Final Report

REACH II: Stage 2

Examining real-life outcomes for UK patients with COPD after initiating Fostair® pMDI according to its licensed indication compared to other licensed FDC ICS/LABA therapies

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TITLE	REACH II: Stage 2		
Subtitle	Comparison of effectiveness of COPD treatment with Fostair® pMDI compared to other licensed FDC ICS/LABA therapies in terms of prevention of moderate/severe exacerbations and cost-effectiveness.		
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Medicinal product	Fostair® pMDI, Seretide® 500 Accuhaler® and Symbicort® 200/400 Turbohaler®		
Marketing authorisation holder	Fostair® pMDI: Chiesi Limited 333 Styal Road Manchester M22 5LG	Seretide® 500 Accuhaler®: Glaxo Wellcome UK Ltd trading as GlaxoSmithKline UK Stockley Park West Uxbridge Middlesex UB11 1BT	Symbicort® 200/400 Turbohaler®: AstraZeneca UK Limited, 600 Capability Green, Luton, LU1 3LU
Marketing authorisation number	PL 08829/0156 (Fostair® pMDI), PL10949/0316 (Seretide® 500 Accuhaler®), PL 17901/0092 (Symbicort® 200 Turbohaler®), PL 17901/0200 (Symbicort® 400 Turbohaler®)		
Study aims and objectives	The aim of this study is to determine whether effectiveness of COPD treatment on Fostair® pMDI is non-inferior to other licensed FDC ICS/LABA therapies for the treatment of COPD, in patients meeting the licensed indication for Fostair® pMDI. The primary objective is to establish whether efficacy, after initiation of COPD treatment on Fostair® pMDI is non-inferior, in terms of the proportion of patients with COPD who experience moderate/severe exacerbations, compared to other licensed FDC ICS/LABA COPD therapies, namely Seretide® 500 Accuhaler® and Symbicort® 200/400 Turbohaler®. A sub-analysis will consider patients diagnosed with COPD and no other respiratory-related diagnoses (ie exclude patients with a history of asthma). The secondary objectives are to compare effectiveness of COPD treatment on Fostair® pMDI to Seretide® 500 Accuhaler® and Symbicort® 200/400 Turbohaler® for other respiratory outcomes; and to compare Fostair® pMDI to Seretide® 500 Accuhaler® and Symbicort® 200/400 Turbohaler® in terms of cost-effectiveness.		
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List of abbreviations

A&E	Accident and Emergency
BDP	Beclomethasone Dipropionate
BUD	Budesonide
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CLR	Conditional Logistic Regression
COPD	Chronic Obstructive Pulmonary Disease
DPI	Dry Powder Inhaler
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERS	European Respiratory Society
FDC	Fixed Dose Combination
FEV_1	Forced Expiratory Volume (1 second)
FOR	Formoterol
GERD	Gastroesophageal Reflux Disease
GOLD	Global Initiative for Chronic Obstructive Disease
GP	General Practitioner
ICS	Inhaled Corticosteroid
IHD	Ischaemic Heart Disease
IQR	Interquartile Range
LABA	Long-Acting Beta2 Agonist
LTRA	Leukotriene Receptor Antagonist
LRTI	Lower Respiratory Tract Infection
mMRC	Modified Medical Research Council
NICE	National Institute for Health and Care Excellence
NSAID	Nonsteroidal Anti-Inflammatory Drug
OPRI	Observational and Pragmatic Research Institute
OR	Odds ratio
pMDI	Pressurised Metered Dose Inhaler
RR	Rate Ratio
SABA	Short-Acting $Beta_2$ Agonist
SAL	Salbutamol
SAMA	Short-acting Muscarinic Agent
SPC	Summary of Product Characteristics

1.0 Executive Summary

1.1 Introduction

Several fixed dose combination inhaled corticosteroid (FDC ICS/LABA) inhalers are licensed in patients with moderate/severe chronic obstructive pulmonary disease in the United Kingdom. This study compares Fostair 100/6 pressurised metered dose inhaler (pMDI) (BDP/FOR) against other licensed FDC ICS/LABAs dry powder inhalers (DPIs), namely; Seretide Accuhaler 500 DPI (FP/SAL) and Symbicort Turbohaler 200/6 & 400/12 DPI (BUD/FOR) in a patient group with previous history of exacerbations and impaired lung function.

1.2 Study aims and objectives

This study compares effectiveness of BDP/FOR against other licensed FDC ICS/LABAs, namely; FP/SAL and BUD/FOR in a patient group with recent exacerbations and impaired lung function.

The primary objective was to establish whether initiation of licensed COPD ICS/LABA treatment with BDP/FOR pMDI is associated with non-inferior effectiveness, in terms of the proportion of patients with COPD who experience moderate/severe exacerbations, compared to other licensed FDC ICS/LABA COPD therapies. Superiority was also examined if non-inferiority was achieved. In addition, a sub-analysis removing patients with a asthma diagnosis codes was performed.

The secondary objectives compared treatment groups by: time to first exacerbation, rate of exacerbations, treatment stability, lung function, respiratory-related hospitalisations, cumulative oral corticosteroid dose, antibiotic prescriptions, modified Medical Research Council (mMRC) dyspnoea score, lung function, reliever inhaler usage, and pneumonia diagnosis.

A cost effectiveness analysis was also run comparing treatment groups.

1.3 Methods

An historical cohort study using data from the Optimum Patient Care Research Database was conducted. Inclusion criteria were: patients with COPD, age ≥35 years, post bronchodilator FEV_1 percent predicted <55%, previous prescriptions for long acting bronchodilators, and a previous exacerbation in the last 18 months initiating FDC ICS/LABA therapy. Patients were excluded if they did not have a subsequent prescription for the same FDC ICS/LABA or switched to a different ICS/LABA. Patients were directly matched 1:1 on categorised age, smoking status, FEV_1 percent predicted and exacerbations.

An additional sub-analysis was repeated for the primary and secondary outcomes for patients without asthma diagnostic codes.

1.4 Results

In the matched comparison of BDP/FOR and FP/SAL, 537 patients in each group were compared. The median age was 70 and 69 respectively and 41.7% of matched patients were current smokers. In the matched comparison BDP/FOR and BUD/FOR, 540 patients in each group were compared. The median age was 70 and 69 respectively and 42% were current smokers. The odds ratio (OR) of an exacerbation was 0.89 (95% CI, 0.67, 1.19) between BDP/FOR and FP/SAL and 0.79 (95% CI, 0.58, 1.08) between BDP/FOR and BUD/FOR after adjustment. There was a significantly lower antibiotic prescription rate in the BDP/FOR compared to FP/SAL (OR=0.77, 95% CI: 0.65, 0.92). No significant difference between BDP/FOR and FP/SAL or BUD/FOR in other secondary outcomes were found. Cost was in favour of BDP/FOR over FP/SAL for real and bootstrapped observations (adjusted mean £730 versus £850 respectively, p<0.001) and equivalent for BDP/FOR vs BUD/FOR (adjusted mean £732 versus £757 respectively, p=0.054).

In the sub-analyses (patients with asthma diagnostic codes excluded) patients prescribed BDP/FOR were at a lower risk of having an exacerbation compared to FP/SAL, and a lower exacerbation rate (RR 0.74, 95% CI 0.56-0.99) the year following initiation (OR 0.64, 95% CI 0.43-0.96, N=315). Compared to BUD/FOR, patients prescribed BDP/FOR were numerically at less risk of an exacerbation, but this was not statistically significant (OR 0.81, 95% CI 0.51-1.28, N=314).

1.5 Conclusion

Treatment with BDP/FOR is non-inferior in terms of exacerbation risk. Antibiotic prescriptions were significantly lower compared to the FP/SAL treatment group, at a lower prescribed ICS dose and compared to FP/SAL and BUD/FOR the cost was lower for BDP/FOR. Sub-analysis showed that in patients without an asthma code, initiating on BDP/FOR were at a significantly lower risk of exacerbation in the first year compared to patients initiating FP/SAL.

2.0 Background

Chronic obstructive pulmonary disease (COPD) is a common, underdiagnosed condition that affects 7.7% of adults in North America and Western Europe.[1] In the UK, it is estimated that three million people have COPD,[2] accounting for 1.4 million general practice consultations per year, and 1 in 8 emergency admissions.[3] COPD is characterised by airflow limitation in the lungs which is largely caused by long term smoking in patients aged over 40 years. Clinical suspicion of COPD is raised by symptoms such as cough and shortness of breath, alongside a positive history of smoking. Acute exacerbations are common at all levels of disease severity, and contributes to the annual COPD mortality of at least 25,000 in the UK alone.[2] Frequency of exacerbations in previous years is the most useful predictor of disease progression, making the number of exacerbations one of the most useful COPD treatment outcomes.[4]

Recommended primary treatment for COPD is an inhaled bronchodilator, either a long-acting muscarinic antagonist (LAMA) and/or long-acting β-agonist (LABA).[5] Inhaled corticosteroids (ICS) are also extensively used in the treatment of COPD, although monotherapy is not recommended.[5,6] Both the National Institute of Care and Excellence (NICE) and Global Initiative for Chronic Lung Disease (GOLD) guidelines recommend the use of inhaled corticosteroid (ICS) as part of a fixed dose combination (FDC) ICS/LABA treatment for patients with moderate to severe COPD (Forced Expiratory Volume in 1 second [FEV_1] <50% predicted normal)[7], with a high risk of exacerbations (GOLD groups C and D)[5].

A limited number of FDC inhalers are licensed in the treatment of COPD. Fostair®*(BDP/FOR) is a FDC ICS/LABA pressurised metered dose inhaler (pMDI) containing 100µg of the ICS beclometasone dipropionate, as an extrafine formulation and 6µg of the LABA formoterol fumarate.[8] The extrafine ICS formulation results in higher lung deposition, which allows for lower doses to be used for the same clinical effect, which may also minimise the side-effects

caused from systemic absorption.[4,9] Other current FDC ICS/LABA therapies licensed for COPD in the United Kingdom[10] include Seretide Accuhaler® 500 (FP/SAL) dry powder inhaler (DPI)[*11] and Symbicort® Turbohaler® 200/6 or 400/12 (BUD/FOR) DPI[†12,13].

BDP/FOR pMDI has previously been prescribed off-licence for the treatment of COPD in the UK (unpublished data from OPRI), but was licensed in April 2014 at a dose of two actuations, twice daily. The licensed indication is for the "symptomatic treatment of patients with severe COPD (FEV_1 <50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators."[6] BDP/FOR pMDI is also a less expensive FDC ICS/LABA, costing £0.98 per day, compared to £1.36 per day for FP/SAL DPI, and £1.27 per day for both Symbicort® 200/6 and 400/12 Turbohaler® as of December 2016.[‡14]

Randomised controlled trials have demonstrated BDP/FOR pMDI to be superior to LABA alone (formoterol, p=0.046), in patients with severe stable COPD, and non-inferior to extrafine formulation (budesonide/formoterol, 95% confidence interval -0.052-0.048), in terms of the change in pre-dose morning FEV_1.[9] Another trial ;The FORWARD study[10,15] compared BDP/FOR pMDI to formoterol in a population of severe COPD patients with a history of exacerbations. BDP/FOR pMDI was demonstrated to reduce exacerbation rates over 48 weeks (rate ratio: 0.72 [95% confidence interval 0.62-0.84], p<0.001), improve pre-dose morning FEV_1 at 12 weeks (mean difference 0.069L [0.043-0.095], p<0.001) and prolong the time to first exacerbation.

However, BDP/FOR pMDI has only been evaluated in real-life clinical practice in patients with asthma. In a previous study carried out by OPRI (OPRI formerly known as RIRL) for Chiesi Ltd (the REACH study), BDP/FOR was demonstrated to be non-inferior to Seretide® in preventing acute respiratory events for patients with asthma at an equivalent or lower dose of

[*]500µg fluticasone propionate (ICS), 50µg salmeterol xinafoate (LABA) per inhalation, requiring slow and deep inhalation for administration.
[†]200µg budesonide (ICS), 6µg formoterol fumarate dihydrate (LABA); or 400µg budesonide (ICS), 12µg formoterol fumarate dihydrate (LABA) per inhalation, requiring forceful inhalation for administration.
[‡] Prices are calculated from the device price listed, where each device contains 30 days' treatment when prescribed according to recommendation: 120-dose Fostair® pMDI (£29.32) and Symbicort® 200 Turbohaler® (£38.00) at two actuations twice daily; 60-dose Seretide® 500 Accuhaler® (£40.92) and Symbicort® 400 Turbohaler® (£38.00) at one actuation twice daily

ICS, and also reduced mean asthma-related healthcare costs by £93.63 per patient per year ($p<0.001$).[16]

The REACH II study will therefore examine the clinical and cost effectiveness of BDP/FOR pMDI in licensed doses in a population of patients with COPD.

3.0 Study aims and objectives

The aim of the study is to compare clinical outcomes associated after the initiation of licensed COPD treatments, specifically comparing BDP/FOR pMDI versus BUD/FOR and FP/SAL

3.1 Study objectives

3.1.1 Primary objective

To establish whether the outcomes after initiation of licensed COPD ICS/LABA treatment with BDP/FOR pMDI is non-inferior, in terms of the proportion of patients with COPD who experience moderate/severe exacerbations, compared to other licensed FDC ICS/LABA COPD therapies (FP/SAL DPI and separately BUD/FOR DPI*). Superiority was tested after non-inferiority was established.

3.1.1.1 Sub-analysis

The primary objective was tested with patients diagnosed with COPD and no other respiratory-related diagnoses (ie: excluding patients with a diagnostic code for asthma) as an exploratory sub-analysis.

3.1.2 Secondary objectives

To compare the outcomes after initiation of licensed COPD ICS/LABA treatment with BDP/FOR pMDI to FP/SAL DPI and separately to BUD/FOR DPI for the time to first exacerbation, rate of exacerbations, treatment stability, lung function, and respiratory-related hospitalisations, cumulative oral corticosteroid dose, antibiotic prescriptions, modified Medical Research Council (mMRC) dyspnoea score, FEV_1 percent predicted, reliever inhaler usage, and pneumonia diagnosis.

3.1.3 Cost effectiveness objective

The cost-effectiveness of BDP/FOR pMDI treatment in the UK National Health Service (NHS) relative to treatment with other licensed COPD therapies was assessed. Incremental cost-effectiveness ratios of total respiratory-related and proportion experiencing any moderate/severe COPD exacerbation in the outcome year for each treatment group was calculated for each pairwise comparison.

* Symbicort® 200 Turbohaler® and Symbicort® 400 Turbohaler combined due to their equivalent daily dose according to recommended prescribing practice.

4.0 Study design

4.1 Medication studied

The investigational product is Fostair®, a FDC ICS/LABA containing 100µg beclometasone dipropionate and 6µg formoterol fumarate per inhalation in a pMDI device (BDP/FOR).[8] BDP/FOR was compared to:

i) Seretide Accuhaler® 500 (FP/SAL) DPI, a FDC ICS/LABA containing 500µg fluticasone propionate and 50µg salmeterol xinafoate per inhalation in a DPI device.[11]

ii)Symbicort® Turbohaler® (BUD/FOR) containing either 200µg budesonide and 6µg formoterol fumarate dihydrate (Symbicort® 200/6), or 400µg budesonide and 12µg formoterol fumarate dihydrate (Symbicort® 400/12) per inhalation in a DPI device.[12,13] These products were analysed as a single group as the daily dose is equivalent.

4.2 Study design

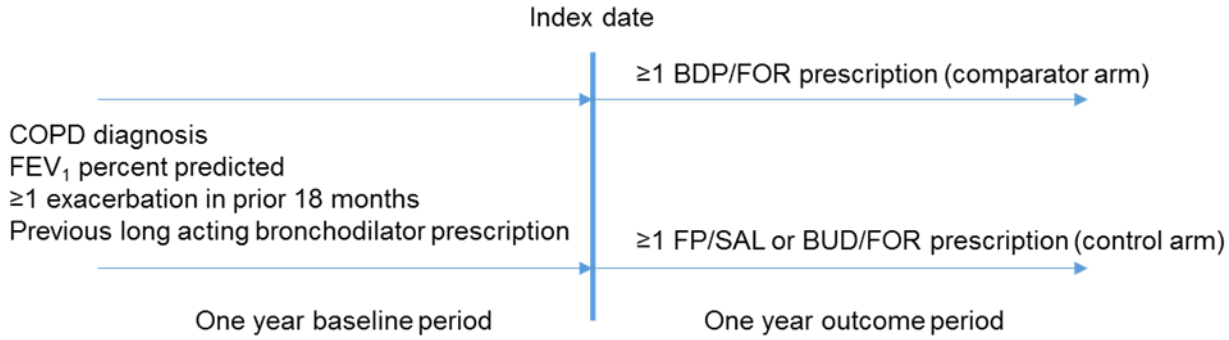
A retrospective matched cohort design comparing outcomes for patients initiating COPD treatment with BDP/FOR pMDI compared to FP/SAL DPI or separately BUD/FOR DPI was used.

The date of first prescription of BDP/FOR pMDI, FP/SAL DPI or BUD/FOR DPI, is considered the “index date”.

Patients were included if they had two years’ continuous practice data, comprising a one-year baseline period to identify demographic, co-morbid and clinical characteristics, ending at the index date, followed by a one-year follow up period (figure 1 and 2). Patient records which fitted more than one cohort* were placed in the BDP/FOR cohort in preference to the FP/SAL or BUD/FOR cohort to maximise paired comparisons.

* ie: Patients who at a date initiated on licensed FDC ICS/LABA, stopped treatment for an extended time, then re-initiated on a licensed FDC ICS/LABA

Figure 1: Study design showing comparison between BDP/FOR and FP/SAL



5.0 Study population

5.1 Inclusion and exclusion criteria

The inclusion criteria were designed to operationalise the licensed indication for BDP/FOR in patients with COPD Table 1.

Table 1: Inclusion and exclusion criteria

Inclusion criteria
Clinician diagnosed COPD (confirmed by spirometry: FEV_1/FVC <0.7)
Age ≥35 years at index date
Two years of continuous practice data comprising 1-year baseline data and 1-year outcome data
≥2 prescriptions of the same licensed FDC ICS/LABA (including the prescription on index date) during the outcome period [BDP/FOR pMDI, FP/SAL DPI, Symbicort® 200 Turbohaler®, and Symbicort® 400 Turbohaler®]
≥1 prescription of LABA and/or LAMA (with or without an ICS alone) and/or an unlicensed FDC ICS/LABA therapy during a 2-year period prior to the index date
≥1 moderate to severe COPD exacerbation during an 18-month period preceding index date*
FEV_1 <55% predicted recorded ever†
Exclusion criteria
No documentation of smoking, and non-smoker documented

* Fulfilling the licensed criteria for recent exacerbations
† Since most spirometry readings in clinical practice are taken during the period where a patient is being treated with a long acting bronchodilator, this reading is higher than the 50% cut off for patients tested without a long acting bronchodilator in the product specification recommendations

5.2 Data source

The study used patient data from the Optimum Patient Care Research Database (OPCRD).[17] The study team worked with anonymised data removed of any patient identifiable information.

The OPCRD currently comprises longitudinal medical records for over 3.6 million patients from over 600 primary care practices across the UK. The OPCRD is the only database in the UK that complements routinely recorded disease coding and prescribing information with patient-reported outcomes using validated questionnaires.

The study was performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices. The database has received a favourable opinion from the Health Research Authority for clinical research use (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 recognised databases. The study was registered on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP, http://www.encepp.eu/) database (EUPAS9142).

6.0 Study variables and study outcomes

A complete list and description of the study variables is found in the appendices.

6.1 Baseline variable

6.1.1 Demographics

Demographic characteristics included Age, Sex, Smoking status, Body Mass Index and Duration of COPD diagnosis.

6.1.2 Comorbidities

Comorbidities included: Allergic/non-allergic rhinitis, Asthma, Bronchiectasis, Eczema diagnosis, Gastro-oesophageal reflux disease, Diabetes Mellitus type 2, Osteoporosis, Heart failure, Hypertension, Ischaemic Heart Disease, Anxiety/Depression, Lung cancer and Charlson Comorbidity Index.

6.1.3 Clinical characteristics

The following clinical characteristics were assessed:

FEV_1

FEV_1/FVC

FEV_1 % predicted

FEV_1 % predicted (categorised)

mMRC dyspnoea score

Global Initiative for Chronic Obstructive Lung Disease (GOLD) group

Number of oral corticosteroid prescriptions used to treat lower respiratory infections

Number of antibiotic prescriptions for lower respiratory tract infections

ICS dose prescribed

Standalone inhaled corticosteroids (ICS) prescription

ICS prescriptions (categorised)

Standalone inhaled corticosteroids (ICS) inhalers

ICS inhalers (categorised)

Combination inhaled corticosteroid (ICS/LABA) prescription

ICS/LABA prescriptions (categorised)

Standalone LAMA prescription

LTRA prescriptions

Theophylline prescriptions

SABA inhalers

SABA inhalers (categorised)

SABA prescriptions

SABA prescriptions (categorised)

SABA daily dose

SABA daily dose (categorised)

SAMA daily dose

ICS daily dose (FP equivalent)

ICS daily dose (categorised – FP equivalent)

COPD exacerbations

COPD exacerbations (categorised)

ICS adherence

Respiratory-related primary care consultations

Respiratory related accident and emergency admission

6.2 Primary outcome

The proportion of patients with moderate/severe* COPD exacerbations in the outcome period.

6.3 Secondary outcomes

6.3.1 Respiratory outcomes

- Rate of moderate/severe COPD exacerbations
- Time to first exacerbation (not considering exacerbations up to 2 weeks after index date)
- Cumulative oral corticosteroid dose, comprising:
    - Acute prescription used to treat lower respiratory exacerbations†
    - Maintenance therapy‡
- Total number of courses of antibiotics
- Treatment stability§
- Respiratory-related hospitalisations
- mMRC dyspnoea score
- Lung function (FEV_1 % predicted closest to index date in outcome period)
- Reliever use (both average SABA daily dose and average SAMA daily dose**)
- Confirmed and suspected cases of pneumonia

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* Moderate/severe exacerbation includes unscheduled respiratory related hospital admissions/A&E attendances, acute OCS prescriptions or antibiotic prescription with a respiratory consultation

† Acute oral steroid use associated with COPD exacerbation treatment will be defined as:

- all courses that are definitely not part of maintenance therapy, and/or
- all courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed), and/or
- all courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions.

‡ "Maintenance therapy" is defined as: >6 prescriptions with daily dosing instructions of <=10mg Prednisolone or prescriptions for 1mg or 2.5mg prednisolone tablets where acute prescription is not suggested.

§ **Stable:** absence of the following:

1. Exacerbations (as defined above); AND
2. Additional or change in therapy:

Unstable: all others.

A more detailed definition of the above terms can be found in Appendix 1.

** As defined above

6.4 Cost-effectiveness outcome

Total and disaggregated COPD-related resource use and costs was reported, including COPD drug prescriptions (FDC ICS/LABA, ICS, LAMA, LABA, SABA, SAMA, LTRA, THEO, acute oral corticosteroids and antibiotics for LTRIs); primary care consultations and respiratory-related hospital costs (eg. outpatient, inpatient and accident and emergency).

6.5 Exploratory subgroup analysis

Patients without a prior asthma diagnosis were selected. There were 322 patients in the BDP/FOR cohort, 1767 patients in the Symbicort cohort, and 2080 patients in the Seretide cohort fitting the criteria available. After matching, there were 315 patients in the comparison between BDP/FOR and FP/SAL, and 314 patients in the comparison between BDP/FOR and BUD/FOR. As this sub-analysis was insufficiently powered all findings from these analyses are considered exploratory.

7.0 Statistical analysis

7.1 Software used and power calculation

The dataset was analysed using SPSS version 23, SAS version 9.3, Stata SE version 14 (StataCorp, College Station, TX) and Microsoft Office EXCEL 2013, as appropriate.

Based on previous work if there is a true difference in the odds ratio in favour of BDP/FOR compared to the standard difference of 1.2, then 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 favour of the pre-defined non-inferiority margin of 20%.[18]

7.2 Baseline characterisation

Summary statistics was produced for all baseline and outcome variables, as a complete dataset, by treatment group and for sub-groups. Sample size (n), Percentage non-missing, Mean, Standard Deviation (SD), Median, Inter-quartile range (IQR – 25th and 75th percentiles), Count and percentage by category are presented as appropriate.

Baseline characteristics were compared between groups using: t-test (normal distribution), Mann-Whitney U test (non-parametric), and chi-square test as appropriate. The statistical significance for all tests will be set at $p<0.05$.

The difference between the treatment arms was quantified using the Standardised Mean Difference (SMD). This measure is not affected by the number of observations, and thus a better way to judge imbalance than a p-value of a hypothesis test of difference. The SMD was calculated for both continuous and categorical variables. An SMD ≤0.1 indicated sufficient balance between the treatment and the reference (control) groups.

In addition, the bias potential was calculated for each variable. Bias potential assesses the degree to which the observed association between the exposure of interest and the outcome is affected by conditioning on the variable. Bias potential was measured using the relative change in co-efficient (RCC) of the exposure when the covariate is added into the model used to predict the outcome.

The baseline variables with the highest bias potential, that are also sufficiently imbalanced (SMD > 0.1) were presented to a panel of clinical experts (the steering committee) for the final selection of variables to use for matching.

Any residual differences between the treatment arms after matching that are potentially significant ($p<0.10$) and any variables predictive of outcome will be adjusted for through further statistical modelling. When items are co-linear in nature, clinical input will be sought to decide which variable should be included in the model.

7.3 Matching

Initially, baseline data was compared between unmatched cohorts (BDP/FOR vs FP/SAL, and BDP/FOR vs BUD/FOR). Patients will be matched 1:1 on baseline therapy to minimise bias. If patient numbers are larger than expected, additional exact matching for categorical variables and coarsened exact matching for numeric variables may be used to match patients using 1:1 nearest neighbour matching, without replacement. Matching variables such as demographic data, disease co-morbidity and indicators of disease severity was considered for selection using a combination of baseline data analysis and predictive modelling of the baseline data in relation to the primary outcome variable (independently of treatment group).

Missing data will be treated as missing completely at random and will not be imputed. If a selected confounder has more than 20% of missing data, it will not be used for matching. If missingness is below 20%, the variable will be encoded into a categorical variable, adding a category for the observations with missing values, enabling this variable to be used for matching.

The matching variables were selected taking into account both data (RCC value > 2%) and clinical relevance. The matching variables are listed below:

- Age categorised ("≥35 to <45", "≥45 to <55", "≥55 to <65" and "≥65")
- Smoking status
- Categorised lowest FEV_1 ("≤ 20% ", "20% to <30%", "30% to <40%", "40% to <55%")
- Baseline exacerbations

7.4 Analysis of study outcomes

7.4.1 Primary outcome: non-inferiority in COPD exacerbations

This primary outcome analysis was repeated for the two comparisons:

1. BDP/FOR pMDI versus FP/SAL DPI
2. BDP/FOR pMDI versus BUD/FOR DPI

To show non-inferiority in terms of COPD exacerbations, the adjusted proportions of patients within each treatment group recording any exacerbations in the outcome period was calculated using a generalised linear model with binomial distribution and logit link (logistic regression). Conditional logistic regression (CLR) analysis was performed on the matched dataset, taking into account matched pairs.

Adjustment for residual confounding was made. Since it can be expected that these variables can have similar associations with exposure and/or outcome, their conditional bias on the variables already in the model was assessed.

Starting with a model with exposure as the only explanatory variable, the variables were added one by one in order of their individual bias potential, highest first. After a variable is added to the model it was kept in if it causes a change-in-estimate of at least 2%, relative to the prior model.

Non-inferiority in exacerbations was achieved if the proportion of BDP/FOR pMDI patients recording any exacerbations in the outcome year is no more than 20% higher than the proportion of patients on the comparator medications (FP/SAL DPI or BUD/FOR DPI)i.e. if the higher confidence interval of the difference in proportions of patients recording any exacerbations is greater than +0.20.[19]

In the case of non-inferiority being achieved, superiority was defined as the proportion with exacerbations in the treatment group was less than the proportion with exacerbations in the control group assessed through conditional logistic regression.

7.4.2 Secondary outcomes

7.4.2.1 Respiratory outcomes: COPD exacerbations

The total number of exacerbations in the outcome period was compared between treatment groups using a conditional Poisson regression model to obtain an estimate of relative exacerbation rates. The model used empirical standard errors (for more conservative confidence interval estimations) and adjustments will be made for potential baseline confounders. Results were presented as a rate ratio with 95% confidence intervals.

Unadjusted comparisons of event rates for first exacerbations from index date were compared between matched groups using Kaplan-Meier estimates and the log-rank test for equality of survival curves. Time to first exacerbation was compared using a Cox proportional hazards regression model with stratification on matched pairs. Results are reported as a hazard ratio with 95% confidence intervals.

7.4.2.2 Other respiratory outcomes

Rates of respiratory-related hospitalisations were compared using conditional Poisson regression models. Results were reported as a rate ratio with 95% confidence intervals.
Treatment stability (a dichotomous outcome) were compared using conditional logistic regression. Results were reported as an odds ratio with 95% confidence intervals.
The mMRC dyspnoea score was compared using analysis of covariance, stratified by matching ID. Results were reported as a mean difference with 95% confidence intervals.
Categorised reliever use, where a higher category denotes more reliance on reliever inhalers, were compared using a conditional ordinal regression model. Results were reported as an odds ratio with 95% confidence intervals.

All models were adjusted for potential confounders (residual differences at baseline and variables predictive of outcome).

All other respiratory outcomes (courses of oral corticosteroids, courses of antibiotics, lung function, and cases of pneumonia) were reported as the proportion of patients in each treatment group.

7.4.2.3 Cost-effectiveness

Resource use and medication costs were reported and compared as follows: total and disaggregated respiratory-related costs, including COPD drug prescriptions (FDC ICS/LABA, ICS, LAMA, LABA, SABA, SAMA, Leukotriene Receptor Antagonists (LTRA), Theophylline (THEO), acute oral corticosteroids and antibiotics for lower respiratory tract infections (LTRIs); primary care consultations and respiratory-related hospital costs (e.g. outpatient, inpatient and accident and emergency).

Estimation of respiratory-related costs

Information on respiratory-related resource use* were extracted from databases and multiplied with unit costs in 2016 sterling (£) based on UK NHS costs. Unit cost estimates were obtained from UK national data sources including:

- Primary care consultation costs will be taken from the latest Personal Social Services Research Unit (PSSRU) document (http://www.pssru.ac.uk/project-pages/unit-costs/2016)
- Secondary care costs based on NHS reference costs 2015-2016 (https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016).†
    - The weighted average cost for each type of secondary care visit (A&E admission, outpatient attendance, inpatient long stay, inpatient short stay and day case) was estimated for each specific-outcome using the appropriate health resource group (HRG) codes.

* Respiratory-related resource use includes drug prescriptions and consultations in the following settings:
- Primary care
- In-patient hospitalisations
- Out-patient hospitalisations
- A&E hospitalisations

† Reference costs are the average unit cost to the NHS of providing defined services to NHS patients in England in a given financial year and have been collected annually by the Department of Health (the Department) since 1997

- Prices assigned to drugs were taken from the Dictionary of Medicines and Devices browser (http://dmd.medicines.org.uk/). In cases of missing data the electronic British National Formulary (eBNF) and the Medical Index of Medicinal Substances (MIMS) were used.

Cost-effectiveness analysis

Costs between treatments were compared using arithmetic mean COPD-related healthcare costs per patient per year during the outcome period, both unadjusted and adjusted for confounding factors. Effectiveness between treatments were compared in terms of proportion of patients who experienced any moderate/severe COPD exacerbations within the one-year outcome period

To test whether unadjusted mean cost differences are statistically different between each comparison group, measures of variability (standard errors, p-values and confidence intervals) were estimated/developed using two methods: (1) a Kruskal-Wallis test; and (2) non-parametric bootstrapping with 1000 samples taken with replacement from the dataset. Adjusted COPD-related healthcare costs during the outcome period were estimated using generalised linear models with a Gamma distribution and log link, controlling for potential confounders at baseline including health care resource utilisation. Differences in adjusted mean costs were reported with 95% confidence intervals developed from non-parametric bootstrapping methods with 1000 random samples taken with replacement from the dataset.

The adjusted two-way differences (relative to comparators) in costs and proportions of patients recording any COPD exacerbations for the 1000 random samples were displayed graphically on a cost-effectiveness plane. The four quadrants of the cost-effectiveness plane (see Figure 2) represent BDP/FOR pMDI being:

- Quadrant I: more costly and more effective (a trade-off);
- Quadrant II: more costly and less effective comparator dominant);
- Quadrant III: less costly and less effective (a trade-off); and
- Quadrant IV: less costly and more effective (BDP/FOR pMDI dominant).

When point estimates resulted in a trade-off (i.e., quadrants I and III) between comparators, an incremental cost-effectiveness ratio (ICER) was calculated as the ratio of the mean

difference in total COPD-related healthcare costs per patient (incremental costs) in the follow-up period to the difference in proportions of patients with any COPD exacerbations in the follow-up period (incremental effectiveness).

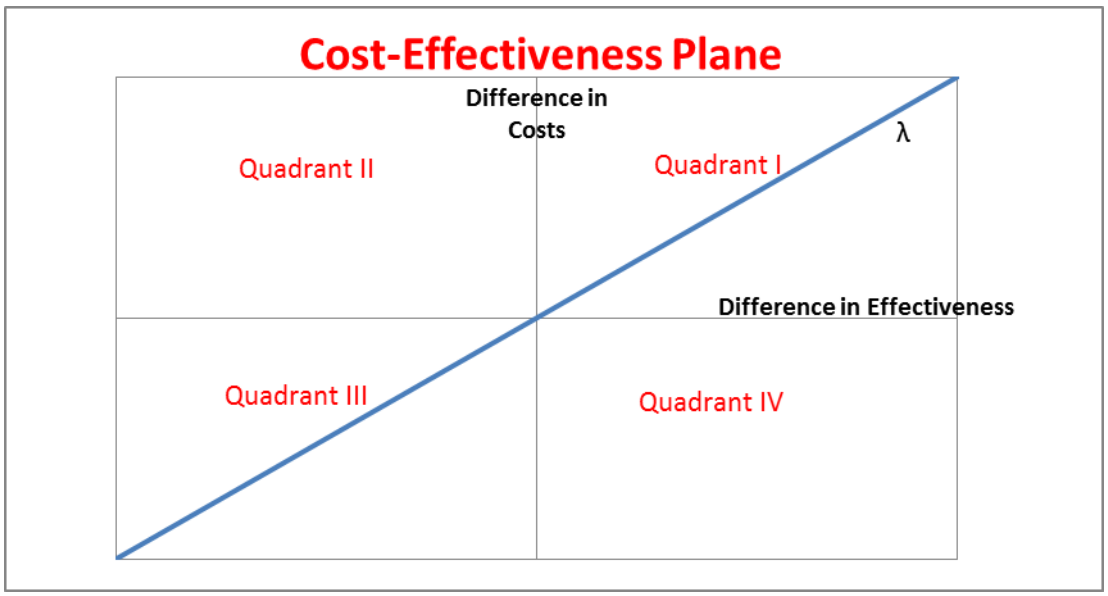


Figure 2: The cost-effectiveness plane

8.0 Patient population

Table 2: Patient numbers before/after inclusion/exclusion criteria

Patient numbers	Inclusion/exclusion Criteria	Number of patients excluded
3 460 270	All patients in OPCRD	NA
FP/SAL 34 842 BDP/FOR 30 933 BUD/FOR 97 997	Initiates on licensed FDC ICS/LABA	3 296 498
FP/SAL 22 854 BDP/FOR 6 744 BUD/FOR 30 819	COPD diagnosis or $FEV_1/FVC<0.7$	FP/SAL 11 988 BDP/FOR 24 159 BUD/FOR 67 178
FP/SAL 15 678 BDP/FOR 3 586 BUD/FOR 22 275	One year of data prior and post initiation of licensed FDC ICS/LABA	FP/SAL 7 176 BDP/FOR 3 188 BUD/FOR 8 544
FP/SAL 15 637 BDP/FOR 3 573 BUD/FOR 22 150	Age 35 or older	FP/SAL 41 BDP/FOR 13 BUD/FOR 125
FP/SAL 13 645 BDP/FOR 2 999 BUD/FOR 18 629	At least 2 prescriptions of licensed FDC ICS/LABA in the outcome period (including index date)	FP/SAL 1 992 BDP/FOR 574 BUD/FOR 3521
FP/SAL 11 339 BDP/FOR 2 405 BUD/FOR 15 805	No change of ICS/LABA in outcome period	FP/SAL 2 306 BDP/FOR 594 BUD/FOR 2 824
FP/SAL 7 929 BDP/FOR 1 550 BUD/FOR 8 577	At least one prescription of LABA and/or LABA and/or unlicensed FDC ICS/LABA prior to index date	FP/SAL 3 410 BDP/FOR 855 BUD/FOR 7 228
FP/SAL 5 640 BDP/FOR 1 065 BUD/FOR 5 969	At least one exacerbation in the prior 18 months	FP/SAL 2 289 BDP/FOR 485 BUD/FOR 2608
FP/SAL 3 628 BDP/FOR 573 BUD/FOR 3 669	$FEV_1<55\%$ ever	FP/SAL 2 012 BDP/FOR 492 BUD/FOR 2 300
FP/SAL 3 416 BDP/FOR 549 BUD/FOR 3 419	Smokers	FP/SAL 212 BDP/FOR 24 BUD/FOR 250
FP/SAL 3 374 BDP/FOR 549 BUD/FOR 3 001	Discarded patient events appearing in both BDP/FOR and another cohort	FP/SAL 42 BDP/FOR 0 BUD/FOR 418

9.0 Unmatched baseline results

This section presents the baseline characteristics one year prior to initiation of FDC ICS/LABA treatment. Baseline characteristics for the sub-analysis are found in the appendix. The exploratory variable for time since COPD diagnosis is provided for illustration, but is not considered a reliable indicator of time since diagnosis due to coding practices.

9.1 Unmatched characteristics of study population (BDP/FOR vs FP/SAL)

Patients were well balanced in terms of gender, BMI and smoking status but not age. In terms of categorised age, the SDD between groups was 12.5, with a greater proportion of patients in the 35-<45, 45-<55, ≥65 category, and fewer in the 55-<65 category.

Table 3: Unmatched baseline characteristics – BDP/FOR versus FP/SAL DPI

		BDP/FOR N=549	FP/SAL DPI N=3374	p-value	SDD	RCC
Gender	Male	298 (54.3)	1,941 (57.5)	0.1539	6.5	0.9
Age (years)	Mean (SD)	68.9 (10.6)	68.2 (9.6)	0.0425	7.0	0.7
	Median (IQR)	70.0 (15.0)	68.0 (13.0)			
Age (years)	≥35 <45	12 (2.2)	38 (1.1)	0.0440	12.5	0.4
	≥45 <55	43 (7.8)	239 (7.1)			
	≥55 <65	118 (21.5)	864 (25.6)			
	≥65	376 (68.5)	2,233 (66.2)			
BMI (kg/m^2)	N (% non-missing)	549 (100.0)	3,362 (99.6)	0.1689	7.0	0.1
	Mean (SD)	27.1 (6.4)	26.7 (6.0)			
	Median (IQR)	26.2 (7.1)	25.8 (7.6)			
BMI (kg/m^2)	N (% non-missing)	549 (100.0)	3,362 (99.6)	0.2593	9.2	0.2
	<18.5	30 (5.5)	191 (5.7)			
	≥18.5-<25	184 (33.5)	1,258 (37.4)			
	≥25-<30	194 (35.3)	1,064 (31.6)			
	≥30	141 (25.7)	849 (25.3)			
Smoking status closest to index date	Non-smoker	24 (4.4)	162 (4.8)	0.9079	2.1	0.0
	Current smoker	228 (41.5)	1,395 (41.3)			
	Ex-smoker	297 (54.1)	1,817 (53.9)			
Time since COPD diagnosis (years)	N (% non-missing)	494 (90.0)	3,150 (93.4)	0.3117	10.6	2.1
	<2	93 (18.8)	655 (20.8)			
	2 to <4	80 (16.2)	598 (19.0)			
	4 to <6	79 (16.0)	481 (15.3)			
	6 to <8	67 (13.6)	423 (13.4)			
	8+	175 (35.4)	993 (31.5)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Prescription practices by treatment group are reported in table 4. The number of prescriptions was different in each group (SDD = 22.1), with a greater proportion of patients in the BDP/FOR cohort having no prescriptions in the baseline year (24.6% vs 16.8%). There was a similar proportion of patients prescribed SAMA (15.3% in the BDP/FOR group vs 17.6% in the FP/SAL group). A higher proportion of patients in the FP/SAL group were prescribed SABA/SAMA combination treatments (9% vs 1.3%, SDD 35.5). Similar proportions of patients were prescribed unlicensed FDC ICS/LABAs (34.2% in the BDP/FOR group had 0 prescriptions compared to 33.9% in the FP/SAL group, SDD 6.5). The proportions of patients prescribed ICS only inhalers were similar with 77.6% in the BDP/FOR group and 75.5% in the FP/SAL group. The proportion of patients prescribed a LAMA inhaler was similar (63.6% in the BDP/FOR group, 60.3% in the FP/SAL group SDD 6.8). A higher proportion of patients are prescribed LABA in the FP/SAL group (16.1% vs 11.7%, SDD 12.8). Numbers of combination LABA/LAMA were very low in this study population. A higher proportion of

FP/SAL patients were prescribed theophylline (11.8% vs 6.9%, SDD 16.9), while a higher proportion of BDP/FOR were prescribed maintenance oral corticosteroid therapy (6.9% vs 4.8% SDD 9.0).

Table 4: Unmatched baseline characteristics – BDP/FOR versus FP/SAL DPI

		BDP/FOR N=549	FP/SAL DPI N=3374	p-value	SDD	RCC
SABA inhaler prescriptions	0	135 (24.6)	568 (16.8)	0.0001	22.1	1.1
	1	39 (7.1)	215 (6.4)			
	2-4	83 (15.1)	627 (18.6)			
	5-10	147 (26.8)	1,097 (32.5)			
	≥11	145 (26.4)	867 (25.7)			
SABA inhalers	0	135 (24.6)	568 (16.8)	0.0002	20.7	1.8
	1	32 (5.8)	163 (4.8)			
	2-4	82 (14.9)	542 (16.1)			
	5-10	128 (23.3)	933 (27.7)			
	≥11	172 (31.3)	1,168 (34.6)			
Average daily dose of SABA	0	449 (81.8)	2,473 (73.3)	0.0002	22.1	1.5
	>0 to <200	84 (15.3)	754 (22.3)			
	200 to <400	3 (0.5)	58 (1.7)			
	≥400	13 (2.4)	89 (2.6)			
SAMA prescriptions	≥1	84 (15.3)	595 (17.6)	0.1800	6.3	0.1
SAMA µg/day	0	449 (81.8)	2,473 (73.3)	0.0004	20.6	1.3
	>0 to <40	99 (18.0)	890 (26.4)			
	40 to <80	1 (0.2)	10 (0.3)			
	≥80	0 (0.0)	1 (0.0)			
SAMA/SABA prescriptions	≥1	7 (1.3)	303 (9.0)	<0.0001	35.5	2.3
FDC ICS/LABA prescriptions	0	188 (34.2)	1,143 (33.9)	0.7330	6.5	0.2
	1	31 (5.6)	164 (4.9)			
	2-4	66 (12.0)	449 (13.3)			
	5-10	153 (27.9)	985 (29.2)			
	≥11	111 (20.2)	633 (18.8)			
FDC ICS/LABA inhalers	0	188 (34.2)	1,143 (33.9)	0.9241	4.3	0.4
	1	26 (4.7)	136 (4.0)			
	2-4	56 (10.2)	354 (10.5)			
	5-10	148 (27.0)	897 (26.6)			
	≥11	131 (23.9)	844 (25.0)			
ICS monotherapy average prescription	0	426 (77.6)	2,548 (75.5)	0.2291	11.5	0.3
	1	18 (3.3)	178 (5.3)			
	2-4	41 (7.5)	239 (7.1)			
	5-10	43 (7.8)	304 (9.0)			
	≥11	21 (3.8)	105 (3.1)			
ICS monotherapy inhalers	0	426 (77.6)	2,548 (75.5)	0.3370	10.4	0.5
	1	16 (2.9)	158 (4.7)			
	2-4	39 (7.1)	216 (6.4)			
	5-10	42 (7.7)	293 (8.7)			
	≥11	26 (4.7)	159 (4.7)			
Total ICS dosage	0-249	240 (43.7)	1,388 (41.1)	0.1768	8.7	0.9
	250-499	151 (27.5)	880 (26.1)			
	500+	158 (28.8)	1,106 (32.8)			
LAMA prescriptions	≥1	349 (63.6)	2,034 (60.3)	0.1437	6.8	0.6
LABA prescriptions	≥1	64 (11.7)	542 (16.1)	0.0081	12.8	0.1
LABA/LAMA combination prescriptions	≥1	2 (0.4)	1 (0.0)	0.0085	7.6	0.5
Theophylline prescriptions	≥1	38 (6.9)	399 (11.8)	0.0007	16.9	1.9
Leukotriene prescriptions	≥1	32 (5.8)	138 (4.1)	0.0635	8.0	0.8
Maintenance OCS	Yes	38 (6.9)	162 (4.8)	0.0362	9.0	0.2

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Comorbidities by treatment group are reported in table 5. The main differences in the comorbidities in the unmatched pairing between BDP/FOR and FP/SAL was the higher proportion of bronchiectasis diagnosis (7.5% vs 4.3%, SDD 13.6), higher eczema 'ever' diagnosis (26.6% vs 22.1%, SDD 10.5), GERD diagnosis (4% vs 2.4%, SDD 8.9), and anxiety depression diagnosis coded ever (37.9% vs 32.1%, SDD 12.2) or actively treated (25.1% vs 20.9% SDD 10.2).

Table 5: Unmatched baseline characteristics – BDP/FOR versus FP/SAL DPI

		BDP/FOR N=549	FP/SAL DPI N=3374	p-value	SDD	RCC
Asthma diagnosis (QOF)	Yes	227 (41.3)	1,294 (38.4)	0.1815	6.1	0.5
Rhinitis diagnosis	Yes	81 (14.8)	417 (12.4)	0.1180	7.0	0.2
Active rhinitis diagnosis	Yes	45 (8.2)	238 (7.1)	0.3371	4.3	0.2
Bronchiectasis diagnosis	Yes	41 (7.5)	144 (4.3)	0.0010	13.6	0.4
Pneumonia diagnosis	Yes	21 (3.8)	87 (2.6)	0.0978	7.1	0.1
Lung cancer diagnosis	Yes	9 (1.6)	40 (1.2)	0.3746	3.8	0.2
Eczema diagnosis	Yes	146 (26.6)	746 (22.1)	0.0201	10.5	0.7
Eczema diagnosis with prescriptions	Yes	58 (10.6)	285 (8.4)	0.1033	7.2	0.2
GERD diagnosis or drugs	Yes	22 (4.0)	82 (2.4)	0.0329	8.9	0.3
Diabetes diagnosis	Yes	87 (15.8)	437 (13.0)	0.0644	8.3	0.0
Ischaemic heart disease diagnosis	Yes	115 (20.9)	626 (18.6)	0.1839	6.0	0.1
Heart failure diagnosis	Yes	15 (2.7)	67 (2.0)	0.2569	4.9	0.2
Hypertension diagnosis	Yes	231 (42.1)	1,319 (39.1)	0.1848	6.1	0.5
Chronic kidney disease Read code diagnosis	Yes	76 (13.8)	358 (10.6)	0.0251	9.9	0.4
Osteoporosis diagnosis	Yes	41 (7.5)	223 (6.6)	0.4564	3.4	0.3
Anxiety and/or depression diagnosis	Yes	208 (37.9)	1,082 (32.1)	0.0071	12.2	1.8
Active anxiety and/or depression diagnosis	Yes	138 (25.1)	704 (20.9)	0.0238	10.2	1.4
Charlson Comorbidity Index	0-2	348 (63.4)	2,170 (64.3)	0.8757	2.4	0.3
	3-4	139 (25.3)	820 (24.3)			
	5+	62 (11.3)	384 (11.4)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Measures of disease severity by treatment group are reported in table 6. In terms of disease severity, there were differences in the categorised number of COPD primary care consultations (SDD 29.6) with a greater proportion of patients in the BDP/FOR group with no consultations (37.7% vs 28.1%), outpatient visits (SDD 16.7), with a greater proportion of patients in the FP/SAL group with no visits and A&E attendances (SDD 13.2), with a greater proportion of patients in the FP/SAL group with no visits. There was also differences in the lowest FEV_1 percentage predicted (SDD 14.7), Gold severity (2016) (SDD 17.2) and mMRC score (SDD 19.2).

Table 6: Unmatched baseline characteristics – BDP/FOR versus FP/SAL DPI

		BDP/FOR N=549	FP/SAL DPI N=3374	p-value	SDD	RCC
COPD related GP consultations	0	207 (37.7)	949 (28.1)	<0.0001	29.6	1.5
	1	128 (23.3)	807 (23.9)			
	2-4	126 (23.0)	1,015 (30.1)			
	5-10	56 (10.2)	506 (15.0)			
	≥11	32 (5.8)	97 (2.9)			
Outpatient visits for COPD	0	484 (88.2)	3,092 (91.6)	0.0001	16.7	0.0
	1	33 (6.0)	197 (5.8)			
	≥2	32 (5.8)	85 (2.5)			
A & E attendances for COPD	0	529 (96.4)	3,315 (98.3)	0.0005	13.2	1.1
	1	16 (2.9)	56 (1.7)			
	≥2	4 (0.7)	3 (0.1)			
Inpatient admissions within 7 days of respiratory consultation	0	507 (92.3)	3,166 (93.8)	0.2196	7.3	1.1
	1	33 (6.0)	177 (5.2)			
	≥2	9 (1.6)	31 (0.9)			
Moderate/severe exacerbations	0	49 (8.9)	284 (8.4)	0.4036	9.3	4.4
	1	164 (29.9)	1,149 (34.1)			
	2	141 (25.7)	792 (23.5)			
	3	76 (13.8)	464 (13.8)			
	4+	119 (21.7)	685 (20.3)			
FEV_1 value (litres)	≤1	217 (39.5)	1,467 (43.5)	0.2101	9.6	0.9
	>1 to ≤2	287 (52.3)	1,691 (50.1)			
	2 to ≤4	35 (6.4)	164 (4.9)			
	>4	10 (1.8)	52 (1.5)			
FEV_1/FVC ratio	0.2 or less	5 (0.9)	24 (0.7)	0.0877	11.9	1.2
	0.2 to <0.4	91 (16.6)	683 (20.2)			
	0.4 to <0.6	250 (45.5)	1,573 (46.6)			
	0.6+	203 (37.0)	1,094 (32.4)			
Lowest percent predicted FEV_1	<20%	25 (4.6)	231 (6.8)	0.0216	14.7	2.0
	20% to <30%	103 (18.8)	723 (21.4)			
	30% to <40%	161 (29.3)	1,026 (30.4)			
	40% to <55%	260 (47.4)	1,394 (41.3)			
Gold severity (2016)	Mild	22 (4.0)	59 (1.7)	0.0007	17.2	2.1
	Moderate	193 (35.2)	1,057 (31.3)			
	Severe	259 (47.2)	1,703 (50.5)			
	Very severe	75 (13.7)	555 (16.4)			
mMRC score	N (% non-missing)	323 (58.8)	2,015 (59.7)	0.0163	19.2	9.5
	mMRC 0	37 (11.5)	129 (6.4)			
	mMRC 1	107 (33.1)	754 (37.4)			
	mMRC 2	98 (30.3)	584 (29.0)			
	mMRC 3	67 (20.7)	445 (22.1)			
	mMRC 4	14 (4.3)	103 (5.1)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

9.2 Unmatched characteristics of study population (BDP/FOR vs BUD/FOR)

Patients were well balanced in terms of gender and BMI but not age as a continuous variable (68.9 years for BDP/FOR vs 67.8 year for BUD/FOR, SDD 10.6).

Table 7: Unmatched baseline characteristics – BDP/FOR versus BUD/FOR DPI

		BDP/FOR N=549	BUD/FOR DPI N=3001	p-value	SDD	RCC
Gender	Male	298 (54.3)	1,713 (57.1)	0.2234	5.6	0.4
Age (years)	Mean (SD)	68.9 (10.6)	67.8 (9.9)	0.0109	10.6	0.4
	Median (IQR)	70.0 (15.0)	68.0 (13.0)			
Age (years)	≥35 <45	12 (2.2)	53 (1.8)	0.3120	8.9	0.2
	≥45 <55	43 (7.8)	244 (8.1)			
	≥55 <65	118 (21.5)	749 (25.0)			
	≥65	376 (68.5)	1,955 (65.1)			
BMI (kg/m^2)	N (% non-missing)	549 (100.0)	2,998 (99.9)	0.4565	4.3	0.0
	Mean (SD)	27.1 (6.4)	26.8 (6.0)			
	Median (IQR)	26.2 (7.1)	26.0 (7.5)			
BMI (kg/m^2)	N (% non-missing)	549 (100.0)	2,998 (99.9)	0.3134	8.7	0.2
	<18.5	30 (5.5)	153 (5.1)			
	≥18.5-<25	184 (33.5)	1,108 (37.0)			
	≥25-<30	194 (35.3)	951 (31.7)			
	≥30	141 (25.7)	786 (26.2)			
Smoking status closest to index date	Non-smoker	24 (4.4)	120 (4.0)	0.3525	6.7	0.1
	Current smoker	228 (41.5)	1,158 (38.6)			
	Ex-smoker	297 (54.1)	1,723 (57.4)			
Time since COPD diagnosis (years)	N (% non-missing)	494 (90.0)	2,711 (90.3)	0.0001	24.0	10.5
	<2	93 (18.8)	725 (26.7)			
	2 to <4	80 (16.2)	506 (18.7)			
	4 to <6	79 (16.0)	429 (15.8)			
	6 to <8	67 (13.6)	322 (11.9)			
	8+	175 (35.4)	729 (26.9)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Prescription practices by treatment group are reported in table 8. There were differences in the number of SABA prescriptions (SDD 16.1) with a greater proportion of patients in the BDP/FOR group having no prescriptions for SABA (24.6% vs 18.2%). The proportion of patients with a SAMA prescription was higher in the BUD/FOR group (19.2% vs 15.3%, SDD = 10.3), along with SABA/SAMA prescriptions (9.3% vs 1.3%, SDD 36.4). The proportion of patients with FDC ICS/LABA prescriptions also differed between unmatched groups; 34.2% of BDP/FOR patients had no prescriptions for FDC ICS/LABA compared to 44.9% of BUD/FOR patients. The SDD between categorised number of prescriptions was 36.4. A lower proportion of BUD/FOR patients were not prescribed ICS inhalers (65.3% vs 77.6%). The difference between the groups was significant (SDD 28.6). A greater proportion of patients in the BDP/FOR group were prescribed a LAMA (63.6% vs 49.8%, SDD 28.1) or maintenance oral corticosteroids (6.9% vs 4.6%, SDD 9.8), whereas a greater proportion of patients in the BUD/FOR group were prescribed a LABA inhaler (25.3% vs 11.7%, SDD 35.8) and theophylline (10.2% vs 6.9%, SDD 11.6).

Table 8: Unmatched baseline characteristics – BDP/FOR versus BUD/FOR DPI

		BDP/FOR N=549	BUD/FOR DPI N=3001	p-value	SDD	RCC
SABA inhaler prescriptions	0	135 (24.6)	547 (18.2)	0.0118	16.1	1.3
	1	39 (7.1)	227 (7.6)			
	2-4	83 (15.1)	522 (17.4)			
	5-10	147 (26.8)	897 (29.9)			
	≥11	145 (26.4)	808 (26.9)			
SABA inhalers	0	135 (24.6)	547 (18.2)	0.0127	16.0	1.8
	1	32 (5.8)	192 (6.4)			
	2-4	82 (14.9)	470 (15.7)			
	5-10	128 (23.3)	806 (26.9)			
	≥11	172 (31.3)	986 (32.9)			
Average daily dose of SABA	0	135 (24.6)	547 (18.2)	0.0035	16.7	0.9
	>0 to <200	85 (15.5)	572 (19.1)			
	200 to <400	113 (20.6)	642 (21.4)			
	≥400	216 (39.3)	1,240 (41.3)			
SAMA prescriptions	≥1	84 (15.3)	576 (19.2)	0.0311	10.3	0.4
SAMA µg/day	0	449 (81.8)	2,153 (71.7)	<0.0001	24.9	0.8
	>0 to <40	84 (15.3)	710 (23.7)			
	40 to <80	3 (0.5)	49 (1.6)			
	≥80	13 (2.4)	89 (3.0)			
SAMA/SABA prescriptions	≥1	13 (2.4)	89 (2.6)			
FDC ICS prescriptions	0	188 (34.2)	1,347 (44.9)	<0.0001	31.1	5.8
	1	31 (5.6)	214 (7.1)			
	2-4	66 (12.0)	430 (14.3)			
	5-10	153 (27.9)	653 (21.8)			
	≥11	111 (20.2)	357 (11.9)			
FDC ICS inhalers	0	188 (34.2)	1,347 (44.9)	<0.0001	31.6	5.4
	1	26 (4.7)	185 (6.2)			
	2-4	56 (10.2)	399 (13.3)			
	5-10	148 (27.0)	619 (20.6)			
	≥11	131 (23.9)	451 (15.0)			
ICS monotherapy average prescription	0	426 (77.6)	1,959 (65.3)	<0.0001	28.6	1.7
	1	18 (3.3)	133 (4.4)			
	2-4	41 (7.5)	334 (11.1)			
	5-10	43 (7.8)	434 (14.5)			
	≥11	21 (3.8)	141 (4.7)			
ICS monotherapy inhalers	0	426 (77.6)	1,959 (65.3)	<0.0001	28.9	1.4
	1	16 (2.9)	113 (3.8)			
	2-4	39 (7.1)	297 (9.9)			
	5-10	42 (7.7)	441 (14.7)			
	≥11	26 (4.7)	191 (6.4)			
Total ICS dosage	0-249	240 (43.7)	1,614 (53.8)	<0.0001	23.6	4.8
	250-499	151 (27.5)	793 (26.4)			
	500+	158 (28.8)	593 (19.8)			
LAMA prescriptions	≥1	349 (63.6)	1,494 (49.8)	<0.0001	28.1	3.1
LABA prescriptions	≥1	64 (11.7)	760 (25.3)	<0.0001	35.8	1.1
LABA/LAMA combination prescriptions	≥1	2 (0.4)	2 (0.1)	0.0560	6.4	0.4
Theophylline prescriptions	≥1	38 (6.9)	305 (10.2)	0.0181	11.6	2.0
Leukotriene prescriptions	≥1	32 (5.8)	150 (5.0)	0.4173	3.7	0.3
Maintenance OCS	Yes	38 (6.9)	139 (4.6)	0.0234	9.8	0.9

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Comorbidities by treatment group are reported in table 9. A greater proportion of patients in the BDP/FOR group compared to the BUD/FOR group had a diagnosis of bronchiectasis (7.5% vs 4.7%, SDD 11.5), diabetes (15.8% vs 11.1%, SDD 13.9), ischaemic heart disease

(20.9% vs 16.5%, SDD 11.5), chronic kidney disease (13.8% vs 8.9%, SDD 15.7), anxiety or depression ever (25.1% vs 17.6%, SDD 14.4), and actively treated anxiety or depression (25.1% vs 17.6%, SDD 18.4).

Table 9: Unmatched baseline characteristics – BDP/FOR versus BUD/FOR DPI

		BDP/FOR N=549	BUD/FOR DPI N=3001	p-value	SDD	RCC
Asthma diagnosis (QOF)	Yes	227 (41.3)	1,233 (41.1)	0.9088	0.5	0.1
Rhinitis diagnosis	Yes	81 (14.8)	413 (13.8)	0.5369	2.8	0.1
Active rhinitis diagnosis	Yes	45 (8.2)	228 (7.6)	0.6280	2.2	0.0
Bronchiectasis diagnosis	Yes	41 (7.5)	142 (4.7)	0.0077	11.5	0.5
Pneumonia diagnosis	Yes	21 (3.8)	71 (2.4)	0.0479	8.4	0.6
Lung cancer diagnosis	Yes	9 (1.6)	30 (1.0)	0.1862	5.6	0.1
Eczema diagnosis	Yes	146 (26.6)	691 (23.0)	0.0702	8.3	0.1
Eczema diagnosis with prescriptions	Yes	58 (10.6)	261 (8.7)	0.1595	6.3	0.4
GERD diagnosis or drugs	Yes	22 (4.0)	69 (2.3)	0.0199	9.8	0.4
Diabetes diagnosis	Yes	87 (15.8)	333 (11.1)	0.0015	13.9	0.5
Ischaemic heart disease diagnosis	Yes	115 (20.9)	494 (16.5)	0.0104	11.5	0.6
Heart failure diagnosis	Yes	15 (2.7)	65 (2.2)	0.4111	3.7	0.1
Hypertension diagnosis	Yes	231 (42.1)	1,094 (36.5)	0.0123	11.5	0.7
Chronic kidney disease Read code diagnosis	Yes	76 (13.8)	266 (8.9)	0.0003	15.7	1.0
Osteoporosis diagnosis	Yes	41 (7.5)	196 (6.5)	0.4187	3.7	0.2
Anxiety and/or depression diagnosis	Yes	208 (37.9)	932 (31.1)	0.0016	14.4	0.8
Active anxiety and/or depression diagnosis	Yes	138 (25.1)	529 (17.6)	<0.0001	18.4	2.3
Charlson Comorbidity Index	0-2	348 (63.4)	1,941 (64.7)	0.2795	7.2	0.5
	3-4	139 (25.3)	786 (26.2)			
	5+	62 (11.3)	274 (9.1)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Measures of disease severity by treatment group are reported in table 10.

In terms of the disease severity, there were differences in the categorised number of COPD related primary care consultations (SDD 26.4) with a greater proportion of patients in the BDP/FOR group with no consultations (37.7% vs 30.6%), outpatient visits (SDD 19.9) with a greater proportion of patients in the BUD/FOR group with no visits (92.0% vs 88.2%), A&E attendances (SDD 12.7) with a greater proportion of patients with no visits in the BUD/FOR group (92% vs 88.2%), inpatient admissions for respiratory reasons (SDD 12.1), exacerbations (SDD 16.3), with a greater proportion of patients with no admissions in the BUD/FOR group (95.2% vs 92.3%) and mMRC score (SDD 14.8).

Table 10: Unmatched baseline characteristics – BDP/FOR versus BUD/FOR DPI

		BDP/FOR N=549	BUD/FOR DPI N=3001	p-value	SDD	RCC
COPD related GP consultations	0	207 (37.7)	919 (30.6)	<0.0001	26.4	0.2
	1	128 (23.3)	681 (22.7)			
	2-4	126 (23.0)	917 (30.6)			
	5-10	56 (10.2)	403 (13.4)			
	≥11	32 (5.8)	81 (2.7)			
Outpatient visits for COPD	0	484 (88.2)	2,760 (92.0)	<0.0001	19.9	0.5
	1	33 (6.0)	181 (6.0)			
	≥2	32 (5.8)	60 (2.0)			
A & E attendances for COPD	0	529 (96.4)	2,951 (98.3)	0.0051	12.7	0.9
	1	16 (2.9)	44 (1.5)			
	≥2	4 (0.7)	6 (0.2)			
Inpatient admissions within 7 days of respiratory consultation	0	507 (92.3)	2,858 (95.2)	0.0183	12.1	1.0
	1	33 (6.0)	116 (3.9)			
	≥2	9 (1.6)	27 (0.9)			
Moderate/severe exacerbations	0	49 (8.9)	281 (9.4)	0.0151	16.3	7.1
	1	164 (29.9)	1,092 (36.4)			
	2	141 (25.7)	632 (21.1)			
	3	76 (13.8)	432 (14.4)			
	4+	119 (21.7)	564 (18.8)			
FEV_1 value (litres)	≤1	217 (39.5)	1,230 (41.0)	0.2490	8.7	0.7
	>1 to ≤2	287 (52.3)	1,586 (52.8)			
	2 to ≤4	35 (6.4)	154 (5.1)			
	>4	10 (1.8)	31 (1.0)			
FEV_1/FVC ratio	0.2 or less	5 (0.9)	20 (0.7)	0.2056	9.9	0.8
	0.2 to <0.4	91 (16.6)	570 (19.0)			
	0.4 to <0.6	250 (45.5)	1,425 (47.5)			
	0.6+	203 (37.0)	986 (32.9)			
Lowest percent predicted FEV_1	<20%	25 (4.6)	160 (5.3)	0.8404	4.3	0.5
	20% to <30%	103 (18.8)	586 (19.5)			
	30% to <40%	161 (29.3)	856 (28.5)			
	40% to <55%	260 (47.4)	1,399 (46.6)			
Gold severity (2016)	Mild	22 (4.0)	71 (2.4)	0.1769	9.4	0.8
	Moderate	193 (35.2)	1,083 (36.1)			
	Severe	259 (47.2)	1,428 (47.6)			
	Very severe	75 (13.7)	419 (14.0)			
mMRC score	N (% non-missing)	323 (58.8)	1,517 (50.5)	0.2051	14.8	7.5
	mMRC 0	37 (11.5)	131 (8.6)			
	mMRC 1	107 (33.1)	597 (39.4)			
	mMRC 2	98 (30.3)	432 (28.5)			
	mMRC 3	67 (20.7)	304 (20.0)			
	mMRC 4	14 (4.3)	53 (3.5)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

10.0 Matched baselines

This section contains presents the baseline characteristics for the matched population. In section 10.1 and 10.2, the whole population for the main analysis is compared, while in section 10.3 and 10.4, the population for the sub-analysis is presented. Time since COPD diagnosis is given for illustrative purposes as this variable is not coded in GP practices consistently.

10.1 Matched characteristics of study population (BDP/FOR vs FP/SAL)

Demographic characteristics were well balanced with no significant difference between groups after matching (table 11).

Table 11: Matched baseline characteristics – BDP/FOR versus FP/SAL DPI

		BDP/FOR N=537	FP/SAL DPI N=537	p-value	SDD	RCC
Gender	Male	292 (54.4)	313 (58.3)	0.1964	7.9	0.5
Age (years)	Mean (SD)	69.4 (10.2)	68.5 (9.6)	0.1080	9.1	0.0
	Median (IQR)	70.0 (14.0)	69.0 (12.0)			
Age (years)	≥35 <45	7 (1.3)	7 (1.3)	1.0000	0.0	0.0
	≥45 <55	39 (7.3)	39 (7.3)			
	≥55 <65	115 (21.4)	115 (21.4)			
	≥65	376 (70.0)	376 (70.0)			
BMI (kg/m^2)	N (% non-missing)	537 (100.0)	536 (99.8)	0.3848	7.9	0.1
	Mean (SD)	27.1 (6.4)	26.6 (5.8)			
	Median (IQR)	26.2 (7.1)	25.9 (7.6)			
BMI (kg/m^2)	N (% non-missing)	537 (100.0)	536 (99.8)	0.8502	5.5	0.2
	<18.5	30 (5.6)	31 (5.8)			
	≥18.5-<25	180 (33.5)	191 (35.6)			
	≥25-<30	192 (35.8)	179 (33.4)			
	≥30	135 (25.1)	135 (25.2)			
Smoking status closest to index date	Non-smoker	19 (3.5)	19 (3.5)	1.0000	0.0	0.0
	Current smoker	224 (41.7)	224 (41.7)			
	Ex-smoker	294 (54.7)	294 (54.7)			
Time since COPD diagnosis (years)	N (% non-missing)	485 (90.3)	508 (94.6)	0.6876	9.6	5.6
	<2	90 (18.6)	98 (19.3)			
	2 to <4	77 (15.9)	94 (18.5)			
	4 to <6	77 (15.9)	86 (16.9)			
	6 to <8	67 (13.8)	63 (12.4)			
	8+	174 (35.9)	167 (32.9)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Prescription practices by treatment group are reported in table 12. SABA prescription was different in each group (SDD 23.9), with more patients prescribed no SABA in the BDP/FOR group (24.6% vs 16.8%). There was a higher number of patients prescribed SABA/SAMA in the FP/SAL group compared to BDP/FOR (9.9 vs 1.3%, SDD 38.0). There were also differences between the categorised numbers of FDC ICS/LABAs (SDD 10.9), with a greater proportion prescribed in the FP/SAL group (67.8% vs 65.2%) and ICS inhalers (SDD 11.7) in the baseline with again a greater proportion prescribed in the FP/SAL group (23.3% vs 22.2%). More patients were prescribed theophylline in the FP/SAL group (12.3% vs 6.1%, SDD 21.4).

Table 12: Matched baseline characteristics – BDP/FOR versus FP/SAL DPI

		BDP/FOR N=537	FP/SAL DPI N=537	p-value	SDD	RCC
SABA inhaler prescriptions	0	132 (24.6)	90 (16.8)	0.0044	23.9	1.5
	1	38 (7.1)	36 (6.7)			
	2-4	82 (15.3)	110 (20.5)			
	5-10	141 (26.3)	169 (31.5)			
	≥11	144 (26.8)	132 (24.6)			
SABA inhalers	0	132 (24.6)	90 (16.8)	0.0067	23.2	1.3
	1	32 (6.0)	27 (5.0)			
	2-4	80 (14.9)	91 (16.9)			
	5-10	122 (22.7)	160 (29.8)			
	≥11	171 (31.8)	169 (31.5)			
Average daily dose of SABA	0	132 (24.6)	90 (16.8)	0.0118	20.3	0.5
	>0 to <200	82 (15.3)	98 (18.2)			
	200 to <400	111 (20.7)	110 (20.5)			
	≥400	212 (39.5)	239 (44.5)			
SAMA prescriptions	≥1	81 (15.1)	95 (17.7)	0.2485	7.0	0.2
SAMA µg/day	0	438 (81.6)	390 (72.6)	0.0036	22.6	2.4
	>0 to <40	83 (15.5)	122 (22.7)			
	40 to <80	3 (0.6)	9 (1.7)			
	≥80	13 (2.4)	16 (3.0)			
SAMA/SABA combination prescriptions	≥1	7 (1.3)	53 (9.9)	<0.0001	38.0	3.6
FDC ICS prescriptions	0	187 (34.8)	173 (32.2)	0.8484	7.2	0.2
	1	30 (5.6)	29 (5.4)			
	2-4	61 (11.4)	71 (13.2)			
	5-10	152 (28.3)	156 (29.1)			
	≥11	107 (19.9)	108 (20.1)			
FDC ICS inhalers	0	187 (34.8)	173 (32.2)	0.5249	10.9	0.1
	1	26 (4.8)	23 (4.3)			
	2-4	51 (9.5)	59 (11.0)			
	5-10	146 (27.2)	135 (25.1)			
	≥11	127 (23.6)	147 (27.4)			
ICS monotherapy prescriptions	0	418 (77.8)	412 (76.7)	0.1747	15.4	0.6
	1	17 (3.2)	31 (5.8)			
	2-4	41 (7.6)	38 (7.1)			
	5-10	41 (7.6)	44 (8.2)			
	≥11	20 (3.7)	12 (2.2)			
ICS monotherapy inhalers	0	418 (77.8)	412 (76.7)	0.4510	11.7	0.3
	1	15 (2.8)	26 (4.8)			
	2-4	39 (7.3)	35 (6.5)			
	5-10	41 (7.6)	44 (8.2)			
	≥11	24 (4.5)	20 (3.7)			
Total ICS dosage	0-249	235 (43.8)	221 (41.2)	0.5092	7.1	0.2
	250-499	148 (27.6)	145 (27.0)			
	500+	154 (28.7)	171 (31.8)			
LAMA prescriptions	≥1	340 (63.3)	323 (60.1)	0.2859	6.5	1.0
LABA prescriptions	≥1	63 (11.7)	79 (14.7)	0.1495	8.8	1.0
LABA/LAMA combination prescriptions	≥1	2 (0.4)	0 (0.0)	0.1569	8.6	0.5
Theophylline prescriptions	≥1	33 (6.1)	66 (12.3)	0.0005	21.4	1.0
Leukotriene prescriptions	≥1	28 (5.2)	23 (4.3)	0.4731	4.4	0.4
Maintenance OCS	Yes	36 (6.7)	25 (4.7)	0.1470	8.9	0.7

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Comorbidities by treatment group are reported in table 13. There were more patients in the BDP/FOR group with a diagnosis of rhinitis (14.5% vs 11.2%, SDD 10.0, eczema (26.8% vs 21.4%, SDD 12.6), GERD (4.1% vs 1.5%, SDD 15.9), ischaemic heart disease (21.2% vs 16.4%, SDD 12.4) compared to the FP/SAL group.

Table 13: Matched baseline characteristics – BDP/FOR versus FP/SAL DPI

		BDP/FOR N=537	FP/SAL DPI N=537	p-value	SDD	RCC
Asthma diagnosis (QOF)	Yes	218 (40.6)	197 (36.7)	0.1882	8.0	0.7
Rhinitis diagnosis	Yes	78 (14.5)	60 (11.2)	0.1007	10.0	0.7
Active rhinitis diagnosis	Yes	43 (8.0)	34 (6.3)	0.2871	6.5	0.4
Bronchiectasis diagnosis	Yes	40 (7.4)	30 (5.6)	0.2164	7.5	0.2
Pneumonia diagnosis	Yes	21 (3.9)	13 (2.4)	0.1632	8.5	0.7
Lung cancer diagnosis	Yes	9 (1.7)	6 (1.1)	0.4354	4.8	0.3
Eczema diagnosis	Yes	144 (26.8)	115 (21.4)	0.0386	12.6	0.7
Eczema diagnosis with prescriptions	Yes	57 (10.6)	43 (8.0)	0.1415	9.0	0.1
GERD diagnosis or drugs	Yes	22 (4.1)	8 (1.5)	0.0095	15.9	1.0
Diabetes diagnosis	Yes	85 (15.8)	76 (14.2)	0.4417	4.7	0.2
Ischaemic heart disease diagnosis	Yes	114 (21.2)	88 (16.4)	0.0423	12.4	0.4
Heart failure diagnosis	Yes	15 (2.8)	9 (1.7)	0.2155	7.6	0.4
Hypertension diagnosis	Yes	228 (42.5)	220 (41.0)	0.6206	3.0	0.1
Chronic kidney disease Read code diagnosis	Yes	76 (14.2)	64 (11.9)	0.2768	6.6	0.1
Osteoporosis diagnosis	Yes	40 (7.4)	32 (6.0)	0.3290	6.0	0.2
Anxiety and/or depression diagnosis	Yes	200 (37.2)	178 (33.1)	0.1598	8.6	1.9
Active anxiety and/or depression diagnosis	Yes	134 (25.0)	123 (22.9)	0.4314	4.8	0.9
Charlson Comorbidity Index	0-2	343 (63.9)	347 (64.6)	0.9387	2.2	0.2
	3-4	134 (25.0)	129 (24.0)			
	5+	60 (11.2)	61 (11.4)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Measures of disease severity by treatment group are reported in table 14. There were significant differences between the BDP/FOR and FP/SAL groups for COPD related GP consultations (SDD 29.6) with more patients having no visits in the BDP/FOR group (37.4% vs 28.1%), outpatient COPD visits (SDD 16.8) with more patients having no outpatient visits in the FP/SAL group (92.9% vs 88.5%) and A&E attendances (SDD 10.5), with more BDP/FOR patients having visits (3.6% vs 1.9%). In addition, there were differences in the GOLD severity score (SDD 15.1), with more patients having a severe score in the FP/SAL group (52.5% vs 47.1%) and mMRC score (SDD 19.9), with more patients having a score of 3 in the BDP/FOR group (20.8% vs 16.8%).

Table 14: Matched baseline characteristics – BDP/FOR versus FP/SAL DPI

		BDP/FOR N=537	FP/SAL DPI N=537	p-value	SDD	RCC
COPD related GP consultations	0	201 (37.4)	151 (28.1)	0.0001	29.6	2.0
	1	125 (23.3)	130 (24.2)			
	2-4	126 (23.5)	164 (30.5)			
	5-10	54 (10.1)	78 (14.5)			
	≥11	31 (5.8)	14 (2.6)			
Outpatient visits for COPD	0	475 (88.5)	499 (92.9)	0.0229	16.8	0.6
	1	32 (6.0)	24 (4.5)			
	≥2	30 (5.6)	14 (2.6)			
A & E attendances for COPD	0	518 (96.5)	527 (98.1)	0.2294	10.5	0.2
	1	16 (3.0)	8 (1.5)			
	≥2	3 (0.6)	2 (0.4)			
Inpatient admissions within 7 days of respiratory consultation	0	498 (92.7)	500 (93.1)	0.8651	3.3	0.6
	1	31 (5.8)	31 (5.8)			
	≥2	8 (1.5)	6 (1.1)			
Moderate/severe exacerbations	0	46 (8.6)	46 (8.6)	1.0000	0.0	0.5
	1	159 (29.6)	159 (29.6)			
	2	139 (25.9)	139 (25.9)			
	3	75 (14.0)	75 (14.0)			
	4+	118 (22.0)	118 (22.0)			
FEV_1 value (litres)	≤1	213 (39.7)	223 (41.5)	0.6618	7.7	0.8
	>1 to ≤2	281 (52.3)	281 (52.3)			
	2 to ≤4	33 (6.1)	26 (4.8)			
	>4	10 (1.9)	7 (1.3)			
FEV_1/FVC ratio	0.2 or less	4 (0.7)	4 (0.7)	0.1441	14.2	1.1
	0.2 to <0.4	91 (16.9)	100 (18.6)			
	0.4 to <0.6	242 (45.1)	269 (50.1)			
	0.6+	200 (37.2)	164 (30.5)			
Lowest percent predicted FEV_1	<20%	24 (4.5)	24 (4.5)	1.0000	0.0	0.0
	20% to <30%	98 (18.2)	98 (18.2)			
	30% to <40%	159 (29.6)	159 (29.6)			
	40% to <55%	256 (47.7)	256 (47.7)			
Gold severity (2016)	Mild	21 (3.9)	10 (1.9)	0.1062	15.1	1.4
	Moderate	190 (35.4)	177 (33.0)			
	Severe	253 (47.1)	282 (52.5)			
	Very severe	73 (13.6)	68 (12.7)			
mMRC score	N (% non-missing)	317 (59.0)	310 (57.7)	0.1910	19.9	11.5
	mMRC 0	37 (11.7)	23 (7.4)			
	mMRC 1	105 (33.1)	121 (39.0)			
	mMRC 2	95 (30.0)	100 (32.3)			
	mMRC 3	66 (20.8)	52 (16.8)			
	mMRC 4	14 (4.4)	14 (4.5)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

10.2 Matched characteristics of study population (BDP/FOR vs BUD/FOR)

Demographic characteristics were well balanced with no significant difference between groups after matching (table 15).

Table 15: Matched baseline characteristics – BDP/FOR versus BUD/FOR

		BDP/FOR N=540	BUD/FOR DPI N=540	p-value	SDD	RCC
Gender	Male	295 (54.6)	293 (54.3)	0.9027	0.7	0.1
Age (years)	Mean (SD)	69.2 (10.4)	68.3 (10.0)	0.1293	8.8	0.1
	Median (IQR)	70.0 (15.0)	69.0 (12.0)			
Age (years)	≥35 <45	10 (1.9)	10 (1.9)	1.0000	0.0	0.0
	≥45 <55	41 (7.6)	41 (7.6)			
	≥55 <65	113 (20.9)	113 (20.9)			
	≥65	376 (69.6)	376 (69.6)			
BMI (kg/m^2)	N (% non-missing)	540 (100.0)	538 (99.6)	0.3958	5.9	0.5
	Mean (SD)	27.1 (6.4)	26.7 (5.9)			
	Median (IQR)	26.2 (7.1)	26.0 (7.6)			
BMI (kg/m^2)	N (% non-missing)	540 (100.0)	538 (99.6)	0.4765	9.6	0.5
	<18.5	30 (5.6)	30 (5.6)			
	≥18.5-<25	179 (33.1)	200 (37.2)			
	≥25-<30	193 (35.7)	171 (31.8)			
	≥30	138 (25.6)	137 (25.5)			
Smoking status closest to index date	Non-smoker	17 (3.1)	17 (3.1)	1.0000	0.0	0.0
	Current smoker	227 (42.0)	227 (42.0)			
	Ex-smoker	296 (54.8)	296 (54.8)			
Time since COPD diagnosis (years)	N (% non-missing)	486 (90.0)	482 (89.3)	0.0001	31.0	10.9
	<2	91 (18.7)	139 (28.8)			
	2 to <4	77 (15.8)	90 (18.7)			
	4 to <6	78 (16.0)	77 (16.0)			
	6 to <8	67 (13.8)	60 (12.4)			
	8+	173 (35.6)	116 (24.1)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Prescription practices by treatment group are reported in table 16. SABA prescription was different in each group (SDD 18.9), with more patients prescribed no SABA in the BDP/FOR group (24.4% vs 17.8%). There was a higher number of patients prescribed SABA/SAMA and SAMA alone in the FP/SAL group compared to BDP/FOR (7.6 vs 1.3%, SDD 30.9 for SABA/SAMA, and 20.4% vs 15.0%, SDD 14.1). There were also differences between the categorised numbers of FDC ICS/LABAs (SDD 27.6), with a greater proportion prescribed in the FP/SAL group (55.2% vs 65.9%) and ICS inhalers (SDD 11.7) in the baseline with again a greater proportion prescribed in the FP/SAL group (32.6% vs 22.0%). More patients were prescribed theophylline in the FP/SAL group (9.6% vs 6.7%, SDD 10.8). More patients were prescribed LAMAs in the BDP/FOR group (63.3% vs 52.8%, SDD 21.5), whereas more patients were prescribed LABAs in the BUD/FOR group (23.5% vs 11.9%, SDD 30.9). A greater number of patients in the BDP/FOR group were prescribed maintenance oral corticosteroid therapy (6.9% vs 4.1%, SDD 12.2).

Table 16: Matched baseline characteristics – BDP/FOR versus BUD/FOR DPI

		BDP/FOR N=540	BUD/FOR DPI N=540	p-value	SDD	RCC
SABA inhaler prescriptions	0	132 (24.4)	96 (17.8)	0.0482	18.9	0.8
	1	38 (7.0)	43 (8.0)			
	2-4	81 (15.0)	93 (17.2)			
	5-10	145 (26.9)	173 (32.0)			
	≥11	144 (26.7)	135 (25.0)			
SABA inhalers	0	132 (24.4)	96 (17.8)	0.0486	18.9	1.0
	1	32 (5.9)	38 (7.0)			
	2-4	80 (14.8)	84 (15.6)			
	5-10	125 (23.1)	155 (28.7)			
	≥11	171 (31.7)	167 (30.9)			
Average daily dose of SABA	0	132 (24.4)	96 (17.8)	0.0244	18.7	0.4
	>0 to <200	82 (15.2)	108 (20.0)			
	200 to <400	111 (20.6)	113 (20.9)			
	≥400	215 (39.8)	223 (41.3)			
SAMA prescriptions	≥1	81 (15.0)	110 (20.4)	0.0207	14.1	0.6
SAMA µg/day	0	442 (81.9)	386 (71.5)	0.0003	-	0.1
	>0 to <40	97 (18.0)	152 (28.1)			
	40 to <80	1 (0.2)	2 (0.4)			
	≥80	0 (0.0)	0 (0.0)			
SAMA/SABA combination prescriptions	≥1	7 (1.3)	41 (7.6)	<0.0001	30.9	0.8
FDC ICS prescriptions	0	184 (34.1)	242 (44.8)	0.0004	27.6	4.2
	1	31 (5.7)	33 (6.1)			
	2-4	62 (11.5)	71 (13.1)			
	5-10	153 (28.3)	123 (22.8)			
	≥11	110 (20.4)	71 (13.1)			
FDC ICS inhalers	0	184 (34.1)	242 (44.8)	0.0004	27.7	4.1
	1	26 (4.8)	29 (5.4)			
	2-4	53 (9.8)	65 (12.0)			
	5-10	147 (27.2)	110 (20.4)			
	≥11	130 (24.1)	94 (17.4)			
ICS monotherapy prescriptions	0	421 (78.0)	364 (67.4)	0.0005	27.6	0.0
	1	17 (3.1)	23 (4.3)			
	2-4	40 (7.4)	47 (8.7)			
	5-10	42 (7.8)	85 (15.7)			
	≥11	20 (3.7)	21 (3.9)			
ICS monotherapy inhalers	0	421 (78.0)	364 (67.4)	0.0003	28.5	0.8
	1	15 (2.8)	17 (3.1)			
	2-4	38 (7.0)	45 (8.3)			
	5-10	41 (7.6)	87 (16.1)			
	≥11	25 (4.6)	27 (5.0)			
Total ICS dosage	0-249	540 (100.0)	539 (99.8)	0.0015	22.0	1.3
	250-499	235 (43.5)	275 (51.0)			
	500+	149 (27.6)	158 (29.3)			
LAMA prescriptions	≥1	342 (63.3)	285 (52.8)	0.0004	21.5	4.1
LABA prescriptions	≥1	64 (11.9)	127 (23.5)	<0.0001	30.9	6.0
LABA/LAMA combination prescriptions	≥1	2 (0.4)	0 (0.0)	0.1569	8.6	0.5
Theophylline prescriptions	≥1	36 (6.7)	52 (9.6)	0.0751	10.8	0.9
Leukotriene prescriptions	≥1	31 (5.7)	18 (3.3)	0.0573	11.6	0.3
Maintenance OCS	Yes	37 (6.9)	22 (4.1)	0.0446	12.2	0.1

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Comorbidities by treatment group are reported in table 17. There were more patients in the BDP/FOR group with a diagnosis of bronchiectasis (7.6% vs 4.4%, SDD 13.3), GERD (3.9% vs 2.0%, SDD 10.9), diabetes (15.9% vs 10.4%, SDD 16.5), hypertension (42.4% vs 37.2%, SDD 10.6), chronic kidney disease (14.1% vs 8.1%, SDD 18.9) and active anxiety/depression (25.0% vs 19.4%, SDD 13.4) compared to the FP/SAL group.

Table 17: Matched baseline characteristics – BDP/FOR versus BUD/FOR DPI

		BDP/FOR N=540	BUD/FOR DPI N=540	p-value	SDD	RCC
Asthma diagnosis (QOF)	Yes	220 (40.7)	230 (42.6)	0.5371	3.8	0.6
Rhinitis diagnosis	Yes	79 (14.6)	81 (15.0)	0.8640	1.0	0.1
Active rhinitis diagnosis	Yes	44 (8.1)	46 (8.5)	0.8257	1.3	0.0
Bronchiectasis diagnosis	Yes	41 (7.6)	24 (4.4)	0.0296	13.3	0.4
Pneumonia diagnosis	Yes	21 (3.9)	14 (2.6)	0.2290	7.3	0.7
Lung cancer diagnosis	Yes	9 (1.7)	8 (1.5)	0.8069	1.5	0.1
Eczema diagnosis	Yes	144 (26.7)	126 (23.3)	0.2059	7.7	0.1
Eczema diagnosis with prescriptions	Yes	57 (10.6)	49 (9.1)	0.4132	5.0	0.4
GERD diagnosis or drugs	Yes	21 (3.9)	11 (2.0)	0.0727	10.9	0.0
Diabetes diagnosis	Yes	86 (15.9)	56 (10.4)	0.0069	16.5	1.3
Ischaemic heart disease diagnosis	Yes	114 (21.1)	105 (19.4)	0.4958	4.1	0.3
Heart failure diagnosis	Yes	15 (2.8)	10 (1.9)	0.3116	6.2	0.3
Hypertension diagnosis	Yes	229 (42.4)	201 (37.2)	0.0818	10.6	0.3
Chronic kidney disease Read code diagnosis	Yes	76 (14.1)	44 (8.1)	0.0019	18.9	1.5
Osteoporosis diagnosis	Yes	40 (7.4)	32 (5.9)	0.3291	5.9	0.0
Anxiety and/or depression diagnosis	Yes	202 (37.4)	181 (33.5)	0.1816	8.1	0.9
Active anxiety and/or depression diagnosis	Yes	135 (25.0)	105 (19.4)	0.0281	13.4	2.4
Charlson Comorbidity Index	0-2	345 (63.9)	349 (64.6)	0.3280	9.1	0.7
	3-4	135 (25.0)	145 (26.9)			
	5+	60 (11.1)	46 (8.5)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Measures of disease severity by treatment group are reported in table 18. There were significant differences between the BDP/FOR and FP/SAL groups for COPD related GP consultations (SDD 29.3) with more patients having no visits in the BDP/FOR group (37.4% vs 30.7%), outpatient COPD visits (SDD 17.4) with more patients having no outpatient visits in the BUD/FOR group (89.8% vs 88.5%). In addition, there were differences in the GOLD severity score (SDD 13.6), with more patients having a severe score in the FP/SAL group (50.0% vs 47.1%) and mMRC score (SDD 17.2), with more patients having a score of 3 in the BUD/FOR group (22.8% vs 20.3%).

Table 18: Matched baseline characteristics – BDP/FOR versus BUD/FOR DPI

		BDP/FOR N=540	BUD/FOR DPI N=540	p-value	SDD	RCC
COPD related GP consultations	0	202 (37.4)	166 (30.7)	0.0001	29.3	1.5
	1	125 (23.1)	121 (22.4)			
	2-4	126 (23.3)	172 (31.9)			
	5-10	55 (10.2)	70 (13.0)			
	≥11	32 (5.9)	11 (2.0)			
Outpatient visits for COPD	0	478 (88.5)	485 (89.8)	0.0172	17.4	0.7
	1	32 (5.9)	42 (7.8)			
	≥2	30 (5.6)	13 (2.4)			
A & E attendances for COPD	0	521 (96.5)	526 (97.4)	0.5132	7.0	0.4
	1	16 (3.0)	13 (2.4)			
	≥2	3 (0.6)	1 (0.2)			
Inpatient admissions within 7 days of respiratory consultation	0	501 (92.8)	502 (93.0)	0.9705	1.5	0.2
	1	30 (5.6)	30 (5.6)			
	≥2	9 (1.7)	8 (1.5)			
Moderate/severe exacerbations	0	48 (8.9)	48 (8.9)	1.0000	0.0	0.4
	1	162 (30.0)	162 (30.0)			
	2	138 (25.6)	138 (25.6)			
	3	75 (13.9)	75 (13.9)			
	4+	117 (21.7)	117 (21.7)			
FEV_1 value (litres)	≤1	213 (39.4)	222 (41.1)	0.9020	4.6	0.4
	>1 to ≤2	283 (52.4)	279 (51.7)			
	2 to ≤4	34 (6.3)	31 (5.7)			
	>4	10 (1.9)	8 (1.5)			
FEV_1/FVC ratio	0.2 or less	5 (0.9)	2 (0.4)	0.7113	7.1	0.5
	0.2 to <0.4	91 (16.9)	94 (17.4)			
	0.4 to <0.6	247 (45.7)	250 (46.3)			
	0.6+	197 (36.5)	194 (35.9)			
Lowest percent predicted FEV_1	<20%	24 (4.4)	24 (4.4)	1.0000	0.0	0.0
	20% to <30%	96 (17.8)	96 (17.8)			
	30% to <40%	161 (29.8)	161 (29.8)			
	40% to <55%	259 (48.0)	259 (48.0)			
Gold severity (2016)	Mild	21 (3.9)	11 (2.0)	0.1713	13.6	0.2
	Moderate	192 (35.6)	200 (37.0)			
	Severe	255 (47.2)	270 (50.0)			
	Very severe	72 (13.3)	59 (10.9)			
mMRC score	N (% non-missing)	315 (58.3)	267 (49.4)	0.3772	17.2	19.8
	mMRC 0	37 (11.7)	21 (7.9)			
	mMRC 1	106 (33.7)	101 (37.8)			
	mMRC 2	94 (29.8)	76 (28.5)			
	mMRC 3	64 (20.3)	61 (22.8)			
	mMRC 4	14 (4.4)	8 (3.0)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

10.3 Sub-analysis: Matched characteristics of study population without asthma codes (BDP/FOR vs FP/SAL)

The demographic characteristics can be found in table 19. Gender, age and smoking status were well balanced between groups. The categorised BMI was different in each group (SDD 10.3), with 36.5% being an ideal BMI (between 18.5 and 25) in the BDP/FOR group compared to 40.9% in the FP/SAL group.

Table 19: Matched baseline characteristics – BDP/FOR versus FP/SAL DPI (excluding asthma)

		BDP/FOR N=315	FP/SAL DPI N=315	p-value	SDD	RCC
Gender	Male	185 (58.7)	184 (58.4)	0.9355	0.6	0.0
Age (years)	Mean (SD)	70.0 (9.6)	68.8 (8.9)	0.0918	12.9	0.1
	Median (IQR)	71.0 (13.0)	69.0 (11.0)			
Age (years)	≥35 <45	1 (0.3)	1 (0.3)	1.0000	0.0	0.1
	≥45 <55	19 (6.0)	19 (6.0)			
	≥55 <65	65 (20.6)	65 (20.6)			
	≥65	230 (73.0)	230 (73.0)			
BMI (kg/m^2)	N (% non-missing)	315 (100.0)	313 (99.4)	0.6446	10.3	1.9
	<18.5	21 (6.7)	16 (5.1)			
	≥18.5-<25	115 (36.5)	128 (40.9)			
	≥25-<30	108 (34.3)	103 (32.9)			
	≥30	71 (22.5)	66 (21.1)			
Smoking status closest to index date	Non-smoker	4 (1.3)	4 (1.3)	1.0000	0.0	0.3
	Current smoker	157 (49.8)	157 (49.8)			
	Ex-smoker	154 (48.9)	154 (48.9)			
Time since COPD diagnosis (years)	N (% non-missing)	286 (90.8)	297 (94.3)	0.0742	24.4	5.3
	<2	62 (21.7)	78 (26.3)			
	2 to <4	53 (18.5)	72 (24.2)			
	4 to <6	50 (17.5)	33 (11.1)			
	6 to <8	29 (10.1)	31 (10.4)			
	8+	92 (32.2)	83 (27.9)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Prescription practices by treatment group are reported in table 20. SABA prescription was different in each group (SDD 20.0), with more patients prescribed no SABA in the BDP/FOR group (24.1% vs 18.1%). There was a higher number of patients prescribed SABA/SAMA in the FP/SAL group compared to BDP/FOR (8.6 vs 1.0%, SDD 36.4 for SABA/SAMA). There were also differences between the categorised numbers of ICS inhalers (SDD 28.2), with a greater proportion prescribed in the FP/SAL group (24.1% vs 18.4%). More patients were prescribed theophylline in the FP/SAL group (11.4% vs 5.1%, SDD 23.2).

Table 20: Matched baseline characteristics – BDP/FOR versus FP/SAL DPI (excluding asthma)

		BDP/FOR N=315	FP/SAL DPI N=315	p-value	SDD	RCC
SABA inhaler prescriptions	0	76 (24.1)	57 (18.1)	0.1809	20.0	2.3
	1	25 (7.9)	21 (6.7)			
	2-4	55 (17.5)	63 (20.0)			
	5-10	81 (25.7)	102 (32.4)			
	≥11	78 (24.8)	72 (22.9)			
SABA inhalers	0	76 (24.1)	57 (18.1)	0.1467	20.9	3.1
	1	20 (6.3)	17 (5.4)			
	2-4	55 (17.5)	47 (14.9)			
	5-10	73 (23.2)	95 (30.2)			
	≥11	91 (28.9)	99 (31.4)			
Average daily dose of SABA	0	76 (24.1)	57 (18.1)	0.0753	21.0	1.1
	>0 to <200	58 (18.4)	62 (19.7)			
	200 to <400	69 (21.9)	57 (18.1)			
	≥400	112 (35.6)	139 (44.1)			
SAMA prescriptions	≥1	44 (14.0)	49 (15.6)	0.5744	4.5	0.0
SAMA µg/day	0	261 (82.9)	236 (74.9)	0.0548	22.1	2.0
	>0 to <40	46 (14.6)	61 (19.4)			
	40 to <80	2 (0.6)	7 (2.2)			
	≥80	6 (1.9)	11 (3.5)			
SAMA/SABA combination prescriptions	≥1	3 (1.0)	27 (8.6)	<0.0001	36.4	1.6
FDC ICS prescriptions	0	125 (39.7)	135 (42.9)	0.8307	9.7	1.1
	1	22 (7.0)	23 (7.3)			
	2-4	35 (11.1)	32 (10.2)			
	5-10	73 (23.2)	75 (23.8)			
	≥11	60 (19.0)	50 (15.9)			
FDC ICS inhalers	0	125 (39.7)	135 (42.9)	0.9313	7.4	1.0
	1	19 (6.0)	18 (5.7)			
	2-4	31 (9.8)	29 (9.2)			
	5-10	71 (22.5)	71 (22.5)			
	≥11	69 (21.9)	62 (19.7)			
ICS monotherapy average prescription	0	257 (81.6)	239 (75.9)	0.0154	28.2	0.7
	1	8 (2.5)	21 (6.7)			
	2-4	20 (6.3)	22 (7.0)			
	5-10	24 (7.6)	18 (5.7)			
	≥11	6 (1.9)	15 (4.8)			
ICS monotherapy inhalers	0	421 (78.0)	364 (67.4)	0.0003	28.5	0.8
	1	15 (2.8)	17 (3.1)			
	2-4	38 (7.0)	45 (8.3)			
	5-10	41 (7.6)	87 (16.1)			
	≥11	25 (4.6)	27 (5.0)			
Total ICS dosage	0-249	160 (50.8)	155 (49.2)	0.3469	11.6	1.9
	250-499	81 (25.7)	71 (22.5)			
	500+	74 (23.5)	89 (28.3)			
LAMA prescriptions	≥1	217 (68.9)	206 (65.4)	0.3508	7.4	1.2
LABA prescriptions	≥1	37 (11.7)	50 (15.9)	0.1333	12.0	0.5
LABA/LAMA combination prescriptions	≥1	2 (0.6)	1 (0.3)	0.5628	4.6	0.6
Theophylline prescriptions	≥1	16 (5.1)	36 (11.4)	0.0038	23.2	4.3
Leukotriene prescriptions	≥1	7 (2.2)	4 (1.3)	0.3615	7.3	0.2
Maintenance OCS	Yes	21 (6.7)	15 (4.8)	0.3031	8.2	0.4

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Comorbidities by treatment group are reported in table 21. There were more patients in the BDP/FOR group with a diagnosis of bronchiectasis (5.7% vs 4.4%, SDD 22.1), GERD (3.8%

vs 1.6%, SDD 13.7), diabetes (16.2% vs 8.3%, SDD 24.4), ischaemic heart disease (22.5% vs 15.2%, SDD 18.7), heart failure (2.2% vs 0.6%, SDD 13.4), chronic kidney disease (14.6% vs 9.8%, SDD 14.6) and osteoporosis (7.9% vs 3.2%, SDD 20.9) compared to the FP/SAL group.

Table 21: Matched baseline characteristics – BDP/FOR versus FP/SAL DPI (excluding asthma)

		BDP/FOR N=315	FP/SAL DPI N=315	p-value	SDD	RCC
Rhinitis diagnosis	Yes	25 (7.9)	32 (10.2)	0.3310	7.8	0.2
Active rhinitis diagnosis	Yes	15 (4.8)	19 (6.0)	0.8257	1.3	0.0
Bronchiectasis diagnosis	Yes	18 (5.7)	5 (1.6)	0.0058	22.1	1.1
Pneumonia diagnosis	Yes	10 (3.2)	5 (1.6)	0.1913	10.4	1.6
Lung cancer diagnosis	Yes	8 (2.5)	9 (2.9)	0.8058	2.0	0.1
Eczema diagnosis	Yes	78 (24.8)	67 (21.3)	0.2978	8.3	0.0
Eczema diagnosis with prescriptions	Yes	28 (8.9)	22 (7.0)	0.3765	7.1	0.4
GERD diagnosis or drugs	Yes	12 (3.8)	5 (1.6)	0.0852	13.7	1.0
Diabetes diagnosis	Yes	51 (16.2)	26 (8.3)	0.0024	24.4	1.2
Ischaemic heart disease diagnosis	Yes	71 (22.5)	48 (15.2)	0.0192	18.7	2.2
Heart failure diagnosis	Yes	7 (2.2)	2 (0.6)	0.0932	13.4	0.8
Hypertension diagnosis	Yes	129 (41.0)	123 (39.0)	0.6256	3.9	0.2
Chronic kidney disease Read code diagnosis	Yes	46 (14.6)	31 (9.8)	0.0681	14.6	2.0
Osteoporosis diagnosis	Yes	25 (7.9)	10 (3.2)	0.0091	20.9	0.3
Anxiety and/or depression diagnosis	Yes	112 (35.6)	109 (34.6)	0.8022	2.0	0.3
Active anxiety and/or depression diagnosis	Yes	81 (25.7)	78 (24.8)	0.7832	2.2	0.3
Charlson Comorbidity Index	0-2	242 (76.8)	251 (79.7)	0.6657	7.2	0.7
	3-4	43 (13.7)	39 (12.4)			
	5+	30 (9.5)	25 (7.9)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Measures of disease severity by treatment group are reported in table 22. There were significant differences between the BDP/FOR and FP/SAL groups for COPD related GP consultations (SDD 28.2) with more patients having no visits in the BDP/FOR group (38.7% vs 27.0%), outpatient COPD visits (SDD 18.8) with more patients having no outpatient visits in the BUD/FOR group (87.9% vs 90.8%). In addition, there were differences in the FEV_1/FVC ratio (SDD 13.5), with more patients having a score ≥0.6 in the BDP/FOR group (33.7% vs 28.3%) and mMRC score (SDD 33.9), with more patients having a score of 0 in the BDP/FOR group (12.8% vs 4.7%).

Table 22: Matched baseline characteristics – BDP/FOR versus FP/SAL DPI (excluding asthma)

		BDP/FOR N=315	FP/SAL DPI N=315	p-value	SDD	RCC
COPD related GP consultations	0	122 (38.7)	85 (27.0)	0.0156	28.2	0.2
	1	67 (21.3)	77 (24.4)			
	2-4	73 (23.2)	94 (29.8)			
	5-10	35 (11.1)	46 (14.6)			
	≥11	18 (5.7)	13 (4.1)			
Outpatient visits for COPD	0	277 (87.9)	286 (90.8)	0.0641	18.8	1.2
	1	21 (6.7)	23 (7.3)			
	≥2	17 (5.4)	6 (1.9)			
A & E attendances for COPD	0	305 (96.8)	308 (97.8)	0.4745	9.7	1.4
	1	9 (2.9)	5 (1.6)			
	≥2	1 (0.3)	2 (0.6)			
Inpatient admissions within 7 days of respiratory consultation	0	295 (93.7)	292 (92.7)	0.7419	6.2	0.1
	1	15 (4.8)	19 (6.0)			
	≥2	5 (1.6)	4 (1.3)			
Moderate/severe exacerbations	0	27 (8.6)	27 (8.6)	1.0000	0.0	3.4
	1	94 (29.8)	94 (29.8)			
	2	82 (26.0)	82 (26.0)			
	3	49 (15.6)	49 (15.6)			
	4+	63 (20.0)	63 (20.0)			
FEV_1 value (litres)	≤1	125 (39.7)	121 (38.4)	0.8496	7.1	0.5
	>1 to ≤2	168 (53.3)	170 (54.0)			
	2 to ≤4	17 (5.4)	16 (5.1)			
	>4	5 (1.6)	8 (2.5)			
FEV_1/FVC ratio	0.2 or less	2 (0.6)	1 (0.3)	0.4147	13.5	0.0
	0.2 to <0.4	60 (19.0)	60 (19.0)			
	0.4 to <0.6	147 (46.7)	165 (52.4)			
	0.6+	106 (33.7)	89 (28.3)			
Lowest percent predicted FEV_1	<20%	16 (5.1)	16 (5.1)	1.0000	0.0	0.3
	20% to <30%	64 (20.3)	64 (20.3)			
	30% to <40%	100 (31.7)	100 (31.7)			
	40% to <55%	135 (42.9)	135 (42.9)			
Gold severity (2016)	Mild	10 (3.2)	9 (2.9)	0.7893	8.2	0.5
	Moderate	108 (34.3)	97 (30.8)			
	Severe	147 (46.7)	158 (50.2)			
	Very severe	50 (15.9)	51 (16.2)			
mMRC score	N (% non-missing)	315 (58.3)	267 (49.4)	0.0419	33.9	10.7
	mMRC 0	24 (12.8)	8 (4.7)			
	mMRC 1	63 (33.5)	74 (43.0)			
	mMRC 2	61 (32.4)	53 (30.8)			
	mMRC 3	31 (16.5)	32 (18.6)			
	mMRC 4	9 (4.8)	5 (2.9)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

10.4 Sub-analysis: Matched characteristics of study population without asthma codes (BDP/FOR vs BUD/FOR)

Demographic characteristics can be found in table 23. Gender, age and smoking status were well balanced between groups. The categorised BMI was different in each group (SDD 10.3), with 35.7% being an ideal BMI in the BDP/FOR group compared to 41.0% in the BUD/FOR group.

Table 23: Matched baseline characteristics – BDP/FOR versus BUD/FOR DPI (excluding asthma)

		BDP/FOR N=314	BUD/FOR DPI N=314	p-value	SDD	RCC
Gender	Male	185 (58.9)	189 (60.2)	0.7450	2.6	0.3
Age (years)	Mean (SD)	70.0 (9.7)	69.3 (8.9)	0.3157	7.4	0.7
	Median (IQR)	71.0 (13.0)	69.0 (12.0)			
Age (years)	≥35 <45	1 (0.3)	1 (0.3)	1.0000	0.0	0.2
	≥45 <55	20 (6.4)	20 (6.4)			
	≥55 <65	63 (20.1)	63 (20.1)			
	≥65	230 (73.2)	230 (73.2)			
BMI (kg/m^2)	N (% non-missing)	314 (100.0)	312 (99.4)	0.2655	16.0	0.2
	<18.5	22 (7.0)	29 (9.3)			
	≥18.5-<25	112 (35.7)	128 (41.0)			
	≥25-<30	110 (35.0)	97 (31.1)			
	≥30	70 (22.3)	58 (18.6)			
Smoking status closest to index date	Non-smoker	4 (1.3)	4 (1.3)	1.0000	0.0	0.0
	Current smoker	156 (49.7)	156 (49.7)			
	Ex-smoker	154 (49.0)	154 (49.0)			
Time since COPD diagnosis (years)	N (% non-missing)	285 (90.8)	290 (92.4)	0.1761	21.1	4.7
	<2	61 (21.4)	82 (28.3)			
	2 to <4	53 (18.6)	53 (18.3)			
	4 to <6	50 (17.5)	47 (16.2)			
	6 to <8	29 (10.2)	36 (12.4)			
	8+	92 (32.3)	72 (24.8)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Prescription practices by treatment group are reported in table 24. SABA prescription was different in each group (SDD 16.9), with more patients prescribed no SABA in the BDP/FOR group (23.9% vs 21.0%). There was a higher number of patients prescribed SABA/SAMA in the BUD/FOR group compared to BDP/FOR (8.6 vs 1.0%, SDD 36.4 for SABA/SAMA). There were also differences between the categorised numbers of FDC ICS/LABAs (SDD 28.9), with a greater proportion of patients prescribed in the BDP/FOR group (60.2% vs 48.4%) and ICS inhalers (SDD 37.5) in the baseline with again a greater proportion of patients prescribed in the BUD/FOR group (32.6% vs 18.5%). More patients were prescribed theophylline in the FP/SAL group (7.6% vs 5.1%, SDD 10.4). More patients were prescribed LAMAs in the BDP/FOR group (69.1% vs 59.1%, SDD 20.7), whereas more patients were prescribed LABAs in the BUD/FOR group (24.2% vs 11.5%, SDD 33.7). A greater number of patients in the BDP/FOR group were prescribed maintenance oral corticosteroid therapy (6.7% vs 2.5%, SDD 19.8). Prescription of LABA/LAMA inhalers was very low, with only 2 patients prescribed them out of both groups.

Table 24: Matched baseline characteristics – BDP/FOR versus BUD/FOR DPI (excluding asthma)

		BDP/FOR N=314	BUD/FOR DPI N=314	p-value	SDD	RCC
SABA inhaler prescriptions	0	75 (23.9)	66 (21.0)	0.3511	16.9	1.6
	1	26 (8.3)	18 (5.7)			
	2-4	54 (17.2)	56 (17.8)			
	5-10	81 (25.8)	101 (32.2)			
	≥11	78 (24.8)	73 (23.2)			
SABA inhalers	0	75 (23.9)	66 (21.0)	0.4603	15.2	0.8
	1	21 (6.7)	15 (4.8)			
	2-4	55 (17.5)	53 (16.9)			
	5-10	72 (22.9)	90 (28.7)			
	≥11	91 (29.0)	90 (28.7)			
Average daily dose of SABA	0	75 (23.9)	66 (21.0)	0.8437	7.2	0.4
	>0 to <200	59 (18.8)	59 (18.8)			
	200 to <400	67 (21.3)	72 (22.9)			
	≥400	113 (36.0)	117 (37.3)			
SAMA prescriptions	≥1	42 (13.4)	50 (15.9)	0.3666	7.2	0.3
SAMA µg/day	0	262 (83.4)	239 (76.1)	0.0768	21.0	1.8
	>0 to <40	44 (14.0)	64 (20.4)			
	40 to <80	2 (0.6)	6 (1.9)			
	≥80	6 (1.9)	5 (1.6)			
SAMA/SABA combination prescriptions	≥1	3 (1.0)	27 (8.6)	<0.0001	36.4	0.3
FDC ICS prescriptions	0	125 (39.8)	162 (51.6)	0.0120	28.9	0.5
	1	22 (7.0)	20 (6.4)			
	2-4	33 (10.5)	31 (9.9)			
	5-10	73 (23.2)	67 (21.3)			
	≥11	61 (19.4)	34 (10.8)			
FDC ICS inhalers	0	125 (39.8)	162 (51.6)	0.0176	27.9	1.6
	1	19 (6.1)	17 (5.4)			
	2-4	30 (9.6)	31 (9.9)			
	5-10	70 (22.3)	61 (19.4)			
	≥11	70 (22.3)	43 (13.7)			
ICS monotherapy prescriptions	0	256 (81.5)	208 (66.2)	0.0003	37.5	0.1
	1	9 (2.9)	9 (2.9)			
	2-4	20 (6.4)	34 (10.8)			
	5-10	23 (7.3)	47 (15.0)			
	≥11	6 (1.9)	16 (5.1)			
ICS monotherapy inhalers	0	256 (81.5)	208 (66.2)	0.0002	37.7	0.4
	1	8 (2.5)	7 (2.2)			
	2-4	18 (5.7)	33 (10.5)			
	5-10	25 (8.0)	48 (15.3)			
	≥11	7 (2.2)	18 (5.7)			
Total ICS dosage	0-249	159 (50.6)	188 (59.9)	0.0197	22.5	3.7
	250-499	81 (25.8)	54 (17.2)			
	500+	74 (23.6)	72 (22.9)			
LAMA prescriptions	≥1	217 (69.1)	186 (59.2)	0.0099	20.7	6.3
LABA prescriptions	≥1	36 (11.5)	76 (24.2)	<0.0001	33.7	1.8
LABA/LAMA combination prescriptions	≥1	2 (0.4)	0 (0.0)	0.1566	11.3	1.0
Theophylline prescriptions	≥1	16 (5.1)	24 (7.6)	0.1911	10.4	1.3
Leukotriene prescriptions	≥1	7 (2.2)	4 (1.3)	0.3615	7.3	0.1
Maintenance OCS	Yes	21 (6.7)	8 (2.5)	0.0134	19.8	0.0

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Comorbidities by treatment group are reported in table 25. There were more patients in the BDP/FOR group with a diagnosis of bronchiectasis (5.7% vs 3.5%, SDD 10.6), lung cancer

(2.5% vs 0.3%, SDD 18.8), eczema diagnosis ever (24.8% vs 19.7%, SDD 12.3), diabetes (16.2% vs 8.3%, SDD 24.5), hypertension (41.1% vs 34.7%, SDD 13.2), chronic kidney disease (14.6% vs 8.0%, SDD 21.2) anxiety/depression diagnosed ever (35.4% vs 29.6%, SDD 12.3) and active anxiety/depression (25.5% vs 18.8%, SDD 16.2) compared to the BUD/FOR group. The categorised Charlson Comorbidity Index was also different, with 9.6% of patients prescribed BDP/FOR having a score ≥5 compared to 7.3% in the BUD/FOR group (SDD 10.1).

Table 25: Matched baseline characteristics – BDP/FOR versus BUD/FOR DPI (excluding asthma)

		BDP/FOR N=314	BUD/FOR DPI N=314	p-value	SDD	RCC
Rhinitis diagnosis	Yes	25 (8.0)	32 (10.2)	0.3309	7.8	0.9
Active rhinitis diagnosis	Yes	15 (4.8)	16 (5.1)	0.8538	1.5	0.1
Bronchiectasis diagnosis	Yes	18 (5.7)	11 (3.5)	0.1832	10.6	1.4
Pneumonia diagnosis	Yes	10 (3.2)	7 (2.2)	0.4607	5.9	0.8
Lung cancer diagnosis	Yes	8 (2.5)	1 (0.3)	0.0188	18.8	1.3
Eczema diagnosis	Yes	78 (24.8)	62 (19.7)	0.1250	12.3	0.3
Eczema diagnosis with prescriptions	Yes	28 (8.9)	27 (8.6)	0.8877	1.1	0.1
GERD diagnosis or drugs	Yes	12 (3.8)	10 (3.2)	0.6642	3.5	0.4
Diabetes diagnosis	Yes	51 (16.2)	26 (8.3)	0.0024	24.5	0.2
Ischaemic heart disease diagnosis	Yes	71 (22.6)	54 (17.2)	0.0893	13.6	1.1
Heart failure diagnosis	Yes	7 (2.2)	6 (1.9)	0.7793	2.2	0.1
Hypertension diagnosis	Yes	129 (41.1)	109 (34.7)	0.1000	13.2	1.7
Chronic kidney disease Read code diagnosis	Yes	46 (14.6)	25 (8.0)	0.0081	21.2	2.2
Osteoporosis diagnosis	Yes	25 (8.0)	20 (6.4)	0.4392	6.2	0.2
Anxiety and/or depression diagnosis	Yes	111 (35.4)	93 (29.6)	0.1251	12.3	2.0
Active anxiety and/or depression diagnosis	Yes	80 (25.5)	59 (18.8)	0.0435	16.2	3.3
Charlson Comorbidity Index	0-2	240 (76.4)	239 (76.1)	0.4508	10.1	0.3
	3-4	44 (14.0)	52 (16.6)			
	5+	30 (9.6)	23 (7.3)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Measures of disease severity by treatment group are reported in table 26. There were significant differences between the BDP/FOR and BUD/FOR groups for COPD related GP consultations (SDD 41.1) with more patients having no visits in the BDP/FOR group (39.2% vs 26.4%), outpatient COPD visits (SDD 18.1) with more patients having no outpatient visits in the BUD/FOR group (90.4% vs 87.6%), and A&E attendances (SDD 11.8) with more patients having no visits in the BUD/FOR group (98.4% vs 96.8%). In addition, there were differences in the GOLD severity score (SDD 13.6), with more patients having a very severe score in the BDP/FOR group (16.2% vs 12.1%) and mMRC score (SDD 26.4), with more patients having a score of 0 in the BDP/FOR group (12.8% vs 6.2%).

Table 26: Matched baseline characteristics – BDP/FOR versus BUD/FOR DPI (excluding asthma)

		BDP/FOR N=314	BUD/FOR DPI N=314	p-value	SDD	RCC
COPD related GP consultations	0	123 (39.2)	83 (26.4)	<0.0001	41.4	3.5
	1	65 (20.7)	53 (16.9)			
	2-4	73 (23.2)	108 (34.4)			
	5-10	35 (11.1)	61 (19.4)			
	≥11	18 (5.7)	9 (2.9)			
Outpatient visits for COPD	0	275 (87.6)	284 (90.4)	0.0790	18.1	1.1
	1	21 (6.7)	23 (7.3)			
	≥2	18 (5.7)	7 (2.2)			
A & E attendances for COPD	0	304 (96.8)	309 (98.4)	0.3356	11.8	1.7
	1	9 (2.9)	5 (1.6)			
	≥2	1 (0.3)	0 (0.0)			
Inpatient admissions within 7 days of respiratory consultation	0	294 (93.6)	299 (95.2)	0.6455	7.5	1.9
	1	15 (4.8)	12 (3.8)			
	≥2	5 (1.6)	3 (1.0)			
Moderate/severe exacerbations	0	26 (8.3)	26 (8.3)	1.0000	0.0	1.7
	1	94 (29.9)	94 (29.9)			
	2	82 (26.1)	82 (26.1)			
	3	49 (15.6)	49 (15.6)			
	4+	63 (20.1)	63 (20.1)			
FEV_1 value (litres)	≤1	125 (39.8)	139 (44.3)	0.4947	12.4	2.5
	>1 to ≤2	165 (52.5)	158 (50.3)			
	2 to ≤4	18 (5.7)	14 (4.5)			
	>4	6 (1.9)	3 (1.0)			
FEV_1/FVC ratio	0.2 or less	2 (0.6)	3 (1.0)	0.7395	9.0	0.2
	0.2 to <0.4	59 (18.8)	64 (20.4)			
	0.4 to <0.6	149 (47.5)	155 (49.4)			
	0.6+	104 (33.1)	92 (29.3)			
Lowest percent predicted FEV_1	<20%	16 (5.1)	16 (5.1)	1.0000	0.0	0.1
	20% to <30%	63 (20.1)	63 (20.1)			
	30% to <40%	99 (31.5)	99 (31.5)			
	40% to <55%	136 (43.3)	136 (43.3)			
Gold severity (2016)	Mild	9 (2.9)	7 (2.2)	0.4094	13.6	0.5
	Moderate	109 (34.7)	109 (34.7)			
	Severe	145 (46.2)	160 (51.0)			
	Very severe	51 (16.2)	38 (12.1)			
mMRC score	N (% non-missing)	187 (59.6)	161 (51.3)	0.2127	26.4	11.8
	mMRC 0	24 (12.8)	10 (6.2)			
	mMRC 1	62 (33.2)	67 (41.6)			
	mMRC 2	60 (32.1)	50 (31.1)			
	mMRC 3	32 (17.1)	28 (17.4)			
	mMRC 4	9 (4.8)	6 (3.7)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

11.0 Post matching adjustment

Variables for adjustment were data driven and based on clinical grounds for the primary outcome. In both outcomes, the demographic variables were well matched. In the BDP/FOR vs FP /SAL comparison, the only comorbidity with an RCC >2 was anxiety/depression which was chosen for adjustment. Inpatient hospitalisations, accident and emergency consultation, oral corticosteroid prescriptions were dropped because they were components of

exacerbations which was matched on. The number of unlicensed fixed dose combination inhalers was chosen as the RCC was 5.1 in the BDP/FOR vs BUD/FOR comparison. Clinically this variable was important to include as it is a marker of prior treatment, and these patients will have switched from a fixed dose combination inhaler instead of stepping up from a type of monotherapy. COPD diagnosis time, and COPD themed GP consultations were dropped as they were not a reliable indicator of actual primary care consultations or time since diagnosis. In addition, SABA/SAMA prescription was chosen as this provided a marker of severity with a RCC of 6.8 in the BUD/FOR vs BDP/FOR comparison. The number of SABA inhalers was added on clinical grounds as it was also used for the same indication as SABA/SAMA inhalers, and provided another marker of severity. SAMA inhalers were not included as they were not prescribed in the majority of patients.

For the secondary outcomes, a purely data driven approach was used for each individual comparison.

12.0 Matched results

12.1 Primary outcomes

12.1.1 BDP/FOR vs FP/SAL

Table 27 presents the primary outcome for BDP/FOR vs FP/SAL.

Table 27: Primary outcome results

N=537	BDP/FOR		FP/SAL DPI	
Patients with ≥1 exacerbation, n (%)	369 (68.72)		377 (70.20)	
Comparison	**Odds ratio**		**95% CI**	**p-value**
BDP/FOR pMDI vs FP/SAL DPI	Crude	0.93	0.71-1.21	0.585
	Adjusted*	0.89	0.67-1.19	0.441

* Adjusted for baseline FDC ICS/LABA prescriptions, baseline SABA prescriptions, baseline SAMA/SABA prescriptions and active anxiety/depression.

The upper confidence interval of the odds ratio after adjustment for baseline confounders was <1.2, thus BDP/FOR can be considered non-inferior to FP/SAL in terms of the proportion of patients with COPD exacerbations. The OR is <1, indicating a trend towards superiority.

12.1.2 BDP/FOR vs BUD/FOR

Table 28 presents the primary outcome for BDP/FOR vs BUD/FOR.

Table 28: BDP/FOR vs BUD/FOR primary outcome results

N=540	BDP/FOR		BUD/FOR DPI	
Patients with ≥1 exacerbation, n (%)	370 (68.52)		375 (69.44)	
Non-inferiority	**Odds ratio**		**95% CI**	**p-value**
BDP/FOR pMDI vs BUD/FOR DPI	Crude	0.95	0.72-1.25	0.724
	Adjusted*	0.79	0.58-1.08	0.146

* Adjusted for baseline FDC ICS/LABA prescriptions, baseline SABA prescriptions, baseline SAMA/SABA prescriptions and active anxiety/depression.

The upper confidence interval of the odds ratio after adjustment for baseline confounders was <1.2, thus BDP/FOR can be considered non-inferior to BUD/FOR in terms of the proportion of patients with COPD exacerbations. The OR is <1, indicating a trend towards superiority.

12.2 Sub-analysis of COPD only patients

12.2.1 BDP/FOR vs FP/SAL COPD only

The baseline number of oral corticosteroid courses for adjustment was dropped as it was a component of exacerbations which was used for matching. In both the crude and the adjusted analysis there was a statistically significant lower risk of exacerbations.

Table 29 presents the main outcome for the sub-analysis for BDP/FOR vs FP/SAL.

Table 29: BDP/FOR vs FP/SAL for risk of exacerbations COPD only

N=315	BDP/FOR		FP/SAL DPI	
Patients with ≥1 exacerbation, n (%)	204 (64.76)		232 (73.65)	
Comparison	**Odds ratio**		**95% CI**	**p-value**
BDP/FOR pMDI vs FP/SAL DPI	Crude	**0.62**	**0.43-0.90**	**0.011**
	Adjusted*	**0.64**	**0.43-0.96**	**0.031**

*adjusted for theophylline prescription, IHD diagnosis, LTRA prescriptions

12.2.2 BDP/FOR vs BUD/FOR Turbohaler

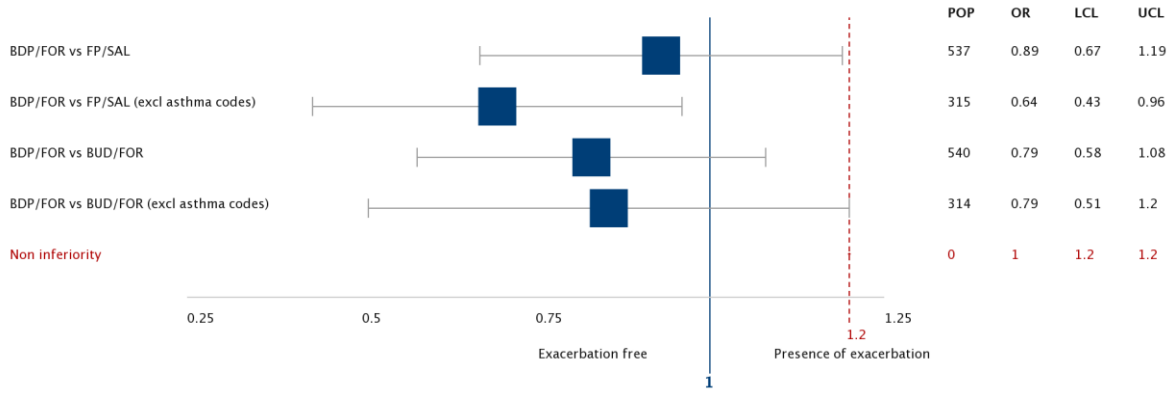
Table 30 presents the main outcome for the sub-analysis for BDP/FOR vs FP/SAL.
Both the crude and adjusted analysis showed a similar risk of exacerbations in each arm. Notably, after adjustment, the odds ratio estimate was 1.997, which was below the non-inferiority margin predefined for the main analysis.

Table 30: BDP/FOR vs BUD/FOR for risk of exacerbations COPD only

N=314	BDP/FOR		BUD/FOR DPI	
Patients with ≥1 exacerbation, n (%)	213 (67.83)		203 (64.65)	
Comparison	**Odds ratio**		**95% CI**	**p-value**
BDP/FOR pMDI vs FP/SAL DPI	Crude	0.85	0.59-1.21	0.366
	Adjusted*	0.79	0.51-1.20**	0.270

*adjusted for SABA daily dose, ICS prescriptions, hypertension diagnosis, diabetes diagnosis **1.1997

Figure 3: Summary of odds ratio of risk of exacerbation for main population and sub-analysis (UCL – upper confidence interval, LCL – lower confidence interval, POP – population)



12.3 Secondary outcomes

The number of patients in each analysis represents the matched pairs having removed pairs with identical outcomes. The total number of matched pairs in each analysis was 537 for BDP/FOR vs FP/SAL and 540 for BDP/FOR vs BUD/FOR.

12.3.1 BDP/FOR vs FP/SAL

The secondary outcomes are shown in table 31 and figure 5. The number of antibiotic courses for lower respiratory tract infections was lower in the BDP/FOR group compared to the FP/SAL group (OR 0.77, 95% CI 0.65-0.92).

Figure 4: Respiratory outcomes comparing BDP/FOR to FP/SAL DPI (treatment stability has been inverted to risk of treatment instability)

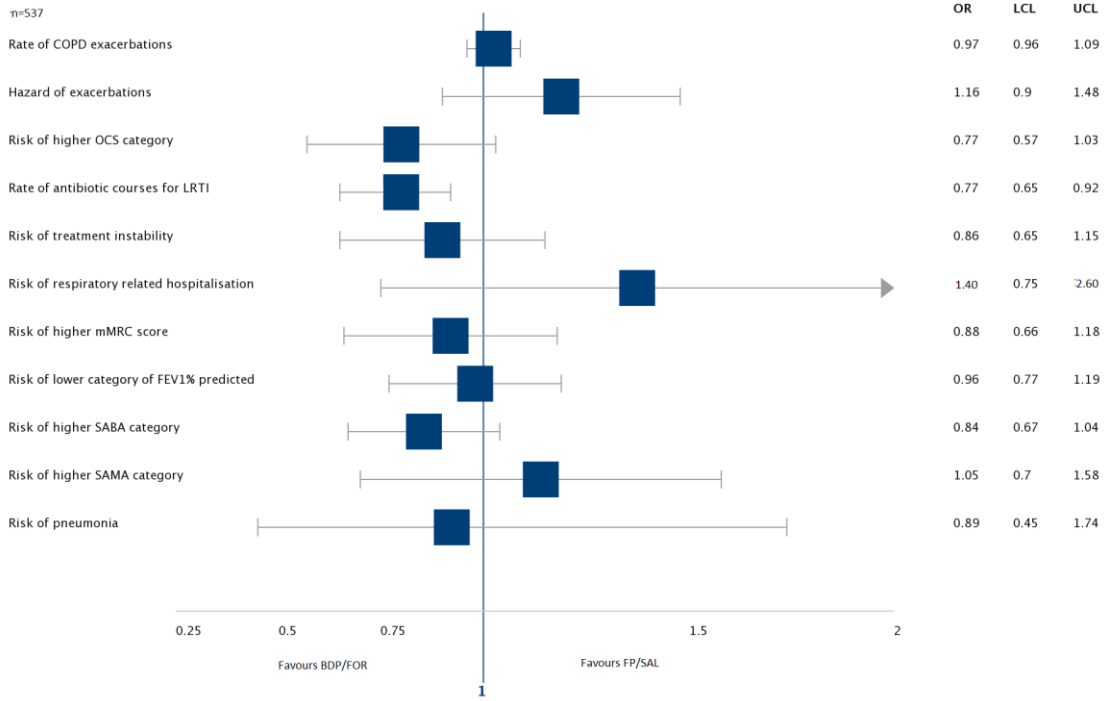


Table 31: Respiratory outcomes comparing BDP/FOR to FP/SAL DPI

Respiratory outcome	Number of patients in analysis N (%)	Ratio	95% confidence interval	p-value
Rate of moderate/ severe COPD exacerbations[1]	1074 (100)	0.97*	0.96, 1.09	0.555
Hazard of exacerbation[2]	736 (68.53)	1.16**	0.90, 1.48	0.247
Risk of higher oral corticosteroid dosage (mg)[3]	706 (65.74)	0.77§	0.57-1.03	0.079
Rate of antibiotic courses for LRTI[4]	758 (70.58)	**0.77***	**0.65, 0.92**	**0.003**
Risk of treatment stability[5]	388 (36.13)	1.16§	0.87, 1.55	0.303
Risk of respiratory-related hospitalisations[6]	114 (10.61)	1.40§	0.75, 2.60	0.286
Risk of higher mMRC dyspnoea score[7]	654 (60.89)	0.88§	0.66, 1.18	0.399
Risk of worse lung function (FEV_1 % predicted)[8]	872 (81.19)	0.96§	0.77, 1.19	0.707
Risk of greater reliever use – average SABA daily	1074 (100)	0.84§	0.67, 1.04	0.112
Risk of greater reliever use – average SAMA daily[9]	1074 (100)	1.05§	0.70, 1.58	0.803
Risk of pneumonia (confirmed and suspected)	68 (6.33)	0.89§	0.45, 1.74	0.732

*Rate ratio; **Hazard ratio; §Odds ratio
[1] Adjusted for acute oral corticosteroid courses
[2] Adjusted for total ICS dosage
[3] Adjusted for SABA inhalers, maintenance OCS, total ICS dosage and acute oral corticosteroid courses – categorised into 0, 1-<150mg, 150mg-450mg, 450mg-<600mg, ≥600mg
[4] Adjusted for SABA inhalers and SAMA/SABA combination prescriptions
[5] Adjusted for active depression/anxiety
[6] Adjusted for COPD related GP consultations
[7] Adjusted for theophylline prescriptions, FDC ICS inhalers, SAMA/SABA combination prescriptions, SABA inhaler prescriptions, COPD related GP consultations and asthma diagnosis
[8] Adjusted for average daily dose of SABA, BMI and rhinitis diagnosis
[9] Adjusted for SAMA daily dosage

12.3.2 BDP/FOR vs BUD/FOR

The secondary outcomes are shown in table 32 and figure 6 and are similar between the two groups.

Figure 5: Respiratory outcomes comparing BDP/FOR to BUD/FOR DPI (treatment stability has been inverted to risk of treatment instability)

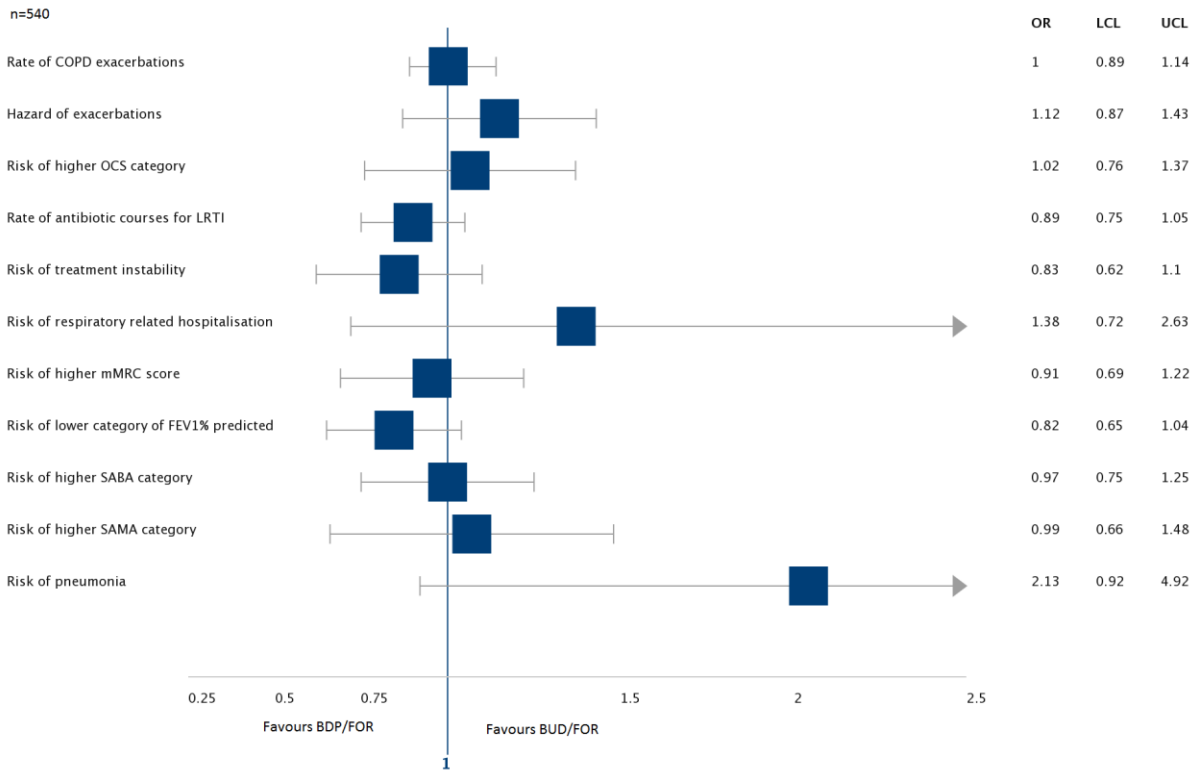


Table 32: Respiratory outcomes comparing BDP/FOR to BUD/FOR DPI

Respiratory outcome	Number of patients in analysis	Ratio	95% confidence interval	p-value
Rate of moderate/ severe COPD exacerbations[1]	1080 (100)	1.00*	0.89, 1.14	0.964
Hazard of exacerbation[2]	730 (67.59)	1.12**	0.87, 1.43	0.382
Risk of higher oral corticosteroid dosage (mg)[3]	898 (83.15)	1.02§	0.76, 1.37	0.904
Rate of antibiotic courses for LRTI[4]	754 (69.81)	0.89*	0.75, 1.05	0.169
Risk of treatment stability[5]	380 (35.19)	1.21§	0.91, 1.61	0.192
Risk of respiratory-related hospitalisations[6]	104 (9.63)	1.38§	0.72, 2.63	0.327
Risk of higher mMRC dyspnoea score[7]	630 (58.33)	0.91§	0.69, 1.22	0.539
Risk of worse lung function (FEV_1 % predicted)[8]	902 (83.52)	0.82§	0.65, 1.04	0.104
Risk of greater reliever use – average SABA daily	1080 (100)	0.97§	0.75, 1.25	0.822
Risk of greater reliever use – average SAMA daily[9]	1080 (100)	0.99§	0.66, 1.48	0.950
Risk of pneumonia (confirmed and suspected)	50 (4.63)	2.13§	0.92, 4.92	0.079

*Rate ratio; **Hazard ratio; §Odds ratio
[1] Adjusted for FDC ICS inhalers and COPD related GP consultations
[2] Adjusted for total ICS dosage
[3] Adjusted for SABA inhalers, maintenance OCS, total ICS dosage and acute oral corticosteroid courses, categorised into 0, 1-<150mg, 150mg-450mg, 450mg-<600mg, ≥600mg
[4] Adjusted for SABA inhalers and SAMA/SABA combination prescriptions
[5] Adjusted for COPD related GP consultations
[6] Adjusted for chronic kidney disease
[7] Adjusted for FEV_1, FDC ICS inhalers, LABA prescriptions and COPD related GP consultations
[8] Adjusted for total ICS dosage, LABA prescriptions, LAMA prescriptions, average daily dose of SABA, FEV_1 value and heart failure diagnosis
[9] Adjusted for SAMA daily dosage

12.3.3 Sub-analysis secondary outcomes BDP/FOR vs FP/SAL

The secondary outcomes are shown in table 33 and figure 7. The rate of exacerbations was lower for BDP/FOR compared to FP/SAL (RR 0.74, 95% CI 0.56-0.99). The number of antibiotic courses for lower respiratory tract infections was lower in the BDP/FOR group compared to the FP/SAL group (OR 0.64, 95% CI 0.51-0.81). Treatment stability was also more likely in the BDP/FOR group compared to the FP/SAL group (OR 1.88, 95% CI 1.18-

3.01). The mean SAMA usage was also lower in the BDP/FOR group compared to the FP/SAL group (0.53, 95% CI 0.33-0.84).

Figure 6: Secondary outcomes BDP/FOR vs FP/SAL (treatment stability has been inverted to risk of treatment instability)

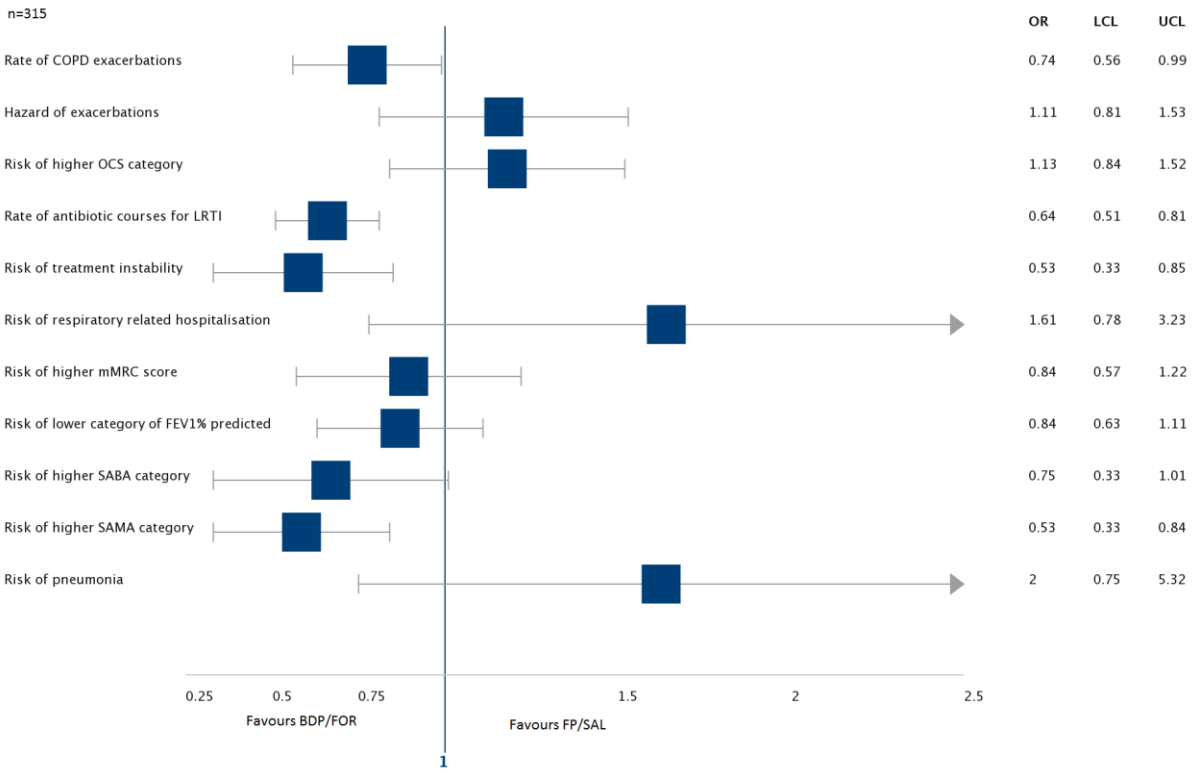


Table 33: Secondary outcomes BDP/FOR vs FP/SAL

Respiratory outcome	Number of patients in analysis N (%)	Ratio	95% confidence interval	p-value
Rate of moderate/ severe COPD exacerbations[1]	628 (100)	0.74	0.56, 0.99	<0.001
Hazard of exacerbation[2]	430 (68.25)	1.11**	0.81, 1.53	0.516
Risk of higher oral corticosteroid dosage (mg)[3]	625 (99.21)	1.13§	0.84-1.52	0.436
Rate of antibiotic courses for LRTI[4]	436 (69.21)	0.64*	0.51, 0.81	<0.001
Risk of treatment stability[5]	232 (36.83)	1.88§	1.18, 3.01	0.008
Risk of respiratory-related hospitalisations[6]	68 (10.8)	1.61§	0.78, 3.23	0.174
Risk of higher mMRC dyspnoea score[7]	387 (61.43)	0.84§	0.57, 1.22	0.354
Risk of worse lung function (FEV_1 % predicted)[8]	502 (79.7)	0.84§	0.63, 1.11	0.221
Risk of greater reliever use – average SABA daily[9]	630 (100)	0.75§	0.56, 1.01	0.057
Risk of greater reliever use – average SAMA daily[10]	162 (25,7)	0.53	0.33, 0.84	0.006
Risk of pneumonia (confirmed and suspected)[11]	20 (3.2)	2.00§	0.75, 5.32	0.166

*Rate ratio; **Hazard ratio; §Odds ratio
[1] Adjusted for acute oral corticosteroid courses
[2] Adjusted for total ICS dosage
[3] Adjusted for SABA inhalers, acute oral corticosteroid courses, and SAMA/SABA combination prescriptions
[4] Adjusted for SABA inhalers, Ischaemic heart disease diagnosis, Baseline COPD consultations, Outpatient visits for COPD and theophylline prescriptions
[5] Adjusted for SABA inhalers, acute oral corticosteroid courses, theophylline prescriptions,
[6] No adjustment for respiratory-related hospitalisations
[7] Adjusted for theophylline prescriptions, FDC ICS inhalers, SAMA/SABA combination prescriptions, FEV1 value categorized, COPD related GP consultations and asthma diagnosis
[8] Adjusted for Total ICS dosage (FP equivalent), Ischaemic heart disease diagnosis and diabetes diagnosis
[9] Adjusted for COPD related GP consultations, theophylline prescriptions, baseline antibiotic prescriptions, Ischaemic heart disease diagnosis, Total ICS dosage (FP equivalent), acute oral corticosteroid courses, Charlson Comorbidity Index
[10] No adjustment for SAMA daily dose
[11] No adjustment for pneumonia

12.3.4 Sub-analysis secondary outcomes BDP/FOR vs BUD/FOR

The secondary outcomes are shown in table 34 and figure 8. The number of antibiotic courses for lower respiratory tract infections was lower in the BDP/FOR group compared to the BUD/FOR group (OR 0.75, 95% CI 0. 6-0.93). Treatment stability was also more likely in the BDP/FOR group compared to the BUD/FOR group (OR 1.45, 95% CI 1.00-2. 01). The mean

SAMA usage was also lower in the BDP/FOR group compared to the BUD/FOR group (0.53, 95% CI 0.33-0.88).

Figure 7: Secondary outcomes BDP/FOR vs BUD/FOR (treatment stability has been inverted to risk of treatment instability)

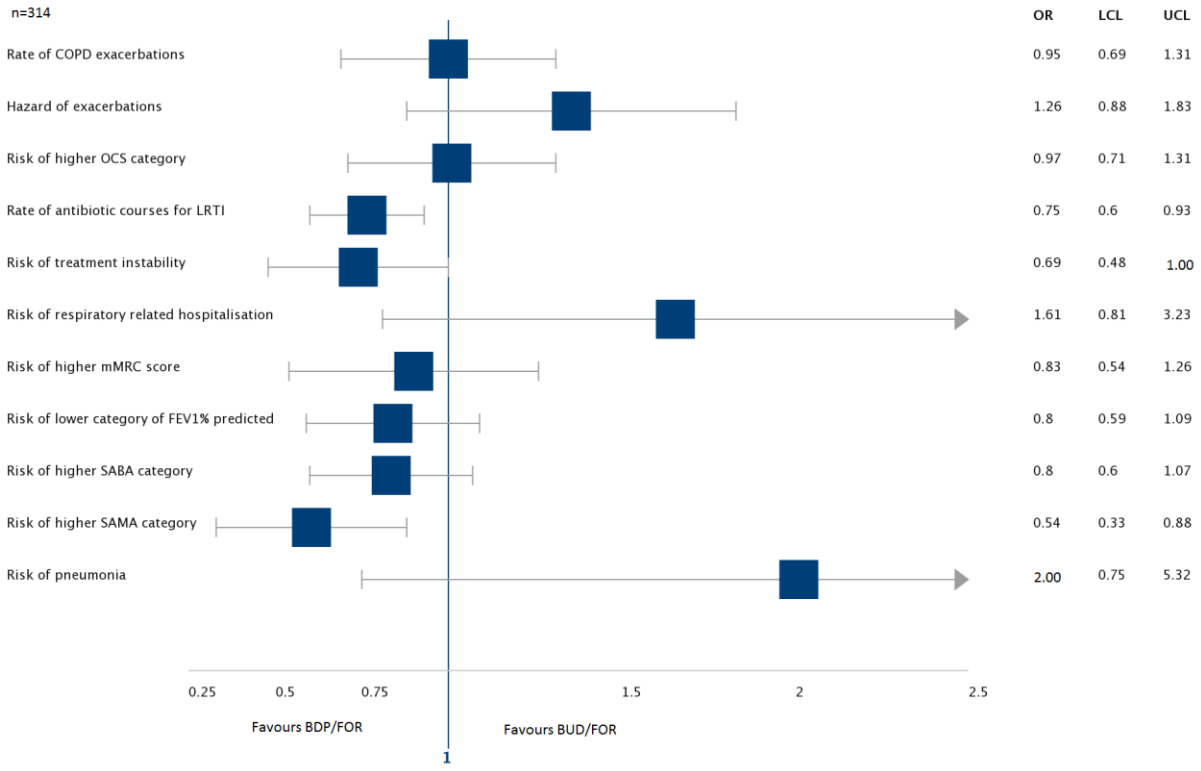


Table 34: Secondary outcomes BDP/FOR vs BUD/FOR

Respiratory outcome	Number of patients in analysis	Ratio	95% confidence interval	p-value
Rate of moderate/ severe COPD exacerbations[1]	628 (100)	0.95*	0.69, 1.31	0.76
Hazard of exacerbation[2]	410 (65.29)	1.26**	0.88, 1.83	0.206
Risk of higher oral corticosteroid dosage (mg)[3]	628 (100)	0.97§	0.71, 1.31	0.833
Rate of antibiotic courses for LRTI[4]	414 (69.81)	0.75*	0.60, 0.93	0.008
Risk of treatment stability[5]	230 (36.62)	1.45§	1.00, 2.10	0.052
Risk of respiratory-related hospitalisations[6]	28 (10.83)	1.61§	0.81, 3.23	0.570
Risk of higher mMRC dyspnoea score[7]	313 (49.84)	0.83§	0.54, 1.26	0.379
Risk of worse lung function (FEV_1 % predicted)[8]	437 (82.77)	0.80§	0.59, 1.09	0.167
Risk of greater reliever use – mean SABA daily[9]	628 (100)	0.80§	0.60, 1.07	0.135
Risk of greater reliever use – mean SAMA daily[10]	142 (26.89)	0.54§	0.33, 0.88	0.014
Risk of pneumonia (confirmed and suspected)	20 (3.2)	2.00§	0.75, 5.33	0.166

*Rate ratio; **Hazard ratio; §Odds ratio
[1] Adjusted for acute oral corticosteroid courses, FDC ICS inhalers, FEV1 value, SABA inhalers
[2] Adjusted for total ICS dosage, monotherapy ICS prescriptions, Rhinitis diagnosis, Outpatient visits for COPD
[3] Adjusted for SABA inhalers, acute oral corticosteroid courses, and SAMA/SABA combination prescriptions
[4] Adjusted for SABA inhalers, total ICS dosage, Diabetes diagnosis, Anxiety depression diagnosis
[5] No adjustments for treatment stability
[6] No adjustment for respiratory-related hospitalisations
[7] Adjusted for SAMA inhalers, CKD diagnosis, LABA inhalers, COPD related GP consultations and IHD diagnosis
[8] Adjusted for Body Mass Index, SAMA inhalers, SABA inhalers, LABA inhalers, Diabetes diagnosis, Outpatient visits for COPD and Maintenance oral corticosteroid
[9] Adjusted for COPD- related hospitalisations
[10] No adjustment for SAMA daily dose

12.4 Cost effectiveness analysis

The estimated costs are followed by the adjusted costs and the cost effectiveness.

For the estimated costs, bootstrap estimations represent the £ value of BDP/FOR compared to either FP/SAL or BDP/FOR.

12.4.1 BDP/FOR vs FP/SAL

Total costs were significantly lower for BDP/FOR compared to FP/SAL (£730 vs £850, SDD 26.1) driven mainly by medication costs (£570 vs £723), which in turn were driven by inhaled corticosteroid therapy. Resource costs were higher for BDP/FOR (£160 vs £140, p = 0.033)

driven by outpatient costs but this was not supported by the bootstrap replication. The comparison for adjusted means showed a similar pattern for total, resource and medication costs.

Table 35: Respiratory outcomes comparing BDP/FOR to FP/SAL DPI

		BDP/FOR N=537	FP/SAL DPI N=537	p-value	SDD	Bootstrap 95% CI
Total cost (£)	Mean (SD)	730.6 (505.0)	850.7 (409.3)	<0.0001	26.1	-175.58, -64.62
	Median (IQR)	651.9 (474.7)	833.5 (528.6)			
Total resource cost (£)	Mean (SD)	159.8 (380.4)	140.2 (345.6)	0.0327	5.4	-23.87, 63.16
	Median (IQR)	42.0 (126.0)	42.0 (168.0)			
Total medication cost (£)	Mean (SD)	570.2 (286.8)	723.0 (312.0)	<0.0001	51.0	-189.16, -116.31
	Median (IQR)	543.3 (415.4)	707.9 (455.6)			
Total A&E cost (£)	Mean (SD)	3.2 (25.5)	5.4 (63.9)	1.0000	-	-8.10, 3.63
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
Total inpatient cost (£)	Mean (SD)	27.2 (170.9)	20.7 (208.6)	0.1272	13.3	-15.94, 29.00
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
Total outpatient cost (£)	Mean (SD)	47.2 (159.7)	28.5 (106.6)	0.0514	13.8	2.44, 34.99
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
Total primary care consultation cost (£)	Mean (SD)	82.2 (182.6)	85.6 (134.4)	0.0048	2.1	-22.23, 15.50
	Median (IQR)	42.0 (84.0)	42.0 (126.0)			
Total antibiotic cost (£)	Mean (SD)	4.3 (9.8)	4.9 (8.5)	0.0236	6.5	-1.70, 0.50
	Median (IQR)	0.0 (5.1)	1.7 (6.8)			
Total SABA cost (£)	Mean (SD)	20.4 (27.7)	24.8 (29.4)	0.0020	15.4	-7.92, -0.86
	Median (IQR)	13.8 (27.6)	18.0 (27.5)			
Total ICS cost (£)	Mean (SD)	321.7 (131.3)	437.0 (170.4)	<0.0001	75.8	-133.64, -97.06
	Median (IQR)	322.5 (175.9)	450.1 (204.6)			
Total LABA cost (£)	Mean (SD)	6.1 (36.4)	2.0 (18.3)	0.0606	14.5	0.81, 7.56
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
Total SAMA cost (£)	Mean (SD)	0.6 (1.7)	0.7 (1.9)	0.5492	5.0	-0.30, 0.13
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
Total LAMA cost (£)	Mean (SD)	196.0 (190.5)	237.0 (200.5)	0.0012	21.0	-64.25, -17.79
	Median (IQR)	171.6 (382.7)	255.1 (382.7)			
Total LTRA cost (£)	Mean (SD)	8.9 (43.5)	8.9 (44.1)	0.6026	0.0	-5.26, 5.23
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
Total THEO cost (£)	Mean (SD)	2.1 (9.0)	4.6 (13.3)	<0.0001	21.3	-3.77, -1.06
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
Total OCS cost (£)	Mean (SD)	10.8 (53.7)	4.4 (10.8)	<0.0001	16.5	1.58, 11.16
	Median (IQR)	1.3 (7.1)	0.0 (3.5)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Table 36: Respiratory outcomes comparing BDP/FOR to FP/SAL DPI – adjusted means

		BDP/FOR N=537	FP/SAL DPI N=537	p-value
Total cost (£)	N (% non-missing)	534 (99.44)	523 (97.39)	<0.001
	Adjusted* mean	730.04	850.77	
Total resource cost (£)	N (% non-missing)	536 (99.81)	531 (98.89)	0.016
	Adjusted* mean	159.65	128.19	
Total medication cost (£)	N (% non-missing)	534 (99.44)	523 (97.39)	<0.001
	Adjusted* mean	570.60	723.97	
Total A&E cost (£)	N (% non-missing)	536 (99.81)	531 (98.89)	0.519
	Adjusted* mean	3.20	2.90	
Total inpatient cost (£)	N (% non-missing)	536 (99.81)	531 (98.89)	0.080
	Adjusted* mean	27.34	13.11	
Total outpatient cost (£)	N (% non-missing)	536 (99.81)	531 (98.89)	0.020
	Adjusted* mean	47.35	28.76	
Total primary care consultation cost (£)	N (% non-missing)	536 (99.81)	531 (98.89)	0.322
	Adjusted* mean	81.76	83.42	
Total antibiotic cost (£)	N (% non-missing)	536 (99.81)	530 (98.70)	0.589
	Adjusted* mean	4.27	4.87	
Total SABA cost (£)	N (% non-missing)	536 (99.81)	531 (98.89)	0.008
	Adjusted* mean	20.44	24.93	
Total ICS cost (£)	N (% non-missing)	536 (99.81)	531 (98.89)	<0.001
	Adjusted* mean	321.35	437.71	
Total LABA cost (£)	N (% non-missing)	536 (99.81)	531 (98.89)	0.013
	Adjusted* mean	6.18	1.94	
Total SAMA cost (£)	N (% non-missing)	536 (99.81)	531 (98.89)	0.445
	Adjusted* mean	0.57	0.66	
Total LAMA cost (£)	N (% non-missing)	536 (99.81)	531 (98.89)	<0.001
	Adjusted* mean	196.16	238.25	
Total LTRA cost (£)	N (% non-missing)	536 (99.81)	531 (98.89)	0.953
	Adjusted* mean	8.92	8.93	
Total THEO cost (£)	N (% non-missing)	536 (99.81)	531 (98.89)	0.002
	Adjusted* mean	2.18	4.40	
Total OCS cost (£)	N (% non-missing)	534 (99.44)	524 (97.58)	0.005
	Adjusted* mean	10.87	4.40	

* Adjusted for COPD related GP consultations and baseline medication & resources costs

The resampled data covered the South-east and South-west quadrants, therefore an ICER estimate is not presented.

The CEAC depicts the relationship between the threshold, or ceiling ratio, of an avoided exacerbation and the probability of BDP/FOR being cost-effective. Due to the large proportion of replicates in the South-east quadrant, at a willingness-to-pay threshold of £0 for one avoided exacerbation, the probability of BDP/FOR being cost-effective was 70.9%. BDP/FOR will be cost-effective (i.e. p=0.90) compared to FP/SAL if a threshold ICER of £10,600 per patient with exacerbation avoided was adopted. If the threshold is 0.95 BDP/FOR will be cost-effective compared to FP/SAL if a threshold ICER of £24,000 per patient with exacerbation avoided was adopted.

Table 37: Distribution of cost effectiveness BDP/FOR vs FP/SAL

Sector	Number (n= 982)	Percentage
North East (more costly, more effective)	0	0%
South East (less costly, more effective)	696	70.9%
North West (more costly, less effective)	0	0%
South West (less costly, less effective)	286	29.1%

Figure 8: Joint distribution of cost and effectiveness differences of BDP/FOR vs FP/SAL

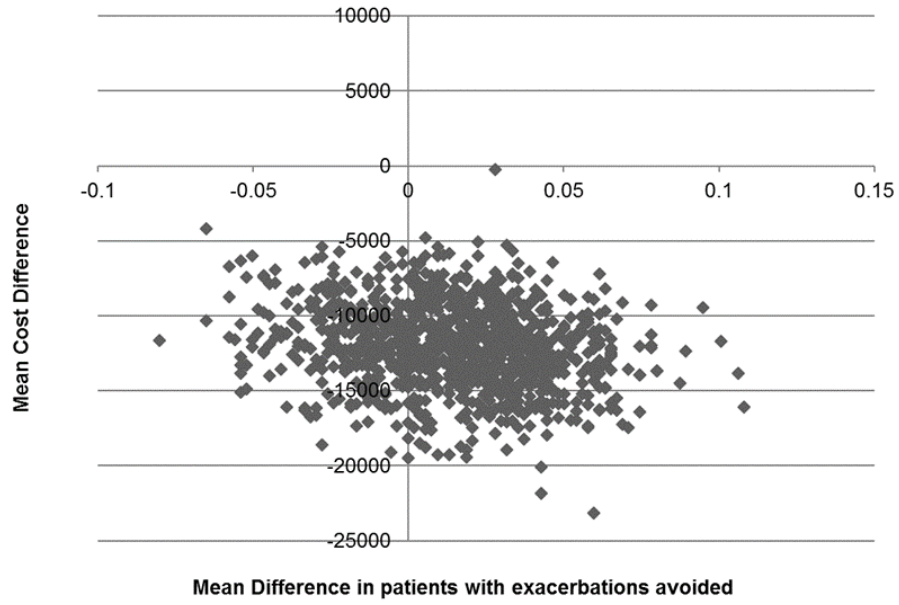
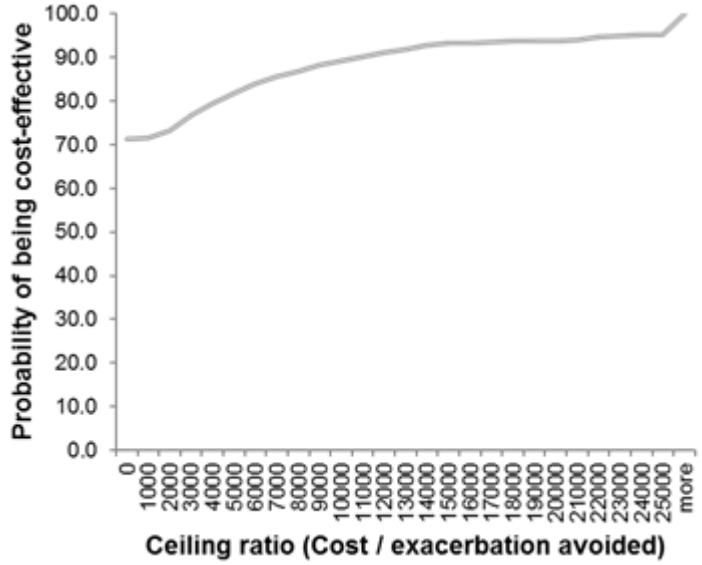


Figure 9: Cost effectiveness curve for BDP/FOR



12.4.2 BDP/FOR vs BUD/FOR

Total costs were similar for BDP/FOR compared to BUD/FOR (£735 vs £754, SDD 4.3) with the difference driven mainly by medication costs (£573 vs £652, with BUD/FOR being more expensive), which in turn were driven by inhaled corticosteroid therapy. Resource costs were

higher for BDP/FOR (£165 vs £102, SDD 26.1) driven by outpatient costs but this was not supported by the bootstrap replication. The comparison for adjusted means showed a similar pattern for total, resource and medication costs.

Table 38: Respiratory outcomes comparing BDP/FOR to BUD/FOR DPI

		BDP/FOR N=540	BUD/FOR DPI N=540	p-value	SDD	Bootstrap 95% CI
Total cost (£)	Mean (SD)	734.7 (510.2)	753.9 (380.2)	0.0079	4.3	-72.33, 34.04
	Median (IQR)	652.6 (470.1)	721.3 (472.3)			
Total resource cost (£)	Mean (SD)	165.4 (394.5)	101.7 (190.2)	0.0444	20.6	27.35, 100.08
	Median (IQR)	42.0 (126.0)	42.0 (126.0)			
Total medication cost (£)	Mean (SD)	573.3 (289.1)	652.4 (317.2)	<0.0001	26.1	-115.43, -42.82
	Median (IQR)	550.7 (411.4)	592.7 (458.9)			
Total A&E cost (£)	Mean (SD)	3.2 (25.4)	1.0 (12.8)	0.0813	-	-0.11, 4.56
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
Total inpatient cost (£)	Mean (SD)	31.4 (197.3)	10.8 (86.5)	0.0544	13.7	2.49, 38.62
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
Total outpatient cost (£)	Mean (SD)	47.5 (160.7)	25.0 (117.2)	0.0097	16.0	6.17, 38.83
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
Total primary care consultation cost (£)	Mean (SD)	83.4 (184.3)	64.9 (101.0)	0.3581	12.4	0.78, 36.09
	Median (IQR)	42.0 (84.0)	42.0 (84.0)			
Total antibiotic cost (£)	Mean (SD)	4.3 (9.8)	3.9 (7.2)	0.4979	4.2	-0.63, 1.35
	Median (IQR)	0.0 (5.1)	0.0 (5.1)			
Total SABA cost (£)	Mean (SD)	19.7 (22.7)	28.3 (36.2)	<0.0001	28.6	-12.23, -5.06
	Median (IQR)	13.8 (27.5)	20.6 (31.8)			
Total ICS cost (£)	Mean (SD)	323.7 (133.2)	409.2 (191.8)	<0.0001	51.8	-105.18, -65.84
	Median (IQR)	322.5 (175.9)	423.8 (211.9)			
Total LABA cost (£)	Mean (SD)	7.3 (44.9)	5.6 (42.9)	0.5331	3.7	-3.73, 6.99
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
Total SAMA cost (£)	Mean (SD)	0.6 (1.7)	0.8 (2.2)	0.0772	12.8	-0.49, -0.01
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
Total LAMA cost (£)	Mean (SD)	197.6 (190.7)	188.5 (188.6)	0.4341	4.8	-13.20, 31.40
	Median (IQR)	191.3 (382.7)	159.4 (382.7)			
Total LTRA cost (£)	Mean (SD)	10.2 (46.6)	9.7 (46.3)	0.7096	1.0	-5.06, 5.96
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
Total THEO cost (£)	Mean (SD)	2.4 (9.5)	3.8 (13.3)	0.0137	12.3	-2.80, -0.03
	Median (IQR)	0.0 (0.0)	0.0 (0.0)			
Total OCS cost (£)	Mean (SD)	10.8 (53.6)	4.2 (17.4)	<0.0001	16.4	1.83, 11.27
	Median (IQR)	1.3 (7.1)	0.0 (2.3)			

P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference; RCC = Relative coefficient change

Table 39: Respiratory outcomes comparing BDP/FOR to BUD/FOR DPI – adjusted means

		BDP/FOR N=540	BUD/FOR DPI N=540	p-value
Total cost (£)	N (% non-missing)	536 (99.26)	529 (97.96)	0.054
	Adjusted* mean	732.36	757.16	
Total resource cost (£)	N (% non-missing)	538 (99.63)	534 (98.89)	0.001
	Adjusted* mean	160.54	101.33	
Total medication cost (£)	N (% non-missing)	536 (99.26)	529 (97.96)	<0.001
	Adjusted* mean	574.23	652.45	
Total A&E cost (£)	N (% non-missing)	538 (99.63)	534 (98.89)	0.083
	Adjusted* mean	3.20	0.95	
Total inpatient cost (£)	N (% non-missing)	538 (99.63)	534 (98.89)	0.075
	Adjusted* mean	27.28	10.81	
Total outpatient cost (£)	N (% non-missing)	538 (99.63)	534 (98.89)	0.008
	Adjusted* mean	47.77	24.07	
Total primary care consultation cost (£)	N (% non-missing)	538 (99.63)	534 (98.89)	0.009
	Adjusted* mean	82.30	65.50	
Total antibiotic cost (£)	N (% non-missing)	538 (99.63)	532 (98.52)	0.546
	Adjusted* mean	4.24	3.96	
Total SABA cost (£)	N (% non-missing)	538 (99.63)	534 (98.89)	<0.001
	Adjusted* mean	19.57	28.57	
Total ICS cost (£)	N (% non-missing)	538 (99.63)	534 (98.89)	<0.001
	Adjusted* mean	323.87	407.90	
Total LABA cost (£)	N (% non-missing)	538 (99.63)	534 (98.89)	0.953
	Adjusted* mean	6.15	5.66	
Total SAMA cost (£)	N (% non-missing)	538 (99.63)	534 (98.89)	0.051
	Adjusted* mean	0.55	0.83	
Total LAMA cost (£)	N (% non-missing)	538 (99.63)	534 (98.89)	0.585
	Adjusted* mean	197.15	189.23	
Total LTRA cost (£)	N (% non-missing)	538 (99.63)	534 (98.89)	0.811
	Adjusted* mean	9.56	9.45	
Total THEO cost (£)	N (% non-missing)	538 (99.63)	534 (98.89)	0.019
	Adjusted* mean	2.24	3.81	
Total OCS cost (£)	N (% non-missing)	536 (99.26)	534 (98.33)	0.014
	Adjusted* mean	10.71	4.32	

* Adjusted for COPD related GP consultations and baseline medication & resources costs

The resampled data covered all four quadrants. An ICER estimate is not presented because the interpretation of the ICER is different in each quadrant. BDP/FOR was dominated by BUD/FOR in 10.9% of replicates, and dominated BUD/FOR in 49.9% of the replicates.

Table 40: Distribution of cost effectiveness BDP/FOR vs BUD/FOR

Sector	Number	Percentage
North East (more costly, more effective)	117	11.7%
South East (less costly, more effective)	499	49.9%
North West (more costly, less effective)	109	10.9%
South West (less costly, less effective)	251	25.1%

At a willingness-to-pay threshold of £0 for one avoided exacerbation, the probability of BDP/FOR being cost-effective was 49.9%. BDP/FOR will be cost-effective (i.e. p=0.90) compared to BUD/FOR if a threshold ICER of £27 500 per patient exacerbation free was adopted. For a threshold of 0.95, an ICER of £60 000 would be required.

Figure 10: Joint distribution of cost and effectiveness differences of BDP/FOR vs BUD/FOR

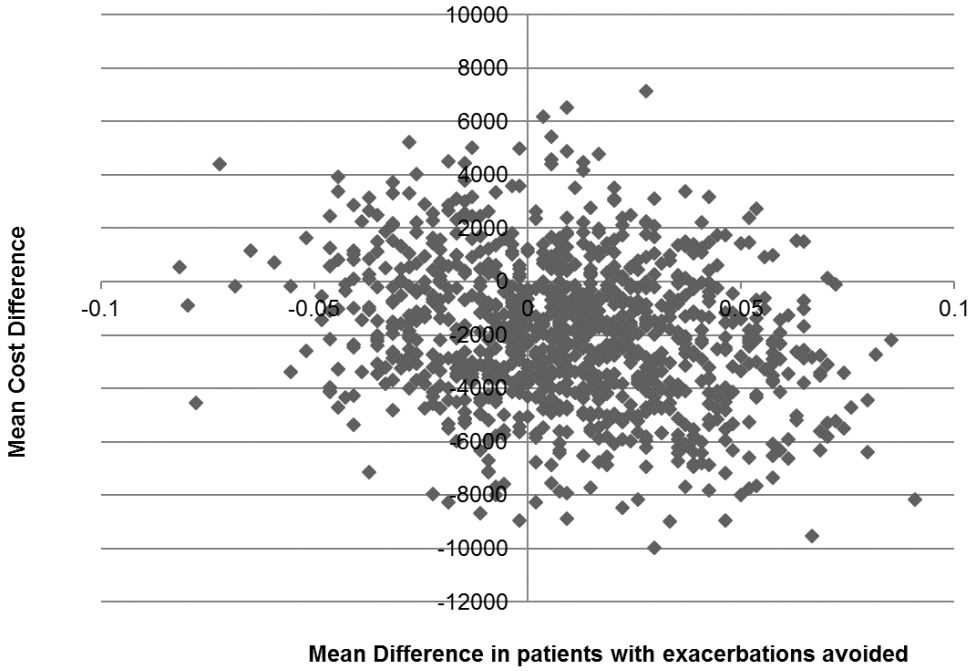
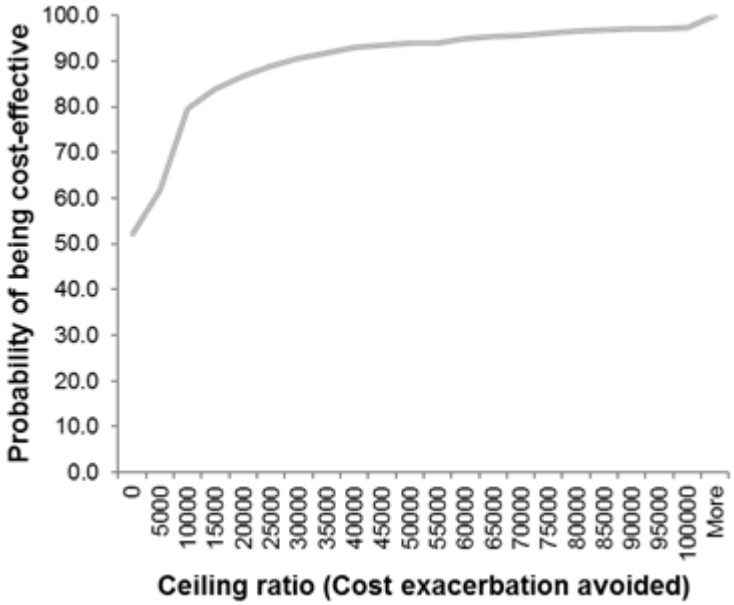


Figure 11: Cost effectiveness curve for BDP/FOR



13.0 Conclusion

The aim of the study was to compare whether the prescription of BDP/FOR was non-inferior to other licensed inhaled FDC ICS/LABA therapies in a population of patients that fit the indication for BDP/FOR. Patients prescribed BDP/FOR as their first licensed FDC ICS/LABA therapy, had non-inferior COPD control in terms of a lower proportion of patients with exacerbations compared to patients prescribed FP/SAL. Patients prescribed BDP/FOR, had non-inferior COPD control in terms of a lower proportion of patients with exacerbations compared to patients prescribed BUD/FOR. In this analysis, there appeared to be a trend towards BDP/FOR being statistically more effective than BUD/FOR.

In the secondary outcome analysis, patients prescribed BDP/FOR had lower rates of antibiotic prescription for lower respiratory tract infections. BDP/FOR was less costly and as effective compared to FP/SAL, whereas BDP/FOR was similar in terms of cost and effectiveness as BUD/FOR. BDP/FOR will be cost-effective (i.e. p=0.90) compared to FP/SAL if a threshold ICER of £10,500 per patient with exacerbation avoided was adopted. If the threshold is 0.95 BDP/FOR will be cost-effective compared to FP/SAL if a threshold ICER of £24,000 per patient exacerbation free was adopted. At a willingness-to-pay threshold of £0 for one patient exacerbation free, the probability of BDP/FOR being cost-effective was 70.9% compared to FP/SAL. BDP/FOR will be cost effective (p=0.90) compared to BUD/FOR if a threshold ICER of £27 500 per patient with exacerbations avoided was adopted. For a threshold of 0.95, an ICER of £60 000 would be required. At £0 per patient with an exacerbation avoided, there is a 49.9% of being cost effective compared to BUD/FOR. In the sub-analysis, where patients who had a diagnostic code for asthma were excluded, BDP/FOR was found to be more effective in terms of fewer patients with exacerbations compared to FP/SAL, coupled with a lower exacerbation rate. The numbers of antibiotic prescriptions are lower for BDP/FOR vs FP/SAL and BUD/FOR. Additionally, the odds of treatment stability are significantly higher for patients initiating BDP/FOR vs FP/SAL and BUD/FOR. The mean SAMA daily dosage is also significantly lower for patients initiating BDP/FOR vs FP/SAL and BUD/FOR.

ICS in combination with a LABA has been recommended by the GOLD 2017 guidelines for patients with a history of COPD exacerbations who have further exacerbations after treatment.[5] There is evidence in this study that initiation of BDP/FOR compared to FP/SAL and BUD/FOR is beneficial for patients without asthma diagnostic codes in terms of better

COPD control, However, further study is needed since there were insufficient patients without asthma codes to power for a non-inferiority/superiority study into COPD control.

14.0 Limitations

Cost data are likely to be an overestimate and can only be compared as a relative cost, not a real cost, due to the assumptions made herein. Other limitations include the absence of recorded intermediate care, such as COPD outreach nurses, district nurses, community matrons and NHS111 calls. Medicines prescribed in hospital out-of-hours services will have incomplete capture. Patients who are prescribed a FDC ICS/LABA will be prescribed a different number of inhalers and thus one FDC ICS/LABA may demonstrate a different adherence rate to their medication to another. The steering committee also suggested that in future studies, patients should be stratified by their adherence to their FDC ICS/LABA.

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18.0 APPENDIX

18.1 Appendix 1: Definitions

18.1.1 Demographics

Age group	At index date
Sex	
Smoking status	Read code closest to and within 5 years prior to index date, grouped as; *never smoker, ex-smoker, current smoke*r
Body Mass Index (BMI)	Calculated in adults (≥18 years) only from height and weight data, if available, and taken from practice-recorded BMI if not, within 10 years of the index date. Defined as the ratio of weight (kg) to squared height (m^2), and categorised as *underweight* (< 18.5 kg/m^2), *normal weight* (≥ 18.5 kg/m^2 and < 25 kg/m^2), *overweight* (≥ 25 kg/m^2 and < 30 kg/m^2) and *obese* (≥ 30 kg/m^2)
Duration of COPD diagnosis	Identified by COPD Read codes, calculated from the first recorded date of COPD diagnosis to the index date. This is exploratory only as patients may have their COPD diagnosis registered when they have their health records recorded at a new practice as opposed to when the disease was first diagnosed

18.1.2 Comorbidities

Allergic/non-allergic rhinitis	*Read coded never, active* or ever at or prior to index date*
Asthma	*Read coded ever at or prior to index date*
Bronchiectasis	*Read code diagnosis ever prior to the index date*
Eczema diagnosis	*never, active, or ever*
Gastro-oesophageal reflux disease (GERD)	*GERD, Read code diagnosis or GERD drugs [proton-pump inhibitors, antacids, H_2 blockers] in year prior to index date*
Diabetes Mellitus type II	*Read code diagnosis and/or antidiabetic drugs ever prior to the index date*
Osteoporosis	*Read code diagnosis or osteoporosis drugs [bisphosphonates, denosumab, strontium ranelate or teriparatide] ever prior to the index date*
Heart failure	*Read code diagnosis ever prior to the index date*
Hypertension	*Read code diagnosis ever prior to the index date*
Ischaemic heart disease	*Read code diagnosis ever prior to the index date*
Anxiety / Depression	*Read coded never, active† or ever at or prior to index date*
Chronic kidney disease	*Read code diagnosis of patients with CKD either in stages 3-5 or with evidence of proteinuria ever prior to the index date*

Lung cancer	*Read code diagnosis ever prior to the index date*
Charlson Comorbidity Index	*based on Read code diagnoses in year prior to index date*

18.1.3 Clinical characteristics

FEV_1	*FEV_1 lowest ever.*
FEV_1/FVC	
FEV_1 % predicted	*FEV_1 % predicted, lowest ever*
FEV_1 % predicted (categorised)	*FEV_1% predicted, lowest ever grouped as <20%, 20-≤30%, 30%-≤40%, 40%-<55%*
mMRC dyspnoea score	*last recorded score before index date*
Global Initiative for Chronic Obstructive Lung Disease (GOLD) group 2016	*calculated using FEV_1, exacerbation and mMRC data recorded closest to index date*
Number of oral corticosteroid prescriptions used to treat lower respiratory infections	*Prior to index date*
Number of antibiotic prescriptions for lower respiratory tract infections	*Prior to index date*
ICS dose prescribed	*Prior to index date*
Standalone inhaled corticosteroids (ICS) prescription	*Numbers of standalone ICS prescription*
ICS prescriptions (categorised)	*Number of ICS prescriptions categorised into 0, 1, 2-4, 5-10, 11+*
Standalone inhaled corticosteroids (ICS) inhalers	*Number of standalone ICS inhalers*
ICS inhalers (categorised)	*Number of ICS inhalers categorised into 0, 1, 2-4, 5-10, 11+*
Combination inhaled corticosteroid (ICS/LABA) prescription	*Numbers of ICS/LABA prescription*
ICS/LABA prescriptions (categorised)	*Number of ICS/LABA prescriptions categorised into 0, 1, 2-4, 5-10, 11+*
Combination inhaled corticosteroid (ICS/LABA) inhalers	*Number of ICS/LABA inhalers*
ICS/LABA inhalers (categorised)	*Number of ICS/LABA inhalers categorised into 0, 1, 2-4, 5-10, 11+*
Standalone LAMA prescription	*Presence of any standalone LAMA prescription*
LTRA prescriptions	*Presence of any LTRA prescription*
Theophylline prescriptions	*Presence of any theophylline prescription*
SABA inhalers	*Number of SABA inhalers listed on prescriptions*
SABA inhalers (categorised)	*Number of SABA inhalers categorised into 0, 1, 2-4, 5-10, 11+*
SABA prescriptions	*Number of prescriptions containing SABA inhalers*
SABA prescriptions (categorised)	*Number of prescriptions containing SABA inhalers categorised into 0, 1, 2-4, 5-10, 11+*
SABA daily dose	*Number of inhalers (typically 200 doses of 100) over study period/365 shown as unit doses and µg*
SABA daily dose (categorised)	*Mean daily dose categorised into 0, >0-<200µg, 200-<400µg, 400-<600µg, >600µg*
SAMA daily dose	*Number of inhalers over study period/365 shown as unit doses and µg*
ICS daily dose (FP equivalent)	*Total number of ICS containing inhalers, multiplied by number of ICS doses in the study year, divided by 365*
ICS daily dose (categorised – FP equivalent)	*Mean daily ICS dose grouped into <250µg, 250-499µg, 500+µg*
COPD exacerbations	*Count of acute respiratory events defined as:*

	Acute prescription of oral corticosteroids OR *Antibiotic prescription associated with a primary care consultation lower respiratory infection OR* *Lower respiratory related Accident and Emergency admission OR* *Unplanned lower respiratory related inpatient admission*
COPD exacerbations (categorised)	*Acute respiratory events categorised into 0, 1, 2, 3, 4+*
ICS adherence	*Medication Possession Ratio (MPR), calculated by dividing the total of one day's supply by the total number of days evaluated, multiplied by 100%. The evaluation period for every person is 365 days in the study year.*
Respiratory-related primary care consultations	*Number in study period*
Respiratory related accident and emergency admission	*Number in study period*
Respiratory related inpatient attendance	*Number in study period*

18.1.4 Body Mass Index (BMI)

The BMI is a representative measure of body weight based on the weight and height of the subject. It is defined as the weight (in kg) divided by the square of the height (in m) and is measured in kg/m^2. BMI will be categorised as follows: underweight (< 18.5), normal BMI (18.5 - 24.99), overweight (25-29.99), obese (≥30).

18.1.5 COPD exacerbation (moderate & severe)

Where an exacerbation is defined as an occurrence* of:

1. COPD-related†: Unscheduled hospital admission / A&E attendance; OR
2. An acute‡ course of oral steroids; OR
3. Antibiotics prescribed with lower respiratory consultation§.

*Where ≥1 oral steroid course / hospitalisation / antibiotics prescription occur within 2 weeks of each other, these events will be considered to be the result of the same exacerbation (and will only be counted once).

†**COPD-related Hospitalisations:** consist of either a definite COPD Emergency Attendance or a definite COPD Hospital Admission; OR a generic hospitalisation read code which has been recorded on the same day as a **Lower Respiratory Consultation**§§§§§ (see below; (a) – (c) only and excluding where the only lower respiratory code recorded on that day was for a lung function test).

‡ Acute oral steroid use associated with COPD exacerbation treatment will be defined as:

- all courses that are definitely not maintenance therapy, and/or
- all courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed), and/or
- all courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions.

where "maintenance therapy" is defined as: daily dosing instructions of <=10mg Prednisolone or prescriptions for 1mg or 2.5mg Prednisolone tablets where daily dosing instructions are not available.

§ **Lower Respiratory Consultations -** consist of the following:

18.1.6 Comorbidities – Charlson Comorbidity Index (CCI)

The CCI was developed in the US in 1987 as a method of classifying prognostic comorbidity in longitudinal studies.[20] It predicts the one-year mortality for a patient who may have a range of comorbid conditions such as heart disease, AIDS or cancer. Each condition is assigned a "weight" depending on the risk of dying associated with the condition; scores are then summed to give a total score predicting mortality.

The weights were revised and updated (for example, mortality due to HIV has fallen) by Dr Foster Intelligence (DFI) in their HSMR Methodology documentation[21] and calibrated using UK data (due to differences in coding practice and hospital patient population characteristics from the US), using ICD-10 codes. As a result:

- DFI have expanded the coding definition of some conditions;
- Only secondary diagnoses (DIAG02-DIAG14) are now considered;
- There is greater variation in weights between conditions and the Charlson Index (the sum of the weights) can be treated as a continuous variable (limited to the range 0-50) for the purposes of risk adjustment.

The weights, codes and conditions used in this study are summarised in the table below.

Table 41: Co-morbid conditions and scores used in the Charlson Co-morbidity Index (CCI)

Condition	Condition name	ICD-10 codes	Weight
1	Acute myocardial infarction	I21, I22, I23, I252, I258	5
2	Cerebral vascular accident	G450, G451, G452, G454, G458, G459, G46, I60-I69	11
3	Congestive heart failure	I50	13
4	Connective tissue disorder	M05, M060, M063, M069, M32, M332, M34, M353	4
5	Dementia	F00, F01, F02, F03, F051	14
6	Diabetes	E101, E105, E106, E108, E109, E111, E115, E116, E118, E119, E131, E131, E136, E138, E139, E141, E145, E146, E148, E149	3
7	Liver disease	K702, K703, K717, K73, K74	8
8	Peptic ulcer	K25, K26, K27, K28	9
9	Peripheral vascular disease	I71, I739, I790, R02, Z958, Z959	6
10	Pulmonary disease	J40-J47, J60-J67	4

a) Lower Respiratory read codes (including Asthma, COPD and LRTI read codes);
b) Asthma/COPD review codes excl. any monitoring letter codes;
c) Lung function and/or asthma monitoring
d) Any additional respiratory examinations, referrals, chest x-rays, or events.

11	Cancer	C00-C76, C80-C97	8
12	Diabetes complications	E102, E103, E104, E107, E112, E113, E114, E117, E132, E133, E134, E137, E142, E143, E144, E147	-1
13	Paraplegia	G041, G81, G820, G821, G822	1
14	Renal disease	I12, I13, N01, N03, N052-N056, N072-N074, N18, N19, N25	10
15	Metastatic cancer	C77, C78, C79	14
16	Severe liver disease	K721, K729, K766, K767	18
17	HIV	B20, B21, B22, B23, B24	2

18.1.7 Treatment stability

Stable: absence of the following:

1. Exacerbations (as defined above); AND
2. Additional or change in therapy*:
    a. Increase in dose of inhaled steroid AND/OR
    b. Change in delivery device AND/OR
    c. Change in ICS AND/OR
    d. Use of additional therapy as defined by LABAs, Theophylline, Long-acting leukotriene receptor antagonists (LTRAs), Long-Acting Muscarinic Antagonists (LAMAs).

Unstable: all others.

18.1.8 Respiratory-related hospitalisations

A lower respiratory-related hospitalisation can be considered as:

- **Definite:** Hospitalisations coded with a lower respiratory code, including COPD and LRTI codes; OR a generic hospitalisation Read code which has been recorded on the same day as a **Lower Respiratory Consultation;**
- **Definite + Probable:** Hospitalisations occuring within a 7-day window (either side of the hospitalisation date) of a lower respiratory Read code.

18.1.9 Confirmed and suspected pneumonia

Cases of pneumonia, both:

1. **Unconfirmed** (i.e. all unique patients with codes for pneumonia); AND
2. **Confirmed** via:

* Additional therapy or change in therapy will be selected as appropriate for each study.

a. Chest X-ray within a month of a pneumonia diagnosis; OR

b. Hospitalisation within a month of a pneumonia diagnosis.

Table 42: Formulae for Standardised Mean Difference

Covariate type	Formula
Continuous	$SMD = \frac{(\bar{x}_t - \bar{x}_r)}{\sqrt{\frac{s_t^2 + s_r^2}{2}}}$, where $\bar{x}_t$, $\bar{x}_r$ denote the sample means and s_t, s_r the standard deviations
Binary	$SMD = \frac{(\hat{p}_t - \hat{p}_r)}{\sqrt{\frac{\hat{p}_t(1-\hat{p}_t)+\hat{p}_r(1-\hat{p}_r)}{2}}}$, where $\hat{p}_t$, $\hat{p}_r$ denote the proportion of patients in each category
Categorical (>2 categories)	$SMD = \sqrt{(T-C)'S^{-1}(T-C)}$ where S is a $(k-1)\times(k-1)$ covariance matrix: $S = [S_{kl}] = \begin{cases} \frac{\hat{p}_{1k}(1-\hat{p}_{1k}) + \hat{p}_{2k}(1-\hat{p}_{2k})}{2}, & k = l \\ \frac{\hat{p}_{1k}\hat{p}_{1l} + \hat{p}_{2k}\hat{p}_{2l}}{2}, & k \neq l \end{cases}$, $T = (\hat{p}_{12}, \dots, \hat{p}_{1k})'$, $C = (\hat{p}_{22}, \dots, \hat{p}_{2k})'$ and $\hat{p}_{jk} = P(category\ k | treatment\ arm\ j)$, $l = 1,2$, $k = 2,3, \dots, k$

Table 43: Formulae for Relative Change in Co-efficient

Outcome type	Regression type	Formula
Continuous	Linear	$RCC = abs\left\{\frac{(\beta_{crude} - \beta_{adjusted})}{\beta_{crude}}\right\}$
Binary	Logistic	$RCC = abs(1 - e^{(\beta_{crude} - \beta_{adjusted})})$
Time-to-event	Cox-Proportional Hazard	
Count	Poisson	
Where β_{crude} is the co-efficient of exposure in the crude model and $\beta_{adjusted}$ is the co-efficient of exposure after adding the covariate in the model.		

18.2 Appendix 2: Unmatched baseline tables – COPD only (sub-analysis)

Table 44: Unmatched baseline characteristics – BDP/FOR versus FP/SAL DPI (COPD only)

		BDP/FOR N=322	FP/SAL DPI N=2,080	P	SDD	RCC
Gender	Male	189 (58.7)	1,255 (60.3)	0.5758	3.3	0.5
Age (years)	Mean (SD)	69.6 (10.0)	69.0 (9.0)	0.1775	6.1	0.5
	Median (IQR)	70.0 (14.0)	69.0 (13.0)			
	≥35 <45	3 (0.9)	7 (0.3)	0.2623	10.7	0.8
	≥45 <55	22 (6.8)	122 (5.9)			
	≥55 <65	67 (20.8)	496 (23.8)			
	≥65	230 (71.4)	1,455 (70.0)			
BMI (kg/m^2)	N (% non-missing)	322 (100.0)	2,074 (99.7)	0.7023	7.1	0.3
	<18.5	22 (6.8)	128 (6.2)			
	≥18.5-<25	116 (36.0)	812 (39.2)			
	≥25-<30	110 (34.2)	658 (31.7)			
	≥30	74 (23.0)	476 (23.0)			

		BDP/FOR N=322	FP/SAL DPI N=2,080	P	SDD	RCC
Smoking status closest to index date	N (% non-missing)	322(100.0)	2080(100.0)	0.0363	16.0	1.1
	Non-smoker	6 (1.9)	74 (3.6)			
	Current smoker	162 (50.3)	906 (43.6)			
	Ex-smoker	154 (47.8)	1,100 (52.9)			
Time since COPD diagnosis (years)	N (% non-missing)	291 (90.4)	1,983 (95.3)	0.3252	14.1	1.6
	<2	65 (22.3)	413 (20.8)			
	2 to <4	54 (18.6)	395 (19.9)			
	4 to <6	51 (17.5)	314 (15.8)			
	6 to <8	29 (10.0)	280 (14.1)			
	8+	92 (31.6)	581 (29.3)			
SABA inhaler prescriptions	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.0495	18.1	0.9
	0	77 (23.9)	369 (17.7)			
	1	26 (8.1)	157 (7.5)			
	2-4	55 (17.1)	410 (19.7)			
	5-10	85 (26.4)	659 (31.7)			
	≥11	79 (24.5)	485 (23.3)			
SABA inhalers	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.0772	16.9	1.9
	0	77 (23.9)	369 (17.7)			
	1	21 (6.5)	117 (5.6)			
	2-4	55 (17.1)	363 (17.5)			
	5-10	77 (23.9)	581 (27.9)			
	≥11	92 (28.6)	650 (31.3)			
Average daily dose of SABA	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.0282	17.7	1.8
	0	77 (23.9)	369 (17.7)			
	>0 to <200	59 (18.3)	411 (19.8)			
	200 to <400	72 (22.4)	432 (20.8)			
	≥400	114 (35.4)	868 (41.7)			
SAMA prescriptions	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.3009	6.3	0.2
	≥1	44 (13.7)	331 (15.9)			
SAMA µg/day	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.0282	19.2	1.7
	0	268 (83.2)	1,576 (75.8)			
	>0 to <40	46 (14.3)	424 (20.4)			
	40 to <80	2 (0.6)	30 (1.4)			
	≥80	6 (1.9)	50 (2.4)			
SAMA/SABA combination prescriptions	N (% non-missing)	322 (100.0)	2,080 (100.0)	<0.0001	33.8	2.0
	≥1	3 (0.9)	160 (7.7)			
FDC ICS prescriptions	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.1450	15.9	0.2
	0	129 (40.1)	752 (36.2)			
	1	22 (6.8)	113 (5.4)			
	2-4	36 (11.2)	268 (12.9)			
	5-10	73 (22.7)	591 (28.4)			
	≥11	62 (19.3)	356 (17.1)			
FDC ICS inhalers	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.4357	11.5	0.9
	0	129 (40.1)	752 (36.2)			
	1	19 (5.9)	94 (4.5)			
	2-4	31 (9.6)	216 (10.4)			
	5-10	72 (22.4)	531 (25.5)			
	≥11	71 (22.0)	487 (23.4)			
ICS monotherapy average prescription	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.3554	13.5	0.8
	0	262 (81.4)	1,655 (79.6)			
	1	9 (2.8)	107 (5.1)			
	2-4	20 (6.2)	132 (6.3)			
	5-10	25 (7.8)	135 (6.5)			
	≥11	6 (1.9)	51 (2.5)			
ICS monotherapy inhalers	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.2401	15.1	1.2
	0	262 (81.4)	1,655 (79.6)			
	1	8 (2.5)	100 (4.8)			
	2-4	18 (5.6)	115 (5.5)			
	5-10	27 (8.4)	142 (6.8)			

		BDP/FOR N=322	FP/SAL DPI N=2,080	P	SDD	RCC
	≥11	7 (2.2)	68 (3.3)			
Total ICS dosage	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.0905	13.5	0.9
	0	164 (50.9)	968 (46.5)			
	1	83 (25.8)	505 (24.3)			
	2	75 (23.3)	607 (29.2)			
LAMA prescriptions	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.1306	9.2	1.2
	≥1	223 (69.3)	1,351 (65.0)			
LABA prescriptions	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.1784	8.3	0.1
	≥1	37 (11.5)	297 (14.3)			
LABA/LAMA combination prescriptions	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.0067	9.9	0.9
	≥1	2 (0.6)	1 (0.0)			
Theophylline prescriptions	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.0055	18.4	2.0
	≥1	16 (5.0)	203 (9.8)			
Leukotriene prescriptions	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.4011	4.7	0.4
	≥1	7 (2.2)	32 (1.5)			
Maintenance OCS	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.0661	10.2	0.0
	Yes	21 (6.5)	88 (4.2)			
Rhinitis diagnosis	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.5682	3.5	0.0
	Yes	27 (8.4)	195 (9.4)			
Active rhinitis diagnosis	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.8944	0.8	0.0
	Yes	16 (5.0)	107 (5.1)			
Bronchiectasis diagnosis	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.1543	8.0	0.2
	Yes	18 (5.6)	81 (3.9)			
Pneumonia diagnosis	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.4878	4.0	0.1
	Yes	10 (3.1)	51 (2.5)			
Lung cancer diagnosis	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.0810	9.1	0.6
	Yes	8 (2.5)	26 (1.3)			
Eczema diagnosis	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.1008	9.6	0.4
	Yes	80 (24.8)	433 (20.8)			
Eczema diagnosis with prescriptions	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.5511	3.5	0.0
	Yes	29 (9.0)	167 (8.0)			
GERD diagnosis or drugs	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.2034	7.1	0.2
	Yes	12 (3.7)	52 (2.5)			
Diabetes diagnosis	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.1474	8.4	0.1
	Yes	53 (16.5)	280 (13.5)			
Ischaemic heart disease diagnosis	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.1614	8.2	0.2
	Yes	72 (22.4)	396 (19.0)			
Heart failure diagnosis	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.9008	0.7	0.0
	Yes	7 (2.2)	43 (2.1)			
Hypertension diagnosis	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.8860	0.9	0.0
	Yes	130 (40.4)	831 (40.0)			
Chronic kidney disease Read code diagnosis	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.1566	8.2	0.4
	Yes	46 (14.3)	240 (11.5)			
Osteoporosis diagnosis	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.2121	7.1	0.3
	Yes	25 (7.8)	124 (6.0)			
Anxiety and/or depression diagnosis	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.0592	11.1	2.1
	Yes	115 (35.7)	634 (30.5)			
Active anxiety and/or depression diagnosis	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.0129	14.4	2.3
	Yes	83 (25.8)	411 (19.8)			
Charlson Comorbidity Index	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.4505	7.7	0.7
	0-2	247 (76.7)	1,527 (73.4)			
	3-4	45 (14.0)	326 (15.7)			
	5+	30 (9.3)	227 (10.9)			
COPD related GP consultations	N (% non-missing)	322 (100.0)	2,080 (100.0)	<0.0001	30.8	1.3
	0	125 (38.8)	568 (27.3)			
	1	71 (22.0)	497 (23.9)			
	2-4	73 (22.7)	633 (30.4)			
	5-10	35 (10.9)	317 (15.2)			
	≥11	18 (5.6)	65 (3.1)			

		BDP/FOR N=322	FP/SAL DPI N=2,080	P	SDD	RCC
Outpatient visits for COPD	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.0035	17.1	0.1
	0	282 (87.6)	1,897 (91.2)			
	1	21 (6.5)	131 (6.3)			
	≥2	19 (5.9)	52 (2.5)			
A & E attendances for COPD	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.2711	8.7	0.4
	0	312 (96.9)	2,043 (98.2)			
	1	9 (2.8)	34 (1.6)			
	≥2	1 (0.3)	3 (0.1)			
Inpatient admissions within 7 days of respiratory consultation	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.6213	5.3	0.8
	0	301 (93.5)	1,954 (93.9)			
	1	16 (5.0)	106 (5.1)			
	≥2	5 (1.6)	20 (1.0)			
Moderate/severe exacerbations	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.2858	13.5	7.8
	0	30 (9.3)	179 (8.6)			
	1	96 (29.8)	745 (35.8)			
	2	83 (25.8)	505 (24.3)			
	3	49 (15.2)	261 (12.5)			
	4+	64 (19.9)	390 (18.8)			
FEV_1 value (litres)	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.3932	10.1	1.0
	≤1	126 (39.1)	895 (43.0)			
	>1 to ≤2	170 (52.8)	1,059 (50.9)			
	2 to ≤4	20 (6.2)	96 (4.6)			
	>4	6 (1.9)	30 (1.4)			
FEV_1/FVC ratio	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.6920	7.3	0.6
	0.2 or less	2 (0.6)	17 (0.8)			
	0.2 to <0.4	60 (18.6)	438 (21.1)			
	0.4 to <0.6	151 (46.9)	972 (46.7)			
	0.6+	109 (33.9)	653 (31.4)			
Lowest percent predicted FEV_1	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.4201	10.5	1.2
	<20%	16 (5.0)	146 (7.0)			
	20% to <30%	66 (20.5)	466 (22.4)			
	30% to <40%	101 (31.4)	623 (30.0)			
	40% to <55%	139 (43.2)	845 (40.6)			
Gold severity (2016)	N (% non-missing)	322 (100.0)	2,080 (100.0)	0.1224	13.6	1.1
	Mild	10 (3.1)	35 (1.7)			
	Moderate	111 (34.5)	632 (30.4)			
	Severe	150 (46.6)	1,059 (50.9)			
	Very severe	51 (15.8)	354 (17.0)			
mMRC score	N (% non-missing)	190 (59.0)	1,282 (61.6)	0.0066	27.5	11.1
	mMRC 0	24 (12.6)	81 (6.3)			
	mMRC 1	63 (33.2)	471 (36.7)			
	mMRC 2	62 (32.6)	362 (28.2)			
	mMRC 3	32 (16.8)	301 (23.5)			
	mMRC 4	9 (4.7)	67 (5.2)			

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

Table 45: Unmatched baseline characteristics – BDP/FOR versus BUD/FOR DPI (COPD only)

		BDP/FOR N=322	BUD/FOR DPI N=1,768	P	SDD	RCC
Gender	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.8904	0.8	0.0
	Male	189 (58.7)	1,045 (59.1)			
Age (years)	N (% non-missing)	322 (100.0)	1,768 (100.0)			
		69.6 (10.0)	69.2 (9.1)	0.3443	4.3	0.1
		70.0 (14.0)	69.0 (13.0)			
	≥35 <45	3 (0.9)	10 (0.6)	0.4390	9.7	0.0
	≥45 <55	22 (6.8)	93 (5.3)			
	≥55 <65	67 (20.8)	416 (23.5)			
	≥65	230 (71.4)	1,249 (70.6)			

		BDP/FOR N=322	BUD/FOR DPI N=1,768	P	SDD	RCC
BMI (kg/m^2)	N (% non-missing)	322 (100.0)	1,765 (99.8)	0.7625	6.5	0.3
	<18.5	22 (6.8)	106 (6.0)			
	≥18.5-<25	116 (36.0)	667 (37.8)			
	≥25-<30	110 (34.2)	563 (31.9)			
	≥30	74 (23.0)	429 (24.3)			
Smoking status closest to index date	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0125	18.0	0.7
	Non-smoker	6 (1.9)	51 (2.9)			
	Current smoker	162 (50.3)	736 (41.6)			
	Ex-smoker	154 (47.8)	981 (55.5)			
Time since COPD diagnosis (years)	N (% non-missing)	291 (90.4)	1,660 (93.9)	0.2066	15.3	8.7
	<2	65 (22.3)	429 (25.8)			
	2 to <4	54 (18.6)	332 (20.0)			
	4 to <6	51 (17.5)	276 (16.6)			
	6 to <8	29 (10.0)	199 (12.0)			
	8+	92 (31.6)	424 (25.5)			
SABA inhaler prescriptions	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.3488	12.6	1.2
	0	77 (23.9)	340 (19.2)			
	1	26 (8.1)	151 (8.5)			
	2-4	55 (17.1)	312 (17.6)			
	5-10	85 (26.4)	534 (30.2)			
	≥11	79 (24.5)	431 (24.4)			
SABA inhalers	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.2958	13.2	1.9
	0	77 (23.9)	340 (19.2)			
	1	21 (6.5)	129 (7.3)			
	2-4	55 (17.1)	281 (15.9)			
	5-10	77 (23.9)	484 (27.4)			
	≥11	92 (28.6)	534 (30.2)			
Average daily dose of SABA	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.2512	12.0	0.8
	0	77 (23.9)	340 (19.2)			
	>0 to <200	59 (18.3)	357 (20.2)			
	200 to <400	72 (22.4)	393 (22.2)			
	≥400	114 (35.4)	678 (38.3)			
SAMA prescriptions	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0223	14.5	0.5
	≥1	44 (13.7)	336 (19.0)			
SAMA µg/day	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0008	26.5	0.0
	0	268 (83.2)	1,282 (72.5)			
	>0 to <40	53 (16.5)	482 (27.3)			
	40 to <80	1 (0.3)	4 (0.2)			
	≥80	0 (0.0)	0 (0.0)			
SAMA/SABA combination prescriptions	N (% non-missing)	322 (100.0)	1,768 (100.0)	<0.0001	38.4	1.8
	≥1	3 (0.9)	163 (9.2)			
FDC ICS prescriptions	N (% non-missing)	322 (100.0)	1,768 (100.0)	<0.0001	30.8	5.0
	0	129 (40.1)	879 (49.7)			
	1	22 (6.8)	127 (7.2)			
	2-4	36 (11.2)	250 (14.1)			
	5-10	73 (22.7)	335 (18.9)			
	≥11	62 (19.3)	177 (10.0)			
FDC ICS inhalers	N (% non-missing)	322 (100.0)	1,768 (100.0)	<0.0001	30.3	5.3
	0	129 (40.1)	879 (49.7)			
	1	19 (5.9)	111 (6.3)			
	2-4	31 (9.6)	229 (13.0)			
	5-10	72 (22.4)	326 (18.4)			
	≥11	71 (22.0)	223 (12.6)			
ICS monotherapy prescriptions	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0012	27.4	1.8
	0	262 (81.4)	1,235 (69.9)			
	1	9 (2.8)	84 (4.8)			
	2-4	20 (6.2)	164 (9.3)			
	5-10	25 (7.8)	217 (12.3)			
	≥11	6 (1.9)	68 (3.8)			

		BDP/FOR N=322	BUD/FOR DPI N=1,768	P	SDD	RCC
ICS monotherapy inhalers	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0010	27.8	2.0
	0	262 (81.4)	1,235 (69.9)			
	1	8 (2.5)	74 (4.2)			
	2-4	18 (5.6)	151 (8.5)			
	5-10	27 (8.4)	222 (12.6)			
	≥11	7 (2.2)	86 (4.9)			
Total ICS dosage	N (% non-missing)	322 (100.0)	1,767 (99.9)	0.0006	22.8	4.1
	0	164 (50.9)	1,090 (61.7)			
	1	83 (25.8)	390 (22.1)			
	2	75 (23.3)	287 (16.2)			
LAMA prescriptions	N (% non-missing)	322 (100.0)	1,768 (100.0)	<0.0001	29.2	4.4
	≥1	223 (69.3)	977 (55.3)			
LABA prescriptions	N (% non-missing)	322 (100.0)	1,768 (100.0)	<0.0001	32.3	1.5
	≥1	37 (11.5)	418 (23.6)			
LABA/LAMA combination prescriptions	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0139	9.7	0.9
	≥1	2 (0.6)	1 (0.1)			
Theophylline prescriptions	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0782	11.4	1.5
	≥1	16 (5.0)	137 (7.7)			
Leukotriene prescriptions	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.3518	5.3	0.0
	≥1	7 (2.2)	26 (1.5)			
Maintenance OCS	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0287	12.1	0.7
	Yes	21 (6.5)	68 (3.8)			
Rhinitis diagnosis	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.2219	7.7	0.5
	Yes	27 (8.4)	188 (10.6)			
Active rhinitis diagnosis	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.6765	2.6	0.0
	Yes	16 (5.0)	98 (5.5)			
Bronchiectasis diagnosis	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0484	10.9	0.5
	Yes	18 (5.6)	59 (3.3)			
Pneumonia diagnosis	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.2921	6.0	0.5
	Yes	10 (3.1)	38 (2.1)			
Lung cancer diagnosis	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0521	10.2	0.1
	Yes	8 (2.5)	20 (1.1)			
Eczema diagnosis	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.2146	7.4	0.1
	Yes	80 (24.8)	384 (21.7)			
Eczema diagnosis with prescriptions	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.5102	3.9	0.2
	Yes	29 (9.0)	140 (7.9)			
GERD diagnosis or drugs	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0625	10.1	0.6
	Yes	12 (3.7)	36 (2.0)			
Diabetes diagnosis	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0041	16.4	1.2
	Yes	53 (16.5)	192 (10.9)			
Ischaemic heart disease diagnosis	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0504	11.5	0.6
	Yes	72 (22.4)	314 (17.8)			
Heart failure diagnosis	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.6940	2.4	0.0
	Yes	7 (2.2)	45 (2.5)			
Hypertension diagnosis	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.2490	6.9	0.7
	Yes	130 (40.4)	654 (37.0)			
Chronic kidney disease Read code diagnosis	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0125	14.2	1.3
	Yes	46 (14.3)	171 (9.7)			
Osteoporosis diagnosis	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.1305	8.7	0.3
	Yes	25 (7.8)	99 (5.6)			
Anxiety and/or depression diagnosis	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0447	12.0	0.5
	Yes	115 (35.7)	532 (30.1)			
Active anxiety and/or depression diagnosis	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0004	20.6	1.8
	Yes	83 (25.8)	307 (17.4)			
Charlson Comorbidity Index	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.7532	4.6	0.3
	0-2	247 (76.7)	1,328 (75.1)			
	3-4	45 (14.0)	276 (15.6)			
	5+	30 (9.3)	164 (9.3)			
	N (% non-missing)	322 (100.0)	1,768 (100.0)	<0.0001	33.7	1.7

		BDP/FOR N=322	BUD/FOR DPI N=1,768	P	SDD	RCC
COPD related GP consultations	0	125 (38.8)	480 (27.1)			
	1	71 (22.0)	398 (22.5)			
	2-4	73 (22.7)	592 (33.5)			
	5-10	35 (10.9)	249 (14.1)			
	≥11	18 (5.6)	49 (2.8)			
Outpatient visits for COPD	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0005	19.7	0.8
	0	282 (87.6)	1,621 (91.7)			
	1	21 (6.5)	110 (6.2)			
	≥2	19 (5.9)	37 (2.1)			
A & E attendances for COPD	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.2627	8.9	0.5
	0	312 (96.9)	1,737 (98.2)			
	1	9 (2.8)	27 (1.5)			
	≥2	1 (0.3)	4 (0.2)			
Inpatient admissions within 7 days of respiratory consultation	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.2257	9.4	1.3
	0	301 (93.5)	1,686 (95.4)			
	1	16 (5.0)	69 (3.9)			
	≥2	5 (1.6)	13 (0.7)			
Moderate/severe exacerbations	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.0327	19.9	13.4
	0	30 (9.3)	177 (10.0)			
	1	96 (29.8)	680 (38.5)			
	2	83 (25.8)	391 (22.1)			
	3	49 (15.2)	241 (13.6)			
	4+	64 (19.9)	279 (15.8)			
FEV_1 value (litres)	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.1999	11.9	1.4
	≤1	126 (39.1)	748 (42.3)			
	>1 to ≤2	170 (52.8)	921 (52.1)			
	2 to ≤4	20 (6.2)	84 (4.8)			
	>4	6 (1.9)	15 (0.8)			
FEV_1/FVC ratio	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.8476	5.5	0.4
	0.2 or less	2 (0.6)	12 (0.7)			
	0.2 to <0.4	60 (18.6)	359 (20.3)			
	0.4 to <0.6	151 (46.9)	837 (47.3)			
	0.6+	109 (33.9)	560 (31.7)			
Lowest percent predicted FEV_1	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.9318	4.0	0.5
	<20%	16 (5.0)	91 (5.1)			
	20% to <30%	66 (20.5)	362 (20.5)			
	30% to <40%	101 (31.4)	524 (29.6)			
	40% to <55%	139 (43.2)	791 (44.7)			
Gold severity (2016)	N (% non-missing)	322 (100.0)	1,768 (100.0)	0.6312	7.7	0.5
	Mild	10 (3.1)	40 (2.3)			
	Moderate	111 (34.5)	625 (35.4)			
	Severe	150 (46.6)	856 (48.4)			
	Very severe	51 (15.8)	247 (14.0)			
mMRC score	N (% non-missing)	190 (59.0)	939 (53.1)	0.1205	20.4	8.7
	mMRC 0	24 (12.6)	70 (7.5)			
	mMRC 1	63 (33.2)	372 (39.6)			
	mMRC 2	62 (32.6)	287 (30.6)			
	mMRC 3	32 (16.8)	171 (18.2)			
	mMRC 4	9 (4.7)	39 (4.2)			

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