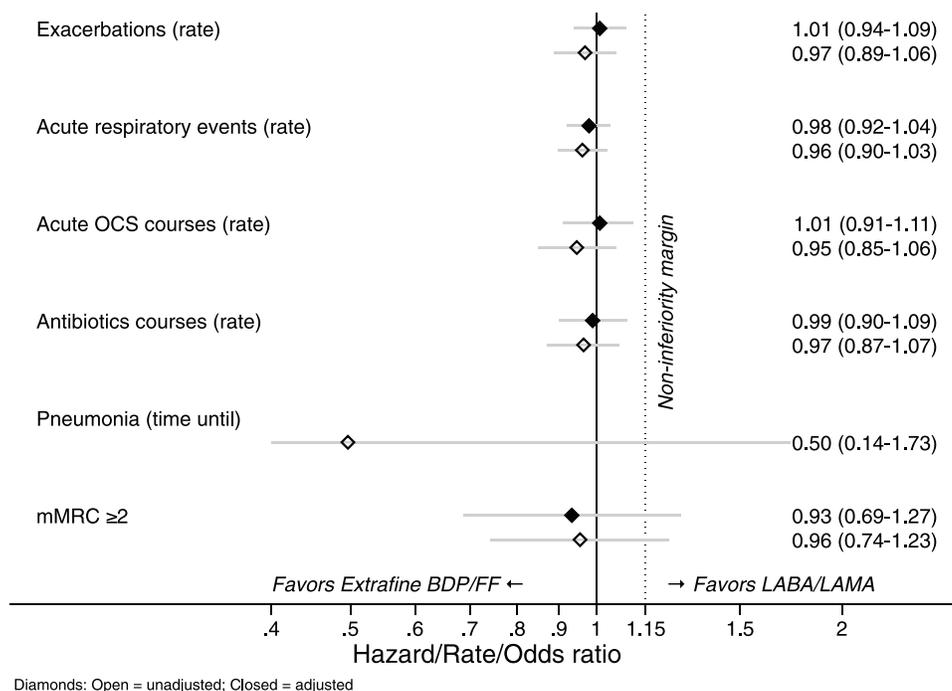


Figure 3 Model results, all patients.

Abbreviations: Extrafine BDP/FF, extrafine beclometasone dipropionate/formoterol fumarate; LABA/LAMA, long-acting beta-agonist plus long-acting muscarinic antagonist; mMRC, Modified Medical Research Council Dyspnea Scale; OCS, oral corticosteroids.

subgroup of patients that came from LAMA or LABA monotherapy, blood eosinophil count showed a clear trend ($p=0.051$) of comparative effectiveness based on the number of SABA inhalers used in favor of extrafine BDP/FF with increasing eosinophil count. See the [Online Supplementary Materials](#) for results of effect modification in the subgroup analyses ([Figures e2–e3](#)).

Discussion

This historical real-world observational study showed similar exacerbation reduction from the baseline to the first outcome year in patients who initiated extrafine BDP/FF and those who initiated LABA/LAMA from no maintenance or monotherapy. Stepping up to extrafine BDP/FF was not inferior to stepping up to double bronchodilation therapy in patients with a history of exacerbations.

Our non-inferiority finding is in agreement with another real-world study comparing LABA/LAMA to any ICS/LABA initiators.²⁴ Our results are in contrast to the finding of superiority of indacaterol/glycopyrronium (LABA/LAMA) over fluticasone/salmeterol (ICS/LABA) in exacerbation reduction in the FLAME study.⁹ Our study population had a comparable exacerbation burden (≥ 2 in a 2-year baseline vs ≥ 1 in a 1-year period in the trial), but we compared different compounds. This might suggest that the extrafine particle size of BDP/FF needs to be taken into account when evaluating the choice between double bronchodilation therapy and ICS/LABA.

For all outcomes (rates of exacerbations, acute OCS courses, antibiotics courses, and acute respiratory events) non-inferiority of extrafine BDP/FF could be claimed with the exception of having an mMRC score ≥ 2 and time until a pneumonia infection. The number of pneumonia cases during follow-up was low ($n = 15$); four with BDP/FF and 11 with LABA/LAMA. This could relate to the molecular characteristics of FF or to the extrafine BDP/FF formulation increasing the volume of drug distribution within the bronchial tree. The pneumonia incidence rate was 0.25 cases per 100 patient-years (in the IMPACT study there was an incidence rate of between 6–10 cases per 100 patient-years¹⁰), resulting in low statistical power as well as the inability to check models for residual confounding. Similarly, for MRC dyspnoea scale the OR is 0.96. However, the 95% CI is wide, and its upper limit crosses the non-inferiority margin. The result is not unexpected as MRC scores are variably associated with patients' perceptions of respiratory symptom burden or disease severity.²⁵

None of the candidate modifiers (blood eosinophil count, exacerbations, GOLD group, FEV₁% predicted, other medication burden) significantly changed the comparative effectiveness. Although extrafine BDP/FF is licensed for patients with COPD and a FEV₁% predicted below 50% and a history of repeated exacerbations,²⁶ we did not find evidence that the comparative effectiveness was different depending on the FEV₁% predicted and exacerbation rate in the one-year baseline period. Missing FEV₁ data may have resulted in loss of power and dilution of any possible effect modification of baseline FEV₁ on the outcomes after initiation of treatments.

We did not find a significant impact of difference of eosinophil count on the comparative effectiveness, despite a trend when comparing the two treatments in a subpopulation of patients stepping up from LAMA or LABA monotherapy, the patients the treatment guidelines⁸ refer to. In addition, in these patients a trend in favor of extrafine BDP/FF on SABA reduction with increasing eosinophil count exists. The limited number of patients analyzed is preventing us reaching the conclusions provided by Suissa et al, who analyzed a population-based cohort of 12,366 initiators of LAMAs (mainly tiotropium) matched to 12,366 initiators of LABA-ICS.²⁷ They found that initial treatment with ICS/LABAs was only more effective than with LAMAs in patients with high blood eosinophil counts.

We used the most recently recorded blood eosinophil count within five years. Almost 45% of the eosinophil counts were recorded within 6 months prior to the index date, 66% within one year, and only 16% were recorded more than two years earlier. Some studies on stability of blood eosinophil counts over time have shown that values remain reasonably stable over a period of two years.^{28,29} Therefore, we do not think this has affected our results.

Our data indicate that treatment exposure lasted 1-year in approximately 38% of patients. It is a higher percentage in comparison to figures reported by Suissa et al, who found that 67% of patients in the LABA/LAMA group and 72% in the ICS/LABA group discontinued the treatment after 3.3 months.²⁴

The strengths of our study include the large cohort of patients from a real-world setting, representative of the UK population, making our results likely generalizable to the wider COPD population. Some limitations however also need consideration. The OPCR dataset represents information collected for clinical and routine use rather than specifically for research purposes but reflects real-

world prescribing practices. However, extensive quality control and validity checks are conducted at practice level. Also, the study had limited power to detect differences in pneumonia events due to low incidence rates. Finally, we could only adjust for confounding by measured and considered baseline characteristics of the patients. Thus, we cannot guarantee that our results are unbiased; however, as the most important disease severity indicators were used for propensity score estimation, it is unlikely that any residual bias is large.

Conclusion

In summary, this observational study found that stepping up to extrafine BDP/FF from no maintenance or monotherapy was not inferior to stepping up to double bronchodilation therapy in patients with a history of COPD exacerbations. The study did not identify patient factors that relevantly modified the comparative effectiveness. Notably, the finding that the FEV₁% predicted did not modify the comparative effectiveness calls for studies to explore the possibility to indicate extrafine BDP/FF for a broader target population. Overall, these real-world findings confirm how extrafine ICS/LABA fits into maintenance therapy of COPD patients at risk of exacerbations. Eosinophilia should be considered a continuum in therapeutic decision making; however, more studies are needed to better understand how blood eosinophil count interacts with exacerbation burden and treatment choice on exacerbation reduction in larger real-world cohorts.

Abbreviations

ADEPT, Anonymised Data Ethics & Protocol Transparency; BDP, beclomethasone dipropionate; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in one second; FF, formoterol fumarate; HR, hazard ratio; ICS, inhaled corticosteroids; IPT, inverse probability of treatment; IQR, interquartile range; IRR, incidence rate ratio; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonists; mMRC, Modified Medical Research Council Dyspnea Scale; NNB, number needed to benefit; OCS, oral corticosteroids; OPCR, Optimum Patient Care Research Database; OR, odds ratio; SABA, short-acting beta-2 agonists; SD, standard deviation; SMD, standardized mean difference.

Data Sharing Statement

The dataset supporting the conclusions of this article was derived from the Optimum Patient Care Research Database

(www.opcrd.co.uk). The OPCR has ethical approval from the National Health Service (NHS) Research Authority to hold and process anonymised research data (Research Ethics Committee reference: 15/EM/0150). This study was approved by the Anonymised Data Ethics Protocols and Transparency (ADEPT) committee – the independent scientific advisory committee for the OPCR. The authors do not have permission to give public access to the study dataset; researchers may request access to OPCR data for their own purposes. Access to OPCR can be made via the OPCR website (<https://opcrd.co.uk/our-database/data-requests/>) or via the enquiries email info@opcrd.co.uk.

Ethics Approval

OPCR has received a favorable opinion for clinical research use from the Health Research Authority (REC reference: 15/EM/0150). Governance is provided by the Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG, <http://www.effectivenessevaluation.org/>) to govern the standard of research conducted on internationally recognized databases. This study was approved by the ADEPT committee (approval reference ADEPT0419) and registered with the European Union electronic Register of Post-Authorization Studies (EUPAS Register number 29223).

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