Study protocol

REACH II: Stage 2

Examining real-life outcomes for UK patients with COPD initiating on 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 the initation of COPD treatment with Fostair® pMDI compared to other licensed FDC ICS/LABA therapies in terms of moderate/severe exacerbations and cost-effectiveness.		
Protocol version number	1.2		
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 initiation 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 initation 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 initiation 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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1.0 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 typical 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] Although ICS are extensively used in the treatment of COPD, monotherapy is not recommended.[5,6] Both NICE and 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 (FEV_1 <50% predicted normal)[7], with a high risk of exacerbations (GOLD groups C and D)[5]. Additional reliever medications include short-acting muscarinic antagonists (SABAs) and short-acting β-agonists (SAMAs), the use of which can be an indication of shortness of breath.

Several FDC inhalers are licensed in the treatment of COPD. Fostair® pMDI is a FDC ICS/LABA pressurised metered dose inhaler (pMDI), requiring slow and deep inhalation for administration. Fostair® pMDI contains 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® 500 Accuhaler®*[11] and Symbicort® Turbohaler® (200 or 400)†[12,13], both of which are dry powder inhalers (DPI) and non-extrafine formulations.

*500µg fluticasone proprionate (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.

Fostair® pMDI has previously been prescribed off-licence for the treatment of COPD in the UK (unpublished data from OPRI), and 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]

In addition to the alternative device type, Fostair® pMDI is also a less expensive FDC ICS/LABA, costing £0.98 per day, compared to £1.36 per day for Seretide® 500 Accuhaler®, and £1.27 per day for both Symbicort® 200 and 400 Turbohaler®.[*14]

Randomised controlled trials have demonstrated other clinical benefits of Fostair® pMDI. One particular trial found Fostair® 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] The FORWARD study[10,15] compared Fostair® pMDI to formoterol in a population of severe COPD patients with a history of exacerbations. Fostair® 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, Fostair® pMDI has only been evaluated in real-life clinical practice in patients with asthma. In a previous study carried out by OPRI (OPRI former RIRL) for Chiesi Ltd (the REACH study), Fostair® was demonstrated to be non-inferior to Seretide® in preventing acute respiratory events for patients with asthma at an equivalent or lower dose of 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 examine the clinical and cost effectiveness of Fostair® pMDI in licensed doses in a population of patients with COPD. Stage 1 of the REACH II study (completed in June 2015) reported the patient numbers and characteristics available in the OPCRD database, according to their therapy pathways. From this data, the availability of

[*] 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

patients for a non-inferiority study of Fostair® pMDI compared to Seretide® 500 Accuhaler® and Symbicort® 200/400 Turbohaler® (combined) in terms of the prevention of moderate to severe COPD exacerbations was confirmed, as a first licensed FDC ICS/LABA therapy for patients previously prescribed a LABA and/or LAMA (in any form), during a baseline period.

2.0 Study aims and objectives

2.1 Study aims

To determine whether initation 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 therapies for the treatment of COPD, in patients meeting the licensed indication for Fostair® pMDI*.

2.2 Study objectives

2.2.1 Primary objective

To establish whether iniation of COPD treatment with 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 to Seretide® 500 Accuhaler® and separately to Symbicort® 200/400 Turbohaler®.†

2.2.1.1 Sub-analysis

To explore patients diagnosed with COPD and no other respiratory-related diagnoses (ie exclude patients with a history of asthma), if numbers allow.

2.2.2 Secondary objectives

Compare initiation of COPD treatment with Fostair® pMDI to Seretide® 500 Accuhaler® and separately to Symbicort® 200/400 Turbohaler® for other respiratory outcomes, including time to first exacerbation, rate of exacerbations, treatment stability, lung function, and respiratory-related hospitalisations, among others.

* 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." This we can operationalise as any prior prescription with either LABA &/or LAMA (as part of a mono- or combination therapy) and FEV_1 recorded <55% predicted (as it is post-bronchodilator so could legitimately be <50% pre-bronchodilator)

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

Compare iniation of COPD treatment with Fostair® pMDI to Seretide® 500 Accuhaler® and separately Fostair® pMDI to Symbicort® 200/400 Turbohaler® in terms of cost-effectiveness.

3.0 Study design

3.1 Products studied

The investigational product is Fostair®, a FDC ICS/LABA containing 100µg beclometasone diproprionate and 6µg formoterol fumarate per inhalation in a pMDI device.[8]

Several reference products are used, the first of which is Seretide® 500 Accuhaler®, a FDC ICS/LABA containing 500µg fluticasone proprionate and 50µg salmeterol xinafoate per inhalation in a DPI device.[11]

Two doses of the Symbicort® Turbohaler® are also used as reference products. These are also FDC ICS/LABA products containing either 200µg budesonide and 6µg formoterol fumarate dihydrate (Symbicort® 200), or 400µg budesonide and 12µg formoterol fumarate dihydrate (Symbicort® 400) per inhalation in a DPI device.[12,13] These products will be analysed as a single group due to equivalent daily dose.

3.2 Study design

A retrospective matched cohort comparison of outcomes for patients meeting the licensed indication for Fostair® initiating COPD treatment as either Fostair® pMDI, Seretide® 500 Accuhaler® or Symbicort® 200/400 Turbohaler®, matched for baseline therapies.

The time of first prescription of Fostair® pMDI, Seretide® 500 Accuhaler® or Symbicort® 200/400 Turbohaler®, will be known as the “index date”.

Patients will have two years continuous practice data, comprising one year baseline period to identify demographic, co-morbid and clinical characteristics, ending at the index date, followed by one year outcome period in which to compare patients initiating COPD treatment on Fostair® pMDI, Seretide® 500 Accuhaler® or Symbicort® 200/400 Turbohaler®.

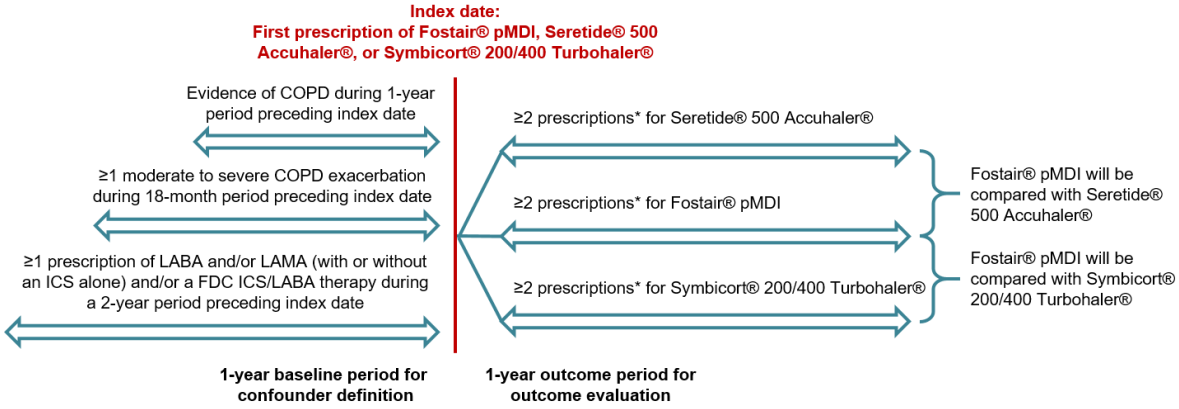

Figure 1: Study design

4.0 Study population

4.1 Inclusion and exclusion criteria

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 [Fostair® pMDI, Seretide® 500 Accuhaler®, Symbicort® 200 Turbohaler®, and Symbicort® 400 Turbohaler®]
≥1 prescription of LABA and/or LAMA (with or without an ICS alone) and/or a 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 OR ≥1 moderate to severe COPD exacerbation preceding index date ever
FEV_1 <55% predicted recorded ever
Exclusion criteria
Never-smokers

4.2 Data source

The study will use patient data from the Optimum Patient Care Research Database (OPCRD).[17] The study team work with anonymous data removed of any patient identifiable information. The OPCRD is developed, maintained, and owned by Optimum Patient Care (OPC), a social enterprise company that aims to improve patient outcomes through medical research and services. OPC provides evidence-based recommendations to UK general practices through bespoke software and practice reports.

The OPCRD currently comprises longitudinal medical records for 2.5 million patients from over 550 primary care practices across the UK. The OPCRD contains two types of data: (1) routinely recorded clinical data and (2) questionnaire responses from over 55,700 patients with respiratory conditions. The OPC questionnaires are a compilation of validated questions covering symptoms, disease control, triggers, side effects, quality of life, and unique adherence measures. Indeed the OPCRD is the only database in the UK that complements routinely recorded disease coding and prescribing information with patient-reported outcomes. The OPCRD also links with nationwide practice prescribing data to enable targeted delivery of dataset needs.

A unique dataset is provided for each study with only the variables necessary to inform the study objectives included. Only studies that evaluate risk-benefit profiles of treatment options will report adverse events of treatments, ensuring confidentiality of data at all stages. The study will be 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. All research using OPCRD will be registered on established study databases such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP, http://www.encepp.eu/).

5.0 Study variables and study outcomes

Refer to Appendices for detailed variable and outcome definitions, and mock tables of demographic and baseline variables and outcome results.

5.1 Demographic and baseline variables

- Gender (male/female)
- Age of patient (years, at index date)
- Body Mass Index (BMI, at time of index date, calculated from height and weight data if available, otherwise taken from practice-recorded BMI value, detailed definition in Appendix 1)
- Smoking status (identified by Read code, closest to index date)
- Duration of COPD diagnosis (identified by COPD Read codes, calculated from the first recorded date of COPD diagnosis to the index date)
- Average SABA daily dose*
- Average SAMA daily dose*
- Lung function (FEV_1 % predicted, closest to index date)
- FEV_1/FVC ratio (closest to index date)
- Modified Medical Research Council (mMRC) dyspnoea score (last recorded score before index date)†
- Exacerbation count‡ (in year prior to index date)
- GOLD group (calculated using FEV_1, exacerbation and mMRC data recorded closest to index date)

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* Calculated as average number of puffs per day over the year multiplied by strength (in mcg);
i.e. $\frac{Number\ of\ inhalers * doses\ per\ inhaler}{365} * strength$

† Respiratory disability categorised as:
1. Not troubled by breathlessness.
2. Short of breath when hurrying or walking up a slight hill.
3. Slower in walking than other of the same on the level because of breathlessness, or have to stop for breath when walking at your own pace.
4. Stopping for breath after about 100m or after a few minutes on the level.
5. Too breathless to leave the house, or breathless when dressing/undressing.

‡ 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.

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

- Number of oral corticosteroid prescriptions used to treat lower respiratory exacerbations*
- Number of antibiotic prescriptions for lower respiratory tract infections
- History of comorbidities related to COPD:
    - Asthma (Read code diagnosis ever prior to the index date, excluding resolved asthma)
    - Anxiety or depression (Read code diagnosis in the year prior to index date)
    - Gastroesophageal reflux disease (GERD, Read code diagnosis or GERD drugs [proton-pump inhibitors, antacids, H_2 blockers] in year prior to index date)
    - Pneumonia (Read code diagnosis in year prior to the index date)
    - Diabetes (Read code diagnosis and/or antidiabetic drugs ever prior to the index date)
    - Ischaemic heart disease (Read code diagnosis ever prior to the index date)
    - Heart failure (Read code diagnosis ever prior to the index date)
    - Hypertension (Read code diagnosis in the year prior to index date)
    - Bronchiectasis (Read code diagnosis ever prior to the index date)
    - Rhinitis (Read code diagnosis, including chronic and allergic rhinitis and prescriptions for nasal steroids in the year prior to index date)
    - Eczema (Read code diagnosis in the year 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)
    - Osteoporosis (Read code diagnosis or osteoporosis drugs [bisphosphonates, denosumab, strontium ranelate or teriparatide] 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, detailed definition in Appendix 1)

* 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

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.

5.2 Primary outcome

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

5.3 Secondary outcomes

5.3.1 Respiratory outcomes

- Rate of moderate/severe COPD exacerbations†
- Time to first exacerbation
- 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 (Read code, detailed definition in Appendix 1)
- mMRC dyspnoea score
- Lung function (FEV_1 % predicted)
- Reliever use (both average SABA daily dose and average SAMA daily dose‡‡)
- Confirmed and suspected cases of pneumonia (Read code, detailed definition in Appendix 1)

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* As defined above
† As defined above
‡ "Cumulative dose" is the total prescribed in the outcome period, considering number of prescriptions, the dose and potency of the ICS. This will be categorised into low/ medium/ high dose following review of the raw data. Calculated as:

$$\sum((Number\ of\ inhalers * doses\ in\ pack) * mcg\ strength)$$

§ 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: daily dosing instructions of <=10mg Prednisolone or prescriptions for 1mg or 2.5mg Prednisolone tablets where daily dosing instructions are not available.
†† **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

5.3.2 Cost-effectiveness outcome

Cost-effectiveness of Fostair® pMDI relative to the other licensed COPD therapies will be considered, where cost-effectiveness describes respiratory-related costs* in terms of moderate/severe COPD exacerbation prevention.

Total and disaggregated COPD-related costs 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).

Cost-effectiveness combines effectiveness results with the costs of therapies to determine whether a treatment can be considered preferable in both respects, or whether there is a trade-off.

Cost data 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.

5.4 Exploratory subgroup analysis

If patient numbers allow, patients will be stratified according to prior asthma diagnosis to enable a subgroup analysis of asthma-free COPD patients.

5.5 Exploratory outcome

- Treatment adherence,** whereby a patient is considered adherent to the prescribed therapy if their refill rate is >70%.

* All hospitalisation costs as an exploratory analysis.
† Leukotriene Receptor Antagonists
‡ Theophylline
§ Lower Respiratory Tract Infection
** Calculated as:
Number days per pack = Number of actuations per pack / Number of actuations per day
Total Pack Days = Σ (Number days per pack)
Refill Rate % = (Total pack days/365) * 100

6.0 Statistical analysis

6.1 Software used and power calculation

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

The study will be powered using Seretide® 500 Accuhaler® as the comparator medication. 58% of patients with COPD would be expected to be exacerbation free in the 12 month outcome period on Seretide® 500 Accuhaler.[18]

80% power will be achieved with **553 subjects per group**, based on a lower limit of an observed one-sided 97.5% confidence interval in excess of 0.084 (20%).

6.2 Baseline characterisation

Data preparation and exploratory analysis will include the investigation of potential outliers and missing data for all variables. Plots will be produced for all explanatory and outcome variables. For variables measured on the interval or ratio scale, these will include:

- Frequency plots to illustrate the distribution of the variable and whether categorisation may be necessary (for example, if heavily skewed)
- Box plots to illustrate the location and spread of the variable and identify potential outliers

For categorical variables, bar plots will be produced to illustrate distributions and highlight differences between exposure groups.
Skewed data will be transformed or categorised, as appropriate.

6.2.1 Summary statistics

Summary statistics will be produced for all baseline and outcome variables, as a complete dataset, by treatment group and for sub-groups. For variables measured on the interval or ratio scale, these will include:

- Sample size (n)
- Percentage non-missing
- Mean
- Standard Deviation (SD)
- Median

- Inter-quartile range (IQR – 25th and 75th percentiles)

For categorical variables, the summary statistics will include:

- Sample size (n)
- Count and percentage by category

Variables measured on the interval/ratio scale will be compared using a t-test (normal distribution) or Mann-Whitney U test (non-parametric). Categorical variables will be compared using a chi-square test. The statistical significance for all tests will be set at $p<0.05$.

6.3 Matching

Initially, baseline data will be compared between unmatched cohorts. Patients will be matched 1:1 on baseline therapy in order 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 will be 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).

Variables that may be matched are:

- Demographic characteristics such as sex, age, BMI category and smoking status
- COPD severity/treatment factors:
    - Symptom score: Modified British Medical Research Council Dyspnea Scale (mMRC)
    - Lung function: FEV_1 % predicted
    - Number of moderate/severe COPD exacerbations in the baseline period
- Corticosteroid exposure other than those inhaled for the lungs* such as inhaled nasal corticosteroid prescriptions
- Comorbidities:
    - Cardiovascular disease
    - Ischemic heart disease
    - Hypertension
    - Cancer

* The analyses will be adjusted for oral corticosteroid prescriptions.

- Charlson Comorbidity Index score*

6.4 Analysis of study outcomes

6.4.1 Primary outcome: non-inferiority in COPD exacerbations

To show non-inferiority in exacerbations, the adjusted proportions of patients within each treatment group recording any exacerbations in the outcome period will be calculated using a generalised linear model with binomial distribution and logit link.

Non-inferiority in exacerbations will be achieved if the proportion of Fostair® pMDI patients recording any exacerbations in the year following their initiation of medication is no more than 20% higher than the proportion of patients on comparator medication (Fostair® pMDI versus Seretide® 500 Accuhaler®, and separately Fostair® pMDI versus Symbicort® 200/400 Turbohaler®) recording any exacerbations: ie if the higher confidence interval of the difference in proportions of patients recording any exacerbations is greater than +0.20.[19]

If non-inferiority is shown, superiority (in exacerbations) will be tested by comparing the odds of experiencing an exacerbation in the outcome period using a conditional logistic regression model reporting an odds ratio and 95% confidence interval.

6.4.2 Secondary outcomes

6.4.2.1 Respiratory outcomes: COPD exacerbations

The total number of exacerbations in the outcome period will be compared between treatment groups using a conditional Poisson regression model to obtain an estimate of relative exacerbation rates (Fostair® pMDI versus Seretide® 500 Accuhaler®, and separately Fostair® pMDI versus Symbicort® 200/400 Turbohaler®). The model will use empirical standard errors (for more conservative confidence interval estimations) and adjustments will be made for potential baseline confounders. Results will be presented as a rate ratio with 95% confidence intervals.

Unadjusted comparisons of event rates for first exacerbations from index date will be compared between matched groups using Kaplan-Meier estimates and the log-rank test for

* The Charlson comorbidity index predicts the ten-year mortality for a patient who may have a range of comorbid conditions. Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. Age is also considered, with older ages assigned higher scores. Scores are summed to provide a total score to predict mortality (Moses, 2014).

equality of survival curves. Time to first exacerbation will be compared using a Cox proportional hazards regression model with stratification on matched pairs. Results will be reported as a hazard ratio with 95% confidence intervals.

6.4.2.2 Other respiratory outcomes

Rates of respiratory-related hospitalisations will be compared using conditional Poisson regression models. Results will be reported as a rate ratio with 95% confidence intervals (Fostair® pMDI versus Seretide® 500 Accuhaler®, and separately Fostair® pMDI versus Symbicort® 200/400 Turbohaler®).

Treatment stability (a dichotomous outcome) will be compared using conditional logistic regression. Results will be reported as an odds ratio with 95% confidence intervals (Fostair® pMDI versus Seretide® 500 Accuhaler®, and separately Fostair® pMDI versus Symbicort® 200/400 Turbohaler®).

The mMRC dyspnoea score will be compared using analysis of covariance, stratified by matching ID. Results will be reported as a mean difference with 95% confidence intervals (Fostair® pMDI versus Seretide® 500 Accuhaler®, and separately Fostair® pMDI versus Symbicort® 200/400 Turbohaler®).

Categorised reliever use, where a higher category denotes more reliance on reliever inhalers, will be compared using a conditional ordinal regression model. Results will be reported as an odds ratio with 95% confidence intervals (Fostair® pMDI versus Seretide® 500 Accuhaler®, and separately Fostair® pMDI versus Symbicort® 200/400 Turbohaler®).

All models will be 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) will be summarised to report the proportion of patients in each treatment group.

6.4.2.3 Cost-effectiveness

All respiratory-related costs will be calculated for each treatment group for the outcome period as all respiratory-related drug costs and consultations in:

- Primary care
- In-patient hospitalisations
- Out-patient hospitalisations
- A&E hospitalisations

Effectiveness and COPD-related healthcare costs will be compared between the following groups: Fostair® pMDI versus Seretide® 500 Accuhaler® (comparison 1), and separately Fostair® pMDI versus Symbicort® 200/400 Turbohaler® (comparison 2).

Costs between treatments will be compared using arithmetic mean COPD-related healthcare costs per patient per year during the outcome period, both unadjusted and adjusted for confounding factors listed in section 6.3.

To test whether unadjusted mean cost differences are statistically different between each comparison group, measures of variability (standard errors, p-values and confidence intervals) will be estimated/developed using two methods: (1) a parametric t-test with unequal standard deviations; and (2) non-parametric bootstrapping with 1000 samples taken with replacement from the dataset. Adjusted COPD-related healthcare costs during the outcome period will be 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 will be reported with 95% confidence intervals developed from non-parametric bootstrapping methods with 1000 random samples taken with replacement from the dataset.

The adjusted proportions of patients within each treatment group recording any exacerbations in the outcome period will be estimated using a generalised linear model with binomial distribution and logit link. Proportions and differences in proportions of patients recording any exacerbations in the outcome period will be reported with 95% confidence intervals developed from bootsrapping methods with 1000 random samples taken with replacement.

The adjusted two-way differences (relative to comparators) in costs and proportions of patients recording any COPD exacerbations for the 1000 random samples will be displayed graphically on a cost-effectiveness plane. The four quadrants of the cost-effectiveness plane (see Figure 2) represent Fostair® 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 (Fostair® pMDI dominant).

When point estimates result in a trade-off (i.e., quadrants I and III) between comparators, an incremental cost-effectiveness ratio (ICER) will be 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). If all replicated data are in one quadrant of the cost-effectiveness plane, the ICER will be reported with a 95% confidence interval developed from bootstrapping methods.

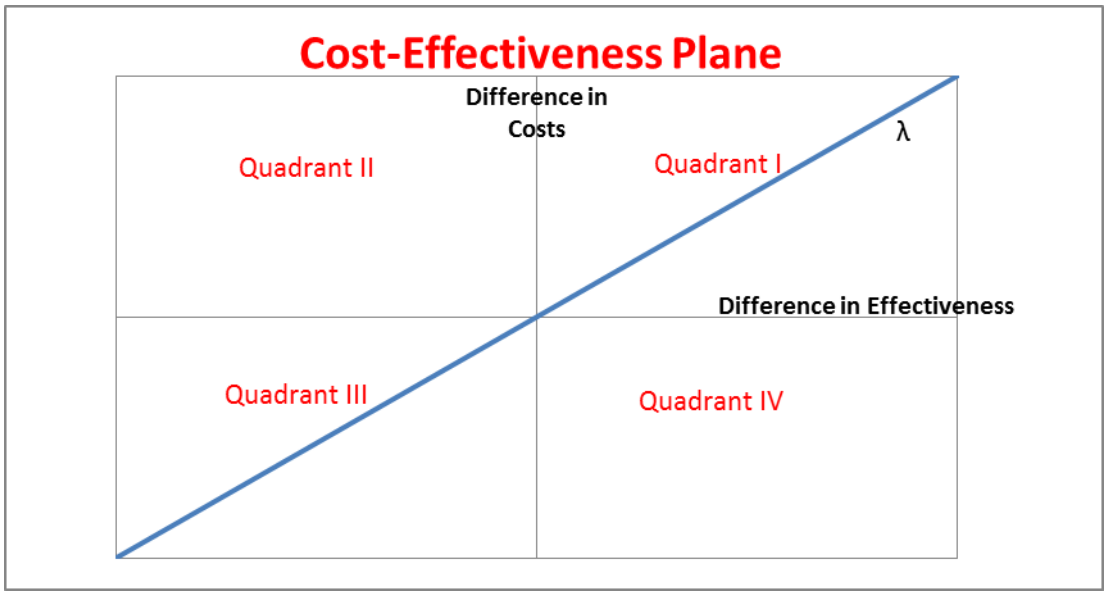

Figure 2: The cost-effectiveness plane

7.0 Regulatory and ethical compliance

This study will be designed and shall be implemented and reported in accordance with the criteria of the "European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study" and follows the ENCePP Code of Conduct (EMA 2014). This study is registered with www.encepp.eu EUPAS9142

8.0 Data dissemination

Initial results will be presented in poster and/or oral format at appropriate thoracic conferences. At least one manuscript containing more detailed results and methodology will be submitted to a journal specialising in respiratory medicine. Submission for publications will be made as soon as the analyses are completed and the results are verified.

9.0 Advisory group

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10.0 Research team

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11.0 Timelines

Table 2: Project timelines

Action	Dates
Protocol development	1st February 2016
Steering committee sign off	15th February 2016
Chiesi sign off	29th February 2016
Practice extractions	completed
Data extraction	28th March 2016
Exploratory and baseline analysis	25th April 2016
Baseline report (PowerPoint)	9th May 2016
Baseline steering committee review	16th May 2016
Baseline Chiesi review	23rd May 2016
Decision to increase patient numbers	15th March 2017
Repeat baseline analysis	16th March 2017
Matching	3rd April 2017
Matched baseline analysis	10th April 2017
Outcome analysis:	14th April 2017
Report of outcome (PowerPoint)	30th April 2017
Steering committee review of primary outcome	14th May 2017
Chiesi review of outcome	21st May 2016
Final report writing (PowerPoint and Word report)	14th June 2017*
Steering committee review	21th June 2017
Chiesi review	30rd June 2017
First draft of manuscript	1st Aug 2017*

* Allowing for Easter and Christmas break

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13.0 APPENDIX

13.1 Appendix 1: Definitions

13.1.1 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).

13.1.2 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§.

13.1.3 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.

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*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:

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.

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 3: 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
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

13.1.4 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.

13.1.5 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.

13.1.6 Confirmed and suspected pneumonia

Cases of pneumonia, both:

1. **Unconfirmed** (i.e. all unique patients with codes for pneumonia); AND
2. **Confirmed** via:
   a. Chest X-ray within a month of a pneumonia diagnosis; OR
   b. Hospitalisation within a month of a pneumonia diagnosis.

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

13.2 Appendix 2: Mock baseline results tables

Table 4: Summary statistic of baseline variables

		Fostair®	Seretide® 500 Accuhaler®	Symbicort® 200/400 Turbohaler®
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Age (years)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Gender, n (%)	Male	x (x)	x (x)	x (x)
	Female	x (x)	x (x)	x (x)
BMI (kg/m^2)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
BMI (categorised), n (%)	Underweight	x (x)	x (x)	x (x)
	Normal	x (x)	x (x)	x (x)
	Overweight	x (x)	x (x)	x (x)
	Obese	x (x)	x (x)	x (x)
Smoking status, n (%)	Current smoker	x (x)	x (x)	x (x)
	Ex-smoker	x (x)	x (x)	x (x)
Duration of COPD diagnosis (years)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose (categorised), n (%)	Low	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
Average SAMA daily dose	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SAMA daily dose (categorised), n (%)	Low	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
Lung function (FEV_1 % predicted)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
FEV_1/FVC ratio	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
mMRC dyspnoea score, n (%)	1	x (x)	x (x)	x (x)
	2	x (x)	x (x)	x (x)
	3	x (x)	x (x)	x (x)

	4	x (x)	x (x)	x (x)
	5	x (x)	x (x)	x (x)
Exacerbation count	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
GOLD group, n (%)	A	x (x)	x (x)	x (x)
	B	x (x)	x (x)	x (x)
	C	x (x)	x (x)	x (x)
	D	x (x)	x (x)	x (x)
Oral corticosteroids prescriptions	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Antibiotic prescriptions for LRTI	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Table 5: Summary statistics for diagnoses of co-morbidities at baseline

		Fostair®	Seretide® 500 Accuhaler®	Symbicort® 200/400 Turbohaler®
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Asthma	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Anxiety/depression	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
GERD	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Pneumonia	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Diabetes	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Ischaemic heart disease	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Heart failure	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Hypertension	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Bronchiectasis	N (% non-missing)	x (x)	x (x)	x (x)

	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Rhinitis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Eczema	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Chronic kidney disease	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Osteoporosis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Lung cancer	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Charlson comorbidity index, n (%)	0	x (x)	x (x)	x (x)
	1-4	x (x)	x (x)	x (x)
	5+	x (x)	x (x)	x (x)

13.3 Appendix 3: Mock outcome results tables

Table 6: Summary statistics of outcome variables

		Fostair®	Seretide® 500 Accuhaler®	Symbicort® 200/400 Turbohaler®
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Moderate/ severe COPD exacerbations	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Number of oral corticosteroid courses	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Number of antibiotic courses for LRTI	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Treatment stability, n (%)	Stable	x (x)	x (x)	x (x)
	Unstable	x (x)	x (x)	x (x)
Respiratory-related hospitalisations	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
mMRC dyspnoea score, n (%)	1	x (x)	x (x)	x (x)
	2	x (x)	x (x)	x (x)
	3	x (x)	x (x)	x (x)
	4	x (x)	x (x)	x (x)
	5	x (x)	x (x)	x (x)
Lung function (FEV_1 % predicted)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Reliever use (categorised), n (%)	Low	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
Cases of pneumonia (confirmed and suspected)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Table 7: Primary outcome results

	Fostair®	Seretide® 500 Accuhaler®	Symbicort® 200/400 Turbohaler®
Patients with exacerbations, n (%)	x (x)	x (x)	x (x)
Non-inferiority	Proportion	95% confidence interval	p-value
Fostair® compared to Seretide® 500 Accuhaler®	x	x-x	x
Fostair® compared to Symbicort® 200/400 Turbohaler®	x	x-x	x
Superiority	Odds ratio	95% confidence interval	p-value
Fostair® compared to Seretide® 500 Accuhaler®	x	x-x	x
Fostair® compared to Symbicort® 200/400 Turbohaler®	x	x-x	x

Table 8: Respiratory outcomes comparing Fostair® to Seretide® 500 Accuhaler®

Respiratory outcome	Fostair®, n (%)	Seretide® 500 Accuhaler®, n (%)	Ratio	95% confidence interval	p-value
Number of exacerbations	x (x)	x (x)	x*	x-x	x
Treatment stability	x (x)	x (x)	x	x-x	x
Number of respiratory-related hospitalisations	x (x)	x (x)	x*	x-x	x
mMRC dyspnoea score	x (x)	x (x)	x	x-x	x
Reliever usage	x (x)	x (x)	x***	x-x	x

*Rate ratio; **Hazard ratio; ***Odds ratio

Table 9: Respiratory outcomes comparing Fostair® to Symbicort® 200/400 Turbohaler®

Respiratory outcome	Fostair®, n (%)	Symbicort® 200/400 Turbohaler®, n (%)	Ratio	95% confidence interval	p-value
Number of exacerbations	x (x)	x (x)	x*	x-x	x
Treatment stability	x (x)	x (x)	x	x-x	x
Number of respiratory-related hospitalisations	x (x)	x (x)	x*	x-x	x
MRC dyspnoea score	x (x)	x (x)	x	x-x	x
Lung function	x (x)	x (x)	x***	x-x	x
Reliever usage	x (x)	x (x)	x***	x-x	x
Cases of pneumonia	x (x)	x (x)	x***	x-x	x

*Rate ratio; **Hazard ratio; ***Odds ratio