Research in Real Life Ltd Study Protocol for Chiesi Ltd

REACH II: Characterising patients and examining real-life outcomes for UK patients with COPD initiating on or changing to Fostair®

Contents

Background

Chronic obstructive pulmonary disease (COPD) affects 7.7% of adults in North America and Western Europe (Price, 2010). COPD is characterised by restricted airflow in the lungs and is usually caused by smoking, with symptoms such as cough, sputum production and breathlessness. It is defined clinically by a post-bronchodilator FEV_1/FVC[1] ratio of <0.7 on spirometry. COPD mainly affects people over 40 years old who have smoked for 10 years or more and is increasingly common with age. The average age for diagnosis is 67 (patient.co.uk, 2015).

COPD varies in severity and treatment is tailored accordingly. If patients continue to smoke they experience a decline in their wellbeing. At least 25,000 people die each year in the UK from COPD (patient.co.uk, 2015).

Treatments for COPD depend on the severity of the condition and the frequency of exacerbations experienced by the patient. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (GOLD, 2015) classifies the severity of COPD (GOLD stage 1-4, mild-very severe), based on FEV_1, the patient's symptoms and frequency of exacerbations. Treatment strategies are tailored according to severity, symptoms and frequency of exacerbations.

The primary maintenance treatment for COPD is a bronchodilator (long-acting muscarinic antagonist (LAMA) and/or long-acting β-agonist (LABA)), with an inhaled corticosteroid (ICS) added for more severe patients with a history of exacerbations. Guidelines recommend the use of a fixed dose combination (FDC) ICS/LABA treatment only for moderate to severe patients with COPD (FEV_1 <50% predicted). Additional medications include short-acting muscarinic antagonists (SABAs) and short-acting β-agonists (SAMAs), as relievers.

Fostair® is a FDC ICS/LABA that contains 100µg of the ICS beclometasone dipropionate (BDP) and 6µg of the LABA formoterol (FOR). In a previous study carried out by Research in Real Life Ltd (RiRL) for Chiesi Ltd (the REACH study), Fostair® delivered via a pressurised metered dose inhaler (pMDI) was demonstrated to be non-inferior to Seretide® in preventing acute respiratory events for patients with asthma at an equivalent or lower ICS dose (Price, 2013).

Fostair® pMDI has previously been prescribed off-licence for the treatment of COPD in the UK (unpublished data from RiRL), 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." (Fostair SPC, October 2014). The study outlined in this protocol aims to perform a similar analysis to the REACH study for Fostair®, in patients with COPD.

[1] FEV_1: Forced expiratory volume in 1 second in litres; FVC: Forced volume vital capacity in litres; FEV_1/FVC represents the proportion of a person's vital capacity that they are able to expire in the first second of expiration.

Overall Study Objective

To evaluate, in a comparative effectiveness study, whether Fostair® pMDI is non-inferior, in terms of COPD exacerbation prevention, to other FDC ICS/LABA COPD therapies in patients with COPD. COPD exacerbations are defined as an occurrence[2] of:

1. COPD-related[3]: Unscheduled hospital admission / A and E attendance; OR
2. An acute[4] course of oral steroids; OR
3. Antibiotics prescribed with lower respiratory consultation[5]

Hypothesis: Fostair® pMDI is non-inferior to other FDC ICS/LABA therapies (considered in this study) in terms of preventing COPD exacerbations.

This is a two-stage study that aims to analyse the effectiveness of Fostair® pMDI in patients with COPD compared to other FDC ICS/LABA therapies.

In stage 1, all patients with COPD using FDC ICS/LABA during the outcome period will be considered. Patients will be characterised and the therapy pathways taken by these patients will be indicated. A sub-analysis will also be performed on patients that meet the licensed indication for Fostair®. Stage 1 will provide the information regarding the most appropriate comparator(s) for stage 2.

Stage 2 of the study will involve comparison of Fostair® pMDI to the selected comparator(s) to determine whether it is non-inferior in terms of COPD exacerbation prevention. Secondary outcomes include further effectiveness outcomes (such as total number of COPD exacerbations and time to first COPD exacerbation), and the cost-effectiveness (in terms of exacerbation prevention), of Fostair® pMDI relative to the selected comparator(s).

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[2]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).

[3]**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**[5] (see below; (a) – (c) only and excluding where the only lower respiratory code recorded on that day was for a lung function test).

[4] 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.

[5] **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.

Data Source

Optimum Patient Care (OPC) is a social enterprise company led by Professor David Price, a Clinical Academic recognised internationally for his expertise in patient assessment, supported self-management and primary care.

Optimum Patient Care Research Database (OPCRD)

OPC extracts data from primary care practices on patients with chronic respiratory diseases. Two types of anonymised patient data are typically collected:

(1) Routine clinical data

- OPC software interfaces with primary care practice management systems and extracts disease coding and prescribing information

(2) Questionnaires

- Patients identified as eligible for the respiratory review service are invited to complete validated disease assessment questionnaires to better understand their current health status (and/or possible reasons for sub-optimal status)

- Anonymised questionnaires are assigned a unique code to aid matching routine data to questionnaire results

The OPC research database (OPCRD, 2014), which comprises the routine clinical and questionnaire data, has been approved by the Trent Multi Centre Research Ethics Committee for clinical research use. The database is increasing in size daily, but at last validated review included data from over 1 million patients captured across 523 unique practices.

The anonymised, longitudinal patient data offer a high-quality data source for use in clinical, epidemiological and pharmaceutical research. It enables research to be carried out across a broad-range of respiratory areas and, in contrast to other medical research databases (e.g. the Clinical Practice Research Datalink [CPRD] (CPRD, 2014)), OPCRD offers the additional dimension of patient reported data.

Stage 1

Aims and Objectives

1. To explore the pathways taken by patients that are prescribed a FDC ICS/LABA in the outcome period, whether it is their first FDC ICS/LABA for COPD (initiation cohort), a change in type or dose of FDC ICS/LABA (change cohort) or a continuation of their baseline FDC ICS/LABA (repeat cohort).

    a. To report numbers and percentages of patients following each path observed.

    (Where a patient is eligible for multiple index dates, each will be included in the exploratory analysis, but will appear only once in the stage 2 matched analysis.)

2. To describe the baseline demographics of each unique group described above.

    a. To describe those patients that are eligible for Fostair® according to its licensed indication[6] as a sub-analysis.

3. To determine the feasibility / cohort selection for stage 2.

List of FDC ICS/LABA medications

All FDC ICS/LABA therapies identified in the data will be described. Medications of particular interest (that will be reported even if patient numbers are zero) are:

- **Licensed** FDC ICS/LABA medications for COPD:
  - Fostair® 100/6 pMDI
  - Seretide® 500 Accuhaler
  - Symbicort® 200 Turbohaler
  - Symbicort® 400 Turbohaler
  - Relvar® Ellipta® 92/22

- **Unlicensed** FDC ICS/LABA medications for COPD:
  - Fostair® 100/6 NEXThaler
  - Seretide® 50 Evohaler
  - Seretide® 125 Evohaler
  - Seretide® 250 Evohaler
  - Seretide® 250 Accuhaler
  - Symbicort® 100 Turbohaler
  - Flutiform® 50/5
  - Flutiform® 125/5
  - Flutiform® 250/10

[6] Specifically: 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 (forced expiratory volume) recorded <60% predicted (as it is post-bronchodilator so could legitimately be <50% pre-bronchodilator).)

Study Design

This is a historical database study to compare the effectiveness of Fostair® pMDI to other FDC ICS/LABA therapies for COPD, in terms of exacerbation prevention.

For stage 1, the aim is to describe all patients with COPD that are prescribed FDC ICS/LABA therapies at a point in time that allows 1 year of 'outcome' data to be collected, following a 1 year 'baseline' period. Patients with stable therapy (defined as ≥2 prescriptions[8] during baseline) will be considered, to show the therapy routes taken by patients who use a FDC ICS/LABA in the outcome period. Patients with no medications prescribed in the baseline period will also be included in the analyses as part of the 'no COPD therapy' subgroup within the initiation cohort. Each unique pathway identified that fits these criteria will be reported.

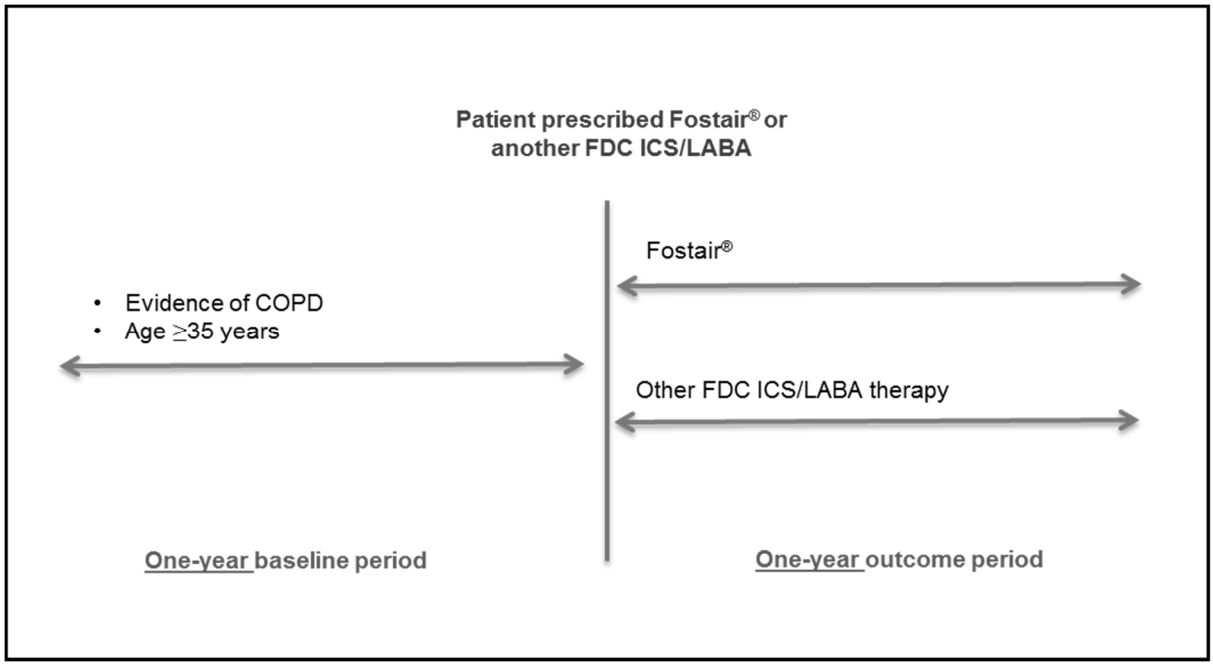

Figure 1: Stage 1 study design.

Study Population

Inclusion/Exclusion Criteria

To be included in this study patients must:

- Have a COPD diagnosis, including patients diagnosed with both asthma and COPD (patients with asthma COPD overlap syndrome (ACOS))[7]
- Be ≥35 years old at the FDC ICS/LABA prescription date
- Have continuous practice data comprising a 1-year baseline period and 1-year outcome period
- Have ≥2 prescriptions[8] of the same respiratory medication (or consistently no medication for the 'no COPD therapy' subgroup of the initiation cohort) during the baseline period
- Have ≥2 prescriptions of the same FDC ICS/LABA (including the prescription on index date) during the outcome period

Excluded patients:

- Patients that do not meet the inclusion criteria

For analysis of the sub-group of patients that meet the licensed indication for Fostair® pMDI, additional inclusion criteria are:

- ≥2 prescriptions of LAMA and/or LABA in baseline, either alone or in combination with other medications for COPD, e.g. FDC ICS/LABA
- FEV_1 <60% predicted[2]
- History of repeated COPD exacerbations (for the initiation cohort only)

[2] Specifically: 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 (forced expiratory volume) recorded <60% predicted (as it is post-bronchodilator so could legitimately be <50% pre-bronchodilator).

[7] Diagnosis Read Codes based on QOF diagnostic Read Codes and screening codes.

[8] Feasibility of ≥2 prescriptions rather than ≥1 prescription in baseline to be used as the definition for stable baseline therapy, to be confirmed as the first step of stage 1, but is preferable for symmetry with the outcome period.

Patient Pathways

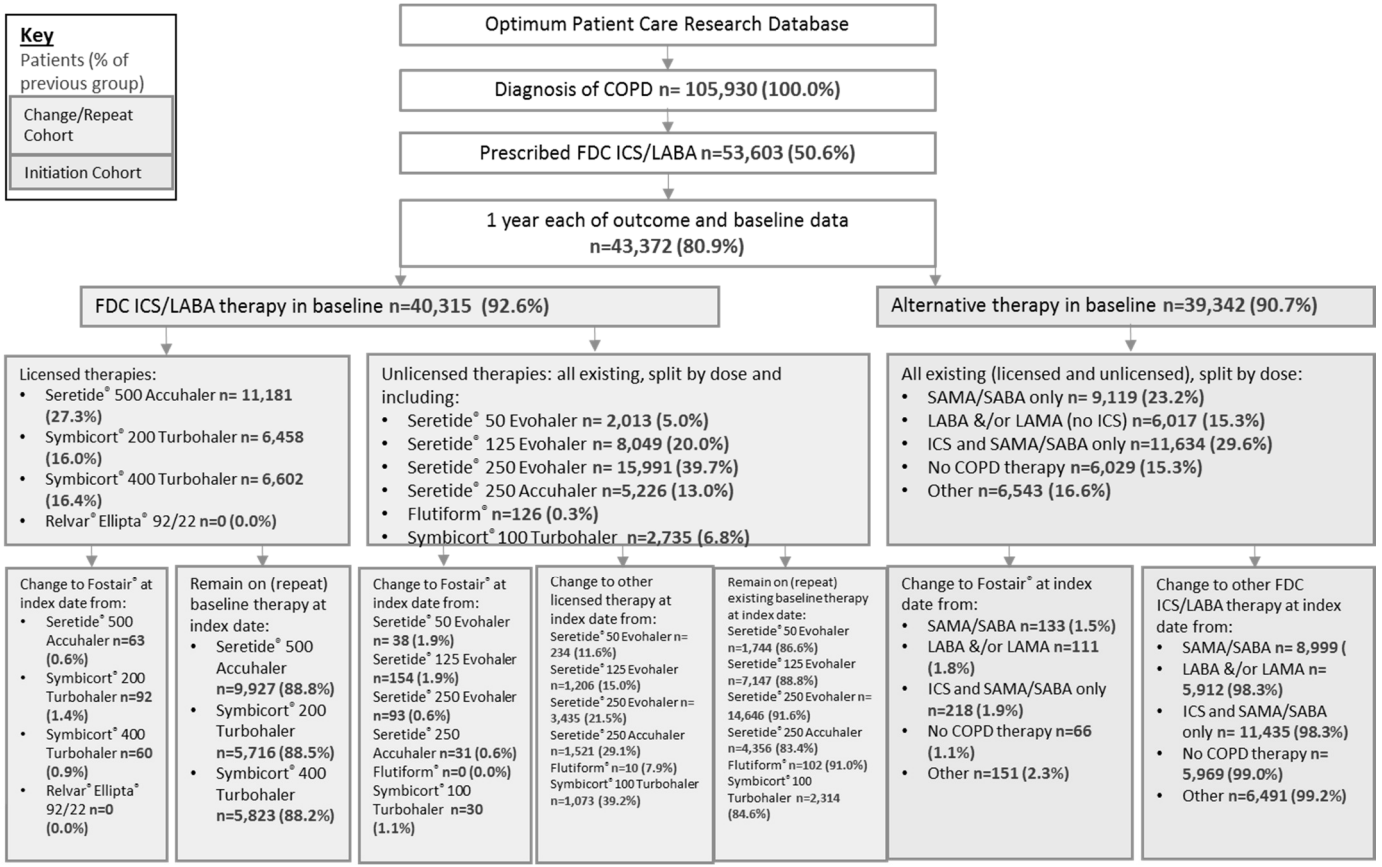

Figure 2: Breakdown of therapy pathways of patients with COPD with ≥2 prescriptions for FDC ICS/LABA in outcome. (Patients may fall into multiple subgroups over the course of their historical therapy pathway.)

The requirement for ≥2 prescriptions in baseline has not been applied at this stage, but will be the initial step for stage 1.

Preliminary patient numbers

Licensed FDC ICS/LABA in baseline	Patients n (% of all patients with FDC ICS/LABA therapy in baseline)	Patients changing to Fostair® in outcome n (% of baseline patients)
Seretide® 500 Accuhaler	11,181 (27.3)	63 (0.6)
Symbicort® 200 Turbohaler*	6,458 (16.0)	92 (1.4)
Symbicort® 400 Turbohaler*	6,602 (16.4)	60 (0.9)
Relvar® Ellipta® 92/22	0 (0.0)	0 (0.0)

Table 1: Preliminary numbers for change cohorts (licensed group), from Figure 2.

* These two medications may be combined due to their equivalency with respect to daily dose for stage 2.

Unlicensed FDC ICS/LABA in baseline	Patients n (% of all patients with FDC ICS/LABA therapy in baseline)	Outcome medication	Patients n (% of baseline patients)
Seretide® 50 Evohaler	2,103 (5.0)	Change to Fostair®	38 (1.8)
		Change to other licensed medication	234 (11.1)
		Remain on baseline therapy	1,744 (82.9)
Seretide® 125 Evohaler	8,049 (20.0)	Change to Fostair®	154 (1.9)
		Change to other licensed medication	1,206 (15.0)
		Remain on baseline therapy	7,147 (88.8)
Seretide® 250 Evohaler	15,991 (39.7)	Change to Fostair®	93 (0.6)
		Change to other licensed medication	3,435 (21.5)
		Remain on baseline therapy	14,646 (91.6)
Seretide® 250 Accuhaler	5,226 (13.0)	Change to Fostair®	31 (0.6)
		Change to other licensed medication	1,521 (29.1)
		Remain on baseline therapy	4,356 (83.4)
Symbicort® 100 Turbohaler	2,735 (6.8)	Change to Fostair®	30 (1.1)
		Change to other licensed medication	1,073 (39.2)
		Remain on baseline therapy	2,314 (84.6)
Flutiform® 50/5	5 (0.0)	Change to Fostair®	0 (0.0)
		Change to other licensed medication	0 (0.0)
		Remain on baseline therapy	3 (60.0)
Flutiform® 125/5	40 (0.1)	Change to Fostair®	0 (0.0)
		Change to other licensed medication	2 (0.1)
		Remain on baseline therapy	28 (7.0)
Flutiform® 250/10	85 (0.3)	Change to Fostair®	0 (0.0)
		Change to other licensed medication	8 (9.4)
		Remain on baseline therapy	73 (85.9)

Table 2: Preliminary numbers for change/repeat cohorts (unlicensed group), from Figure 2. Please note all unlicensed FDC ICS/LABA medications will be reported.

Other therapies in baseline		**Patients n (% of all patients with other therapies in baseline)**	**Therapies in outcome**		**Patients n (% of baseline patients)**
Licensed	LABA &/or LAMA*	6,017 (15.3)	Initiate on Fostair®		111 (1.8)
			Initiate on other licensed FDC ICS/LABA	Seretide® 500 Accuhaler	1,381 (23.0)
				Symbicort® 200 Turbohaler	548 (9.1)
				Symbicort® 400 Turbohaler	811 (13.5)
				Relvar® Ellipta® 92/22	0 (0.0)
Unlicensed	SAMA/SABA only	9,119 (23.2)	Initiate on Fostair®		133 (1.5)
			Initiate on other licensed FDC ICS/LABA	Seretide® 500 Accuhaler	1,294 (14.2)
				Symbicort® 200 Turbohaler	1,215 (13.3)
				Symbicort® 400 Turbohaler	881 (9.7)
				Relvar® Ellipta® 92/22	0 (0.0)
	Others (to be fully broken down by type and dose)	24,206 (61.5)	Initiate on Fostair®		435 (1.8)
			Initiate on other licensed FDC ICS/LABA	Seretide® 500 Accuhaler	3,209 (13.3)
				Symbicort® 200 Turbohaler	3,938 (16.2)
				Symbicort® 400 Turbohaler	2,099 (8.7)
				Relvar® Ellipta® 92/22	0 (0.0)

Table 3: Preliminary numbers for initiation cohorts, from Figure 2.

*LAMA population may include patients on triple therapy (LAMA, LABA and ICS).

Statistical Analysis Plan

General

Statistically significant results will be defined as $p<0.05$ and trends as $0.05 \geq p < 0.10$.

All analyses will be carried out using SPSS version 22 (SPSS, 2015), SAS version 9.3 (SAS, 2015) and Microsoft Office EXCEL 2013.

Data preparation and exploratory analysis will include the investigation of potential outliers and missing data. Skewed data will be transformed or categorised, as appropriate.

Exploratory Analysis: Examining feasibility and baseline characteristics

- Quantify patient numbers and percentage for each unique pathway (in terms of their baseline to outcome therapy pathways).
    - Repeat this for ≥1 and ≥2 COPD therapy prescriptions during baseline to determine the effect on patient numbers (≥2 is preferable, but analysis of the patient numbers will confirm whether they are sufficient for the study).
    - Repeat for the subgroup of patients that meet the licensed COPD indication for Fostair®pMDI.

- Once confirmation is received regarding the preferred inclusion criteria above, basic patient demographics and disease characteristics will be reported for each group of patients following a unique treatment pathway, including:
    - Gender
    - Age
    - Height
    - Weight
    - BMI
    - Smoking status
    - Date of COPD diagnosis
    - Duration of COPD diagnosis
    - Average SABA daily dose
    - Lung function severity[9]
    - GOLD group[10]
    - FEV_1/FVC ratio[11]

[9]The Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage: 1 (Mild COPD, FEV_1 ≥80% normal); 2 (Moderate COPD, FEV_1 50-79% normal); 3 (Severe COPD, FEV_1 30-49% normal); 4 (Very severe COPD, FEV_1 <30% normal)

[10] Group A, B, C or D where GOLD groups are defined as: A = Low risk, low symptom burden (mMRC of 0-1) AND FEV_1 of 50% or greater (old GOLD 1-2) AND low exacerbation rate (0-1/year with no hospital admission required), B = Low risk, higher symptom burden (mMRC of 2 or more) AND FEV_1 of 50% or greater (old GOLD 1-2) AND low exacerbation rate (0-1/year with no hospital admission required), C = High risk, low symptom burden (mMRC of 0-1) AND FEV_1 < 50% (old GOLD 3-4) AND/OR high exacerbation rate (≥2/year or ≥1/year that leads to a hospital admission), D = High risk, higher symptom burden (mMRC of 2 or more) AND FEV_1 < 50% (old GOLD 3-4) AND/OR high exacerbation rate ((≥2/year or ≥1/year that leads to a hospital admission)

[11] Represents the proportion of a person's vital capacity that they are able to expire in the first second of expiration.

- mMRC score[12]
- Baseline exacerbation count
- Use of oral steroids
- Use of antibiotics for lower respiratory tract infections
- Comorbidities

See Appendix C: Variable List for full details.

- Once full details of the patient numbers are known, they will be discussed further with the sponsor / steering committee / chief investigator to allow selection of comparators for stage 2, before proceeding any further.

Summary Statistics

Summary statistics will be produced for baseline demographics, as a complete dataset and by treatment group.

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)
- Range (Minimum / Maximum)

For categorical variables, the summary statistics will include:

- Sample size (n)
- Count and percentage by category
- Range (if applicable)

See Appendix A for stage 1 mock tables.

[12] Modified Medical Research Council Dyspnoea Scale/breathlessness scale

Stage 2

Aims and Objectives

To evaluate whether Fostair® pMDI is non-inferior, in terms of COPD exacerbation prevention, to other FDC ICS/LABA COPD therapies.

Hypothesis: Fostair® pMDI is non-inferior[13] to other FDC ICS/LABA therapies (considered in this study) in terms of preventing COPD exacerbations.

Study Population

Inclusion/Exclusion Criteria

To be included in this study patients must:

- Have a COPD diagnosis, including patients diagnosed with both asthma and COPD (patients with asthma COPD overlap syndrome (ACOS))[14]
- Be ≥35 years old at the FDC ICS/LABA prescription date
- Have continuous practice data comprising a 1-year baseline period and 1-year outcome period
- For initiation cohort:
    - Patients must receive ≥2 prescriptions[8] in baseline of LAMA &/or LABA therapy (either alone or in combination with other medications for COPD, but not including an ICS)
    - Either a prescription for Fostair® pMDI or the comparator FDC ICS/LABA therapy for COPD as a first FDC ICS/LABA treatment at initiation date
- For change/repeat cohort:
    - Patients must receive ≥2 prescriptions[8] of baseline comparator FDC ICS/LABA
    - Either a prescription for Fostair® pMDI or continues on the comparator therapy at change/repeat date
- ≥ 2 prescriptions of Fostair® pMDI or the comparator FDC ICS/LABA during the outcome period (including the prescription on the chosen prescription date)
- FEV_1 < 60% predicted (based on Fostair® pMDI licensed indication, see footnote 2 for details)
- History of repeated COPD exacerbations (for the initiation cohort only)

Exclusion criteria

- Patients with ≥2 different FDC ICS/LABA prescriptions at index date

[8] Feasibility of ≥2 prescriptions rather than ≥1 prescription in baseline to be used as the definition for stable baseline therapy, to be confirmed as the first step of stage 1, but is preferable for symmetry with the outcome period.

[13] Non-inferiority in exacerbation prevention will be achieved if the proportion of Fostair® pMDI patients recording no exacerbations in the year following the chosen prescription date is no more that 20% lower than the proportion of comparator patients recording no exacerbations: i.e. if the lower confidence interval of the difference in proportions of patients recording no exacerbations is greater than -0.20 (Magnussen, 2014)

[2] Specifically: 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 (forced expiratory volume) recorded <60% predicted (as it is post-bronchodilator so could legitimately be <50% pre-bronchodilator).

[14] Diagnosis Read Codes based on QOF diagnostic Read Codes and screening codes.

Study Design

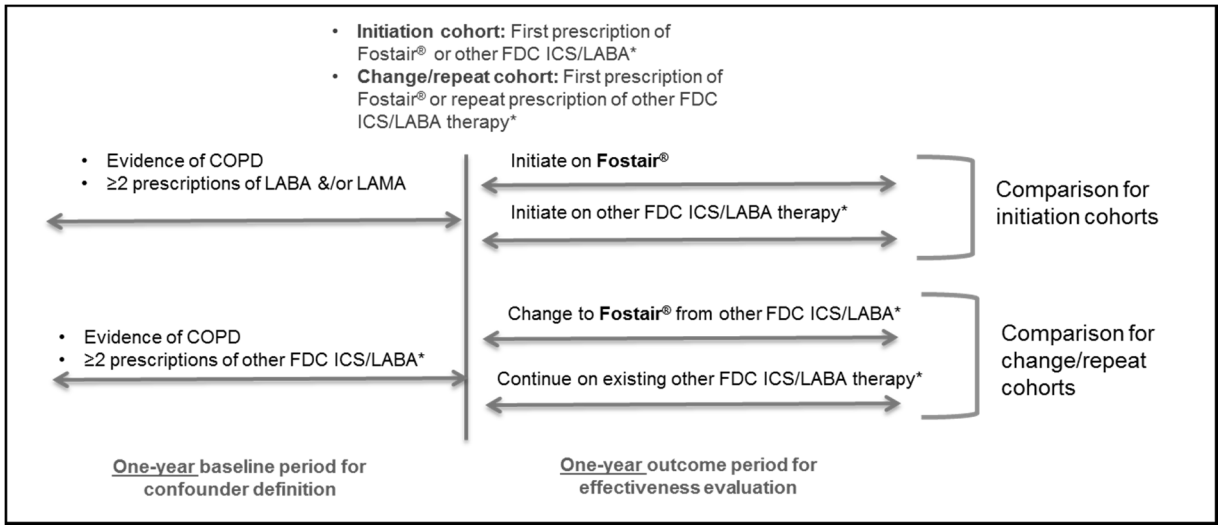

Figure 3: Stage 2 study design.

Statistical Analysis Plan

Data preparation and exploratory analysis will include the investigation of potential outliers and missing data for all variables. Skewed data will be transformed or categorised, as appropriate.

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 – 25^{th} and 75^{th} percentiles)
- Range (Minimum / Maximum)

For categorical variables, the summary statistics will include:

- Sample size (n)
- Count and percentage by category
- Range (if applicable)

Identification of matching criteria:

- Compare all variables at baseline (t-test, Mann-Whitney U test or chi-squared test, as appropriate)
- Matching criteria are selected according to clinical importance and baseline distribution across the treatment arms, to ensure comparison of like patients

Matching

Matching criteria are likely to include:

- Age (± 5 years)
- Sex
- Smoking status (current smoker/ex-smoker/non-smoker)
- Baseline therapy (exact match)
- Baseline ICS dose (for change cohort only – exact match)
- Lung function (FEV_1% predicted)
- Baseline exacerbation count and use of oral steroids &/or antibiotics (0 / 1 / 2+)
- Year of index date (closest matches ± 2 years)
- Charlson Comorbidity Index[24] (exact match)

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

Evaluation of potential confounders:

- Those highly predictive of outcome (found through multivariate modelling)
- Those with a residual difference after matching

Primary and Secondary Outcomes

Primary Outcome

- The proportion of patients with no COPD exacerbations in the outcome period.

Secondary Outcomes

Respiratory outcomes for Fostair® relative to the other COPD therapies considered:

- The proportion of patients, under the licensed indication for Fostair®[15] pMDI, with no COPD exacerbations in the outcome period.
- Total number of COPD exacerbations[2]
  - During the 1 year outcome period
- Total number of oral steroid courses
  - During the 1 year outcome period
- Total number of courses of antibiotics
  - During the 1 year outcome period
- Time to first COPD exacerbation
  - Following the prescription date
- Treatment stability
  - Treatment stability defined as the absence of COPD exacerbations and no additional or change in therapy
- Respiratory-related hospitalisations
  - In-patient, out-patient or A&E attendance for COPD or with a lower respiratory code, plus any vague in-patient admissions
- mMRC score
  - GP recorded score
- Prescribing index (prescribing compliance measure)
  - Adherence to therapy (based on prescription refills)
- Lung function (FEV_1% predicted)
  - Forced expiratory volume in 1 second as a percentage of the maximum predicted for the patient, based on their height and age
- Reliever treatment usage
  - Average daily SABA and/or SAMA usage
- Confirmed and suspected cases of pneumonia
  - A diagnostic Read Code for pneumonia, diagnosis plus chest x-ray within 1 month of diagnosis or hospitalisation within 1 month of diagnosis

Cost-effectiveness outcome

- Cost-effectiveness of Fostair® pMDI relative to the other COPD therapies, where cost-effectiveness describes respiratory-related costs[15] in terms of COPD exacerbation prevention.
  - Total and disaggregated COPD-related costs including COPD drug prescriptions (FDC ICS/LABA, ICS, LAMA, LABA, SABA, SAMA, THEO, acute oral steroids and antibiotics for LTRIs); primary care consultations and respiratory-related hospital costs (e.g. out-patient, in-patient and A&E).
  - Cost-effectiveness combines effectiveness results with the costs of therapies to determine whether a treatment can be considered preferable (in terms of cost-effectiveness) or whether there is a trade-off between cost and effectiveness.

[15] All hospitalisation costs as an exploratory analysis.

Exploratory outcome

- Confirmed and suspected cases of diabetes
    - A diagnostic Read Code for diabetes or prescription of medication for diabetes, for the first time, during the outcome period.

Methods

Non-inferiority in COPD exacerbation prevention:

- To show non-inferiority in exacerbation prevention, the adjusted proportions of patients within each treatment group, recording no exacerbations in the outcome period will be calculated using a generalised linear model with binomial distribution and logit link.
- Non-inferiority in exacerbation prevention will be achieved if the proportion of Fostair® patients (both initiating and changing to Fostair® in the outcome period) recording no exacerbations in the year following their initiation/change of medication is no more than 20% lower than the proportion of patients on comparator medication recording no exacerbations (initiation and change): i.e. if the lower confidence interval of the difference in proportions of patients recording no exacerbations is greater than -0.20 (Magnussen, 2014).
    - If non-inferiority is shown, superiority (in exacerbation prevention) will be tested, as an exploratory analysis, by comparing the odds of being exacerbation-free in outcome (using a conditional logistic regression model).

COPD exacerbation rate:

- 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. 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.

Respiratory outcomes

- Time to first exacerbation will be compared using a Cox regression model. Results will be reported as a hazard ratio with 95% confidence intervals.
- 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.
- Dichotomous outcomes (e.g. treatment stability), will be compared using conditional logistic regression. Results will be reported as an odds ratio with 95% confidence intervals.
- Categorised variables such as reliever use will be compared using a conditional ordinal regression model. Results will be reported as an odds ratio with 95% confidence intervals.

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

Cost-effectiveness

- All respiratory-related costs will be calculated for each treatment group for the outcome period as:
    - all respiratory-related drug costs, including
        - FDC ICS/LABA
        - LABA

        - LAMA
        - ICS
        - SAMA
        - SABA
        - Theophylline
        - Oral steroids for lower respiratory event (acute and maintenance)
        - Antibiotics for lower respiratory event
    - and consultations in:
        - Primary care
        - In-patient hospitalisations
        - Out-patient consultations
        - A&E visits
    - Costs will be calculated as follows:
        - Drug costs = the sum of (unit cost of drug multiplied by the number of units prescribed per year) for every drug prescribed
        - Primary care consultation costs = the sum of (unit cost of consultation multiplied by the number of consultations per year) for every consultation type
        - Hospital costs = the sum of (unit cost of secondary care visit multiplied by the number of visits per year) for every visit type
        - In each case, where a prescription or consultation cannot be matched to a specific cost, an average cost, for example of a SABA or of an outpatient appointment will be used. Values used for these calculations will be presented in a table and used as a multiplier of the number of events for determining overall annual cost.

- Summary costs will be compared between matched treatment groups using conditional logistic regression.

- Adjusted costs will be compared across matched treatment groups using a generalised linear model with a Gamma distribution and log link.

- The adjusted differences (relative to comparator[s]) in costs and proportions of patients recording no COPD exacerbations will be displayed graphically on a cost-effectiveness plane. The four quadrants of the cost-effectiveness plane (see Figure 4) represent Fostair 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® dominant).

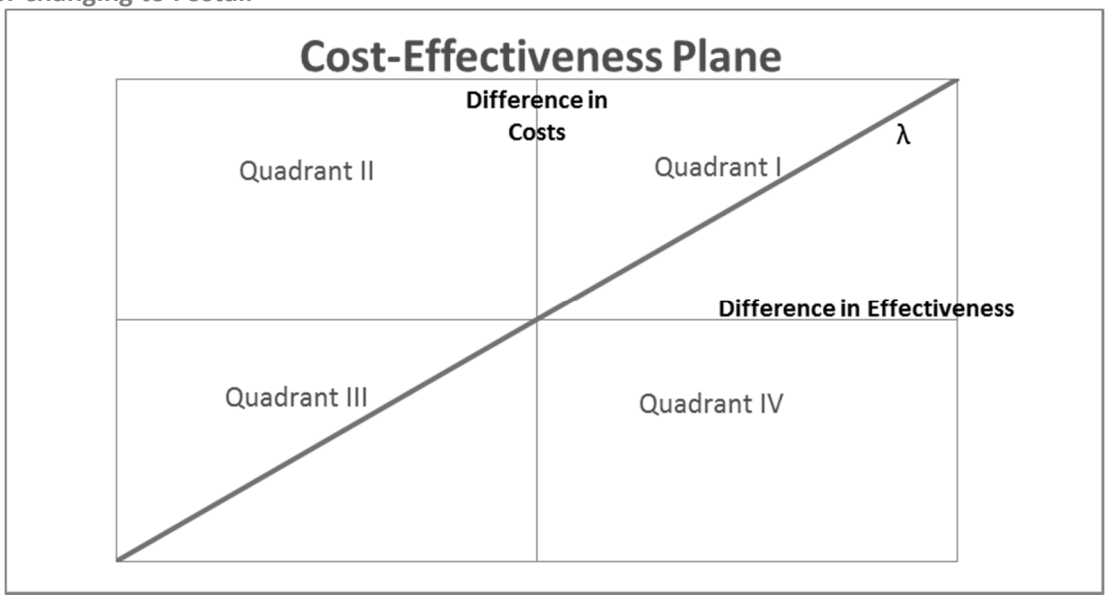

Figure 4: The cost-effectiveness plane.

Mock Tables

Results generated will be presented in tables (and plots where appropriate) under the following headings:

1. Full matched cohort: Initiation (Fostair vs chosen comparator(s))
    - 1.1. Baseline data: All patients
        - 1.1.1. Demographics
        - 1.1.2. Comorbidities and therapies
        - 1.1.3. Baseline characteristics
    - 1.2. Baseline data: Fostair® sub-group
        - 1.2.1. Demographics
        - 1.2.2. Comorbidities and therapies
        - 1.2.3. Baseline characteristics
    - 1.3. Outcome data: All patients
        - 1.3.1. Outcome characteristics
    - 1.4. Outcome data: Fostair® sub-group
        - 1.4.1. Outcome characteristics
    - 1.5. Primary outcome: All patients
    - 1.6. Primary outcome: Fostair® sub-group
    - 1.7. Secondary outcomes: All patients
        - 1.7.1. Respiratory outcomes

1.7.2. Cost-effectiveness outcomes

1.8. Secondary outcomes: Fostair® sub-group

1.8.1. Respiratory outcomes

1.8.2. Cost-effectiveness outcomes

1.9. Exploratory outcomes: All patients

1.10. Exploratory outcomes: Fostair® sub-group

2. Full matched cohort: Change (Fostair vs no change from chosen comparator(s))

2.1. Baseline data: All patients

2.1.1. Demographics

2.1.2. Comorbidities and therapies

2.1.3. Baseline characteristics

2.2. Baseline data: Fostair® sub-group

2.2.1. Demographics

2.2.2. Comorbidities and therapies

2.2.3. Baseline characteristics

2.3. Outcome data: All patients

2.3.1. Outcome characteristics

2.4. Outcome data: Fostair® sub-group

2.4.1. Outcome characteristics

2.5. Primary outcome: All patients

2.6. Primary outcome: Fostair® sub-group

2.7. Secondary outcomes: All patients

2.7.1. Respiratory outcomes

2.7.2. Cost-effectiveness outcomes

2.8. Secondary outcomes: Fostair® sub-group

2.8.1. Respiratory outcomes

2.8.2. Cost-effectiveness outcomes

2.9. Exploratory outcomes: All patients

2.10. Exploratory outcomes: Fostair® sub-group

An example is given in Appendix B: Stage 2 mock tables.

Summary of Statistical Tests

Test	Use
Chi-square (χ^2) test	Tests for the association between two categorical variables (data presented in contingency tables).
Mann-Whitney U test	Nonparametric test to compare the distribution of a variable measured on the interval scale across two groups when the variable is not normally distributed.
Logistic regression model	Used to examine the impact of predictors on the odds of a certain event/outcome.
Conditional Logistic Regression Model	Used to examine the impact of predictors on the odds of a certain event/outcome in a matched analysis.
Ordinal Logistic regression model	Used to examine the impact of predictors on the odds of levels of an ordinal variable having higher / lower ordered values.
Conditional Ordinal Logistic Regression Model	Used to examine the impact of predictors on the odds of levels of an ordinal variable having higher / lower ordered values in a matched analysis.
Odds ratio (OR)	Measure of effect size when the outcome measure is binary (the ratio of two odds). Estimated using logistic regression.
Poisson Regression Model	A form of generalized linear model used to relate one or more predictors to the log of the expected rate of event. Used to model count data such as number of exacerbations.
Conditional Poisson Regression Model	A form of generalised linear model used to relate one or more predictors to the log of the expected rate of event in a matched analysis.
Rate Ratio	A comparison of two Poisson means. Estimated using Poisson Regression.
Generalised Linear Model with gamma distribution and log link	A generalised linear model used to model data where residuals follow a gamma distribution. Used to model expected health care costs.

Table 4: Summary of statistical tests.

Power Calculations

- 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 (Hagedorn, 2013).
- **90%** power will be achieved with 312 subjects per group, given a lower limit of an observed one-sided 95% confidence interval in excess of -0.116 (-20%).
- **80%** power will be achieved with 226 subjects per group, given a lower limit of an observed one-sided 95% confidence interval in excess of -0.116 (-20%).

Timelines

Event	Timescale/Due date*
RiRL to finalise protocol and sent to Chiesi for review	13th March 2015
Chiesi to review protocol and return comments to RiRL	27th March 2015
RiRL to address comments to protocol	3rd April 2015
Data Extraction	17th April 2015
Stage I - Exploratory analysis completed	15th May 2015
Report written and sent to Chiesi	29th May 2015
Approval of final study report by RiRL and Chiesi	19th June 2015
Decision to proceed with Stage 2	26th June 2015
Matching	2 weeks per comparator
Data Extraction (Cost-effectiveness dataset)	2 weeks
Stage II – Outcome analysis (PowerPoint and Word report)	
Primary outcome: Non-inferiority	2 weeks per comparator
Secondary outcome: Respiratory outcomes	2 weeks per comparator
Tertiary outcome: Respiratory-related cost-effectiveness	4 weeks per comparator
Report writing	4 weeks
Steering committee review	3 weeks
First draft of manuscript	6 weeks from approval of final report

*Timelines to be updated and agreed after completion of stage 1.

Research Team

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Research Team: Research in Real Life

Commercial and Compliance Director: Catherine Hutton

Performance Director: Zlatko (Giano) Terzic

Project Co-ordinator: Daina Lim

Research Lead: Sam Thompson

Senior Statistician: Annie Burden

Data Analyst: Derek Skinner

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Appendix A: Stage 1 mock tables

Example medications, for illustrative purposes only. All therapies will be described, including medication, device (if applicable) and dose. These tables will be created for both potential inclusion criteria: ≥1 and ≥2 COPD therapy prescriptions in baseline.

Change/repeat cohorts

Baseline FDC ICS/LABA therapy		**Patients n(% of all patients with FDC ICS/LABA therapy in baseline)**	**Outcome FDC ICS/LABA therapy**	**Patients n(% of baseline group)**
Licensed	Seretide® 500 Accuhaler		Change to Fostair®	
			Remain on baseline therapy	
Unlicensed	Seretide® 50 Evohaler		Change to Fostair®	
			Remain on baseline therapy	
	Seretide® 125 Evohaler		Change to Fostair®	
			Remain on baseline therapy	
	Seretide® 250 Evohaler		Change to Fostair®	
			Remain on baseline therapy	

Table 5: Example table to summarise the number of unique patients following each pathway that includes a change in FDC ICS/LABA therapy for COPD in outcome.

Initiation cohorts

Baseline therapy		**Patients n(% of all patients with FDC ICS/LABA therapy in baseline)**	**Outcome therapy**		**Patients n(% of baseline group)**
Licensed	LABA &/or LAMA		Initiate on Fostair®		
			Initiate on other licensed FDC ICS/LABA	Symbicort® 200 Turbohaler	
				Symbicort® 400 Turbohaler	
				Seretide® 500 Accuhaler	
Unlicensed	SAMA &/or SABA only		Initiate on Fostair®		
			Initiate on other licensed FDC ICS/LABA	Symbicort® 200 Turbohaler	
				Symbicort® 400 Turbohaler	
				Seretide® 500 Accuhaler	

Table 6: Example table to summarise the number of unique patients following each pathway that includes initiation of FDC ICS/LABA therapy for COPD in outcome.

Summary statistics tables

Example table of the baseline demographics to be reported for each baseline therapy (3 shown here as examples), once a choice between ≥1 and ≥2 COPD therapy prescriptions during baseline has been made.

Baseline demographics		Fostair®	Seretide® 500 Accuhaler	Seretide® 250 Evohaler
Age at event date (years)	n (% non-missing)			
	Mean (SD)			
	Median (IQR)			
	Range (Min, Max)			
Age (categorised)	35-54 n (%)			
	55-74 n (%)			
	75+ n (%)			
Gender	n (% non-missing)			
	Male n (%)			
	Female n (%)			
Height (m) – closest to event date	n (% non-missing)			
	Mean (SD)			
	Median (IQR)			
	Range (Min, Max)			
Weight (kg) - closest to event date	n (% non-missing)			
	Mean (SD)			
	Median (IQR)			
	Range (Min, Max)			
BMI (kg/m^2)	n (% non-missing)			
	Mean (SD)			
	Median (IQR)			
	Range (Min, Max)			
BMI (categorised)	Underweight (<18.5) n (%)			
	Normal (18.5-24.9) n (%)			
	Overweight (25.0-29.9) n (%)			
	Obese (≥30) n (%)			
Smoking status – closest to event date in baseline	n (% non-missing)			
	Never n (%)			

	Current n (%)			
	Ex-smoker n (%)			
Year of COPD diagnosis	n (% non-missing)			
	Mean (SD)			
	Median (IQR)			
	Range (Min, Max)			
Duration of COPD diagnosis (years)	n (% non-missing)			
	Mean (SD)			
	Median (IQR)			
	Range (Min, Max)			
Average SABA daily dose (µg)	n (% non-missing)			
	Mean (SD)			
	Median (IQR)			
	Range (Min, Max)			
Lung function severity (GOLD grades)[16]	n (% non-missing)			
	1 n (%)			
	2 n (%)			
	3 n (%)			
	4 n (%)			
GOLD[17] group	n (% non-missing)			
	A n (%)			
	B (n (%)			
	C n (%)			
	D n (%)			
FEV_1/FVC ratio[18]	n (% non-missing)			
	Mean (SD)			
	Median (IQR)			
	Range (Min, Max)			
mMRC score[19]	n (% non-missing)			
	0 n (%)			
	1 n (%)			

[16] Classified by spirometry as 1(Mild), 2(Moderate), 3 (Severe), 4(Very severe), (see variable list for full details).
[17] Global initiative for chronic obstructive lung disease classification based on exacerbation risk, symptoms and spirometry readings combined.
[18] Represents the proportion of a person's vital capacity that they are able to expire in the first second of expiration.
[19] Modified Medical Research Council Dyspnoea Scale (breathlessness scale), (see variable list for full details).

	2 n (%)			
	3 n (%)			
	4 n (%)			
Baseline exacerbation count	n (% non-missing)			
	Mean (SD)			
	Median (IQR)			
	Range (Min, Max)			
Number of oral steroids prescriptions	n (% non-missing)			
	Mean (SD)			
	Median (IQR)			
	Range (Min, Max)			
Number of prescriptions for antibiotics for lower respiratory tract infections	n (% non-missing)			
	Mean (SD)			
	Median (IQR)			
	Range (Min, Max)			
Comorbidities				
Rhinitis[20]	Yes n (%)			
	No n (%)			
	Total n (%)			
Rhinitis diagnosis and/or nasal sprays[21]	Yes n (%)			
	No n (%)			
	Total n (%)			
Gastroesophageal reflux disease (GERD) diagnosis and/or drugs[22]	Yes n (%)			
	No n (%)			
	Total n (%)			
Ischaemic heart disease[20]	Yes n (%)			
	No n (%)			
	Total n (%)			
Eczema[22]	Yes n (%)			
	No n (%)			
	Total n (%)			
Chronic kidney disease[20]	Yes n (%)			
	No n (%)			
	Total n (%)			
Diabetes[22]	Yes n (%)			
	No n (%)			

[20] Read Code at any time
[21] Read Code at any time and/or prescription for nasal spray during baseline period
[22] Read Code in baseline period or diagnosis ever plus medication in the baseline year

	Total n (%)			
Osteoporosis[20]	Yes n (%)			
	No n (%)			
	Total n (%)			
Candidiasis[22]	Yes n (%)			
	No n (%)			
	Total n (%)			
Anxiety and Depression (medications)[23]	Yes n (%)			
	No n (%)			
	Total n (%)			
Pneumonia[20]	Yes n (%)			
	No n (%)			
	Total n (%)			
CCI[24] Score	n (% non-missing)			
	0 n (%)			
	1-4 n (%)			
	5+ n (%)			

Table 7: Summary statistics of patients according to their baseline therapy.

[23] Medication in the baseline year excluding the event date.
[24] Charlson Comorbidity Index – method of classifying prognostic comorbidity, by predicting one-year mortality.

Appendix B: Stage 2 mock tables

Example tables for stage 2 analysis.

Full matched cohort: Initiation (Fostair vs chosen comparator(s))

Baseline data: All patients

Demographics

Baseline demographics: all patients		**Outcome treatment**		**Total**	***p*-value**
		Fostair®	**Alternative therapy**		
Age at event date (years)	n (% non-missing)				
	Mean (SD)				
	Median (IQR)				
	Range (Min, Max)				
Age (categorised)	35-54 n (%)				
	55-74 n (%)				
	75+ n (%)				
Gender	n (% non-missing)				
	Male n (%)				
	Female n (%)				
Height (m) – closest to event date	n (% non-missing)				
	Mean (SD)				
	Median (IQR)				
	Range (Min, Max)				
Weight (kg) – closest to event date	n (% non-missing)				
	Mean (SD)				
	Median (IQR)				
	Range (Min, Max)				
BMI (kg/m^2)	n (% non-missing)				
	Mean (SD)				
	Median (IQR)				
	Range (Min, Max)				
BMI (categorised)	Underweight (<18.5) n (%)				
	Normal (18.5-24.9) n (%)				
	Overweight (25.0-29.9) n (%)				
	Obese (≥30) n (%)				
Smoking status - closest to event date in baseline	n (% non-missing)				
	Never n (%)				
	Current n (%)				
	Ex-smoker n (%)				
	n (% non-missing)				

Year of COPD diagnosis	Mean (SD)				
	Median (IQR)				
	Range (Min, Max)				
Duration of COPD diagnosis (years)	n (% non-missing)				
	Mean (SD)				
	Median (IQR)				
	Range (Min, Max)				
FEV_1 % predicted[25]	n (% non-missing)				
	Mean (SD)				
	Median (IQR)				
	Range (Min, Max)				
No. of prescriptions of the same baseline respiratory medication	n (% non-missing)				
	Mean (SD)				
	Median (IQR)				
	Range (Min, Max)				
No. of prescriptions of the same baseline respiratory medication (categorised)	0 (no medication cohort)				
	1				
	2+				

[25] FEV_1 value as a percentage of the predicted value based on height and weight (see variable list for further details).

Appendix C: Variable List

List of variables for the study. NB 'IPD' or 'event date' refers to the prescription date used to distinguish the baseline and outcome periods.

Variable_Name	Description	Period
Unique_ID	Unique ID for each patient row based on a combination of IPD, Patient_ID and Eventdate (if necessary, Category as well)	N/A
Patient_ID	Unique Patient ID	N/A
Cohort	Initiating Fostair, Initiating other FDC ICS/LABA (specified medication and dose), change to Fostair from other FDC ICS/LABA, continuing on baseline FDC ICS/LABA (specified medication and dose), change to non-Fostair FDC in outcome from unlicensed FDC in baseline	At IPD
Category	Identifies which category of change occurred at the event date for each patient: Init_Fostair, Change_Fostair, Init_FDC, Same_FDC, other_FDC	At IPD
Category_code	1= Init_Fostair, 2=Init_FDC, 3=Change_Fostair, 4=Same_FDC, 5=Change_FDC	At IPD
IP_Date	Index prescription date (IPD)/event date	N/A
Year_of_IPD	Year of IPD/event date	N/A
Practice	Unique identifier/number to designate practice	N/A
Registered	Number of days patient has been registered at practice prior to IPD	Prior to IPD
Age	Age at Event Date (IPD)	At IPD
Age_Group	Age group at event date, defined as 0 (35-54 years); 1 (55-74 years); 2 (75+ years)	At IPD
Gender	0 = FEMALE, 1 = MALE	N/A
Year_of_Birth	Actual year of birth used to calculate age	N/A
Height	Height (m) - closest to IPD	N/A
Weight	Weight (kg) - closest to IPD	N/A
Weight_Date	Closest date of recorded Weight to IPD	N/A
BMI	Calculated BMI for patient - kg / m2	N/A
Smoking_Status	"1 indicates 'Non-smoker', 2 indicates 'Current smoker', 3 indicates 'Ex-smoker', -1 indicates 'Unknown'	Closest prior to IPD
COPD_Diagnosis	Indicate if patient has ever had a COPD read code recorded : 0 = No, 1 = Yes	At any time
COPD_First_Diag	Date COPD first diagnosed	At any time
Dur_COPD_Diag	Duration of COPD diagnosis (years)	At IPD
Rhinitis_Diagnosis	Rhinitis Read Code: 0 = No, 1 = Yes	At any time
Rhinitis_Dx_Nasal_Spray	Indicate if patient has ever had a Rhinitis diagnosis and/or nasal spray prescribed in baseline: 0 = No, 1 = Yes	At any time
Eczema_diag	Indicate if the patient has ever had an eczema Read Code: 1=Yes, 0=No	At any time
Other_Resp_Disease	Indicate if patient has ever had any other chronic pulmonary disease diagnosed : 0 = No, 1 = Yes	At any time
GERD_Diagnosis	Indicate if patient has ever had a GERD Read Code : 0 = No, 1 = Yes	Baseline including IPD
GERD_Dx_Drugs	Indicate if patient has ever received any drugs for GERD (BNF[26] 1.3.5) and/or GERD diagnosis : 0 = No, 1 = Yes	Baseline including IPD
IHD_Diagnosis	Indicate if patient has ever received an ischaemic heart disease Read Code: 0 = No, 1 = Yes	At any time
Hypertension_Dx	Indicate if the patient has ever had a hypertension Read Code: 0=No, 1=Yes	Baseline including IPD

[26] British National Formulary – pharmaceutical reference

Osteoporosis	Indicate if the patient has ever had an osteoporosis Read Code: 0=No, 1=Yes	At any time
CKD	Indicate if the patient has ever had an chronic kidney disease Read Code: 0=No, 1=Yes	At any time
Heart_Failure	Indicate if the patient has ever had a heart failure Read Code: 0=No, 1=Yes	At any time
CVD_Diagnosis	Indicate if the patient has ever had a cardiovascular disease Read Code: 0=No, 1=Yes	At any time
Ba_pneumonia	Indicate is the patient has a confirmed or suspected[27] case of pneumonia: 1=Yes, 0=No	Baseline period including IPD
Out_pneumonia	Indicate is the patient has a confirmed or suspected[27] case of pneumonia: 1=Yes, 0=No	Outcome period excluding IPD
Diabetes_Diagnosis	Indicate if patient has history of diabetes mellitus, defined as diabetes therapy or diagnostic code in the specific period 0=No, 1=Yes	Baseline (Incl IPD)
First_Diabetes_Date	Date of first diabetes diagnostic code EVER	At any time
First_Diabetes_Drug_Date	Date of first script for diabetes therapy EVER	At any time
Diabetes_Test	Indicate if patient had a HbA1c test done in specific period: 0 = No, 1 = Yes	Baseline including IPD
ba_Diabetes_Last_Tested	Date of when the last test was done in baseline period	Baseline period (Incl IPD)
ba_Diabetes_Last_Value	Last value recorded if done in baseline period	Baseline period (Incl IPD)
Insulin_Drug	Indicate if patient received any insulin in specific period: 0 = No, 1 = Yes	Baseline (Incl IPD)
Insulin_Date	Date when patient received FIRST script for insulin in specific period	At any time
Insulin_Scripts	Total number of insulin scripts received in baseline period	Baseline (Incl IPD)
out_Diabetes_Dx	Indicate if the patient has a diabetes diagnosis for the first time ever in outcome: 0=No, 1=Yes	Outcome (excl IPD)
out_Diabetes_Date	Date of first diabetes diagnostic code in outcome	Outcome (excl IPD)
out_Diabetes_Drug_Date	Date of first script for diabetes therapy in outcome	Outcome (excl IPD)
out_Diabetes_First_Tested	Date of when the FIRST HbA1c test was done in outcome period	Outcome (excl IPD)
out_Diabetes_First_Value	First HbA1c value recorded if done in outcome period	Outcome (excl IPD)
out_Diabetes_Eligible	Indicate if patient received a HbA1c test during the 20-180 days during the outcome period: 0 = No, 1 = Yes	Outcome (excl IPD)
Ba_Beta_Blockers	0 = No – none received over period, 1 = Yes – received over period	Baseline including IPD
Out_Beta_Blockers	0 = No – none received over period, 1 = Yes – received over period	Outcome (excl IPD)
Ba_NSAIDS	0 = No – none received over period, 1 = Yes – received over period	Baseline including IPD
Out_NSAIDS	0 = No – none received over period, 1 = Yes – received over period	Outcome (excl IPD)

[27] A diagnostic Read code for pneumonia, diagnosis plus chest x-ray within 1 month of diagnosis or hospitalisation within 1 month of diagnosis.

Ba_Paracetamol	0 = No – none received over period, 1 = Yes – received over period	Baseline including IPD
Out_Paracetamol	0 = No – none received over period, 1 = Yes – received over period	Outcome (excl IPD)
CCI_Score	Calculated using Charlson Comorbidity Index	1 Year Prior & incl IPD
Lung function severity	GOLD grades: 1 (Mild COPD, FEV_1 ≥80% normal); 2 (Moderate COPD, FEV_1 50-79% normal); 3 (Severe COPD, FEV_1 30-49% normal); 4 (Very severe COPD, FEV_1 <30% normal)	Prior to and closest to event date
GOLD group	Group A, B, C or D where GOLD groups are defined as: A = Low risk, low symptom burden (mMRC of 0-1) AND FEV1 of 50% or greater (old GOLD 1-2) AND low exacerbation rate (0-1/year with no hospital admission required), B = Low risk, higher symptom burden (mMRC of 2 or more) AND FEV1 of 50% or greater (old GOLD 1-2) AND low exacerbation rate (0-1/year with no hospital admission required), C = High risk, low symptom burden (mMRC of 0-1) AND FEV1 < 50% (old GOLD 3-4) AND/OR high exacerbation rate (≥2/year or ≥1/year that leads to a hospital admission), D = High risk, higher symptom burden (mMRC of 2 or more) AND FEV1 < 50% (old GOLD 3-4) AND/OR high exacerbation rate ((≥2/year or ≥1/year that leads to a hospital admission)	Prior to and closest to event date
mMRC score	GP recorded mMRC score: Description of Breathlessness -0:I only get breathless with strenuous exercise, 1: I get short of breath when hurrying on level ground or walking up a slight hill, 2: On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace, 3: I stop for breath after walking about 100 yards or after a few minutes on level ground; 4: I am too breathless to leave the house or I am breathless when dressing.	Prior to and closest to event date
Ba_ICS_scripts	No. of ICS scripts during baseline	Baseline excluding IPD
Ba_ICS_Dose	Average mcg daily dose of ICS	Baseline excluding IPD
Ba_ICS_Inhalers	No. of inhalers prescribed during baseline	Baseline excluding IPD
Ba_ICS_Total_Dosage	Based on average number of puffs per day over the year, x mcg (bpd equivalent)	Baseline excluding IPD
Ba_FDC_scripts	No. of repeat FDC ICS/LABA during the 1 year period	Baseline excluding IPD
Ba_ LABA_Scripts	No. of LABA scripts during baseline	Baseline excluding IPD
Ba_LABA_Dose	Total daily dose of LABA (mcg)	Baseline excluding IPD
Ba_LABA_Total_Dosage	Total dosage in micrograms prescribed, based on average number of puffs per day over the year, x mcg	Baseline excluding IPD
Ba_LAMA_Scripts	No. of LAMA scripts during baseline	Baseline excluding IPD
Ba_SABA _Scripts	No. of SABA scripts during baseline	Baseline excluding IPD
Ba_SABA_Inhalers	No. of SABA inhalers	Baseline excluding IPD
Ba_SABA _Daily_Dose	mcg daily dose of SABA prescribed	Baseline excluding IPD
Ba_SABA _Daily_Dosage	Based on average number of puffs per day over the year x mcg	Baseline excluding IPD

Ba_SAMA _Scripts	No. of SAMA scripts during baseline	Baseline excluding IPD
Ba_LTRA _Scripts	No. of LTRA scripts during baseline	Baseline excluding IPD
Ba_THEO _Scripts	No. of THEO scripts during baseline	Baseline excluding IPD
Ba_no_meds	Indicate if patient received no respiratory medication in baseline: 1=TRUE 0=FALSE	Baseline excluding IPD
Out_ICS_scripts	No. of ICS scripts during outcome	Outcome including IPD
Out_ICS_Dose	mcg daily dose of ICS prescribed	Outcome including IPD
Out_ICS_Inhalers	No. of inhalers prescribed	Outcome including IPD
Out_ICS_Total_Dosage	Total dosage in micrograms prescribed in outcome period – BDP	Outcome including IPD
Out_FDC_scripts	No. of repeat FDC ICS/LABA during the 1 year period	Outcome including IPD
Out_FDC_Inhalers	No. of inhalers prescribed	Outcome including IPD
Out_FDC_Device	FDC Device name	Outcome including IPD
Out_LABA_Scripts	No. of LABA scripts during outcome	Outcome including IPD
Out_LABA_Daily_Dose	Total daily dose of LABA (mcg)	Outcome including IPD
Out_LABA_Total_Dosage	Total dosage in micrograms prescribed in outcome period	Outcome including IPD
Out_LAMA_Scripts	No. of LAMA scripts during the 1 year period	Outcome including IPD
Out_SABA _Scripts	No. of SABA scripts during the 1 year period	Outcome including IPD
Out_SAMA _Scripts	No. of SAMA scripts during the 1 year period	Outcome including IPD
Out_LTRA _Scripts	No. of LTRA scripts during the 1 year period	Outcome including IPD
Out_THEO _Scripts	No. of THEO scripts during the 1 year period	Outcome including IPD
ba_COPD_Consults	Count of consultations where COPD was recorded for GP specific type consultations	1 Year Prior & incl IPD
ba_IPD_Consult	Indicate if patient recorded a consultation at IPD or within 7 days after IPD.	IPD or 7 days after
ba_IPD_COPD_Consult	Indicate if patient recorded a COPD consultation at IPD or within 7 days after IPD.	IPD or 7 days after
ba_All_Consults	Count of all the Primary Care consultations	1 Year Prior & incl IPD
ba_COPD_AE	Count of A & E attendances for COPD as well as any admissions with a lower respiratory code	1 Year Prior & incl IPD
ba_COPD_InP	Count of in-patient hospital admissions for COPD as well as any admissions with a lower respiratory code	1 Year Prior & incl IPD
ba_COPD_InP_Vague	Count of in-patient hospital admissions for COPD as well as any admissions with a lower respiratory code and any vague admissions	1 Year Prior & incl IPD
ba_COPD_OPD	Count of all out-patient admissions for COPD as well as any admissions for lower respiratory codes	1 Year Prior & incl IPD

ba_Acute_OS	Count of all acute oral steroid scripts	1 Year Prior & incl IPD
ba_Acute_OS_Courses	Count of courses of acute oral steroid scripts based on excluding scripts within a two week window of each other	1 Year Prior & incl IPD
ba_Total_OS	Total number of all oral steroid courses prescribed – acute and maintenance	1 Year Prior & incl IPD
ba_Maint_OS_Ind	Indicate if patient had maintenance oral steroids in baseline period: 1 = Yes, 0 = No	1 Year Prior & incl IPD
ba_COPD_Exac	Total count of COPD exacerbations in baseline period	1 Year Prior & incl IPD
ba_Antibiotics	Count of all primary care consultations for any lower respiratory event treated with antibiotics	1 Year Prior & incl IPD
ba_Cand_Definite	Count of definite oral candidiasis diagnosed	1 Year Prior IPD
ba_anx_dep	Indicate if patient received any medication for anxiety and/or depression in period: 0 = No, 1 = Yes	1 Year Prior IPD
ba_FDC_Actual_Period	Actual prescription days	1 Year Prior IPD
ba_FDC_Compliance	Based on prescription refills	1 Year Prior IPD
ba_Spacer_Device	Indicate if patient received a spacer device with their inhaler: 0 = No, 1 = Yes	1 Year Prior IPD
out_COPD_Consults	Count of consultations where COPD was recorded for GP specific type consultations	1 Year After IPD
out_All_Consults	Count of all the primary care consultations	1 Year After IPD
out_COPD_AE	Count of A & E attendances for COPD as well as any admissions with a lower respiratory code	1 Year After IPD
out_COPD_InP	Count of in-patient hospital admissions for COPD as well as any admissions with a lower respiratory code	1 Year After IPD
out_COPD_InP_Vague	Count of in-patient hospital admissions for COPD as well as any admissions with a lower respiratory code and any vague admissions	1 Year After IPD
out_COPD_OPD	Count of all out-patient admissions for COPD as well as any admissions with lower respiratory codes	1 Year After IPD
out_Acute_OS	Count of all acute oral steroid scripts	1 Year After IPD
out_Acute_OS_1st	Date of first acute oral steroid script that is prescribed after IPD	1 Year After IPD
out_Acute_OS_Courses	Count of courses of acute oral steroid based on excluding scripts within a two week window of each other	1 Year After IPD
out_Total_OS	Total number of all oral steroid courses prescribed	1 Year After IPD
out_Antibiotics	Count of all primary care consultations for any lower respiratory event treated with antibiotics	1 Year After IPD
out_COPD_Exac	Total count of all COPD exacerbations in outcome period	1 Year After IPD
out_COPD_Exac_1st	Days to first COPD exacerbation	1 Year After IPD
out_COPD_Exac_2nd	Days to second COPD exacerbation	1 Year After IPD
out_COPD_Exac_Excl_Wk1	Days to first COPD exacerbation excluding those in week 1	1 Year After IPD
out_COPD_Exac_Excl_Wk2	Days to first COPD exacerbation excluding those in week 1 and 2	1 Year After IPD
out_Cand_Definite	Count of definite oral candidiasis diagnosed	1 Year After IPD(incl IPD)
out_anx_dep	Indicate if patient received any medication for anxiety or depression in period: 0 = No, 1 = Yes	1 Year After IPD(incl IPD)
out_FDC_Actual_Period	Actual prescription days	1 Year After IPD(incl IPD)

out_FDC_Compliance	Based on prescription refills	1 Year After IPD(incl IPD)
out_Spacer_Device	Indicate if patients were issued with a spacer device: 1 = Yes, 0 = No	1 Year After IPD(incl IPD)
Death	Indicate if patient has a statement of death code: 0 = No, 1 = Yes	At any time
Death_Resp_Def	Indicate if patient had a respiratory read code recorded on day of death: 0 = No, 1 = Yes	Date of death
Death_Resp_Vag	Indicate if patient had a respiratory read code recorded within 7 days prior to or after date of death: 0 = No, 1 = Yes	+/- 7 days of date of death
Death_Date	Date of death if relevant	At any time
ba_FVC	Last FVC value recorded - Read Code = 3396.00	Last recorded prior to & incl IPD
ba_FVC_Ratio	Actual ratio recorded - Read Code = 339M.00 or 339l.00	Last recorded prior to & incl IPD
ba_FVC_Perc	FeV_1 / FVC Ratio Percentage - Read Code = 339R.00	Last recorded prior to & incl IPD
ba_FEV1_Date	Date of FeV_1 value	Closest to IPD
ba_FEV1	Actual FeV_1 value recorded - Read Code = 339O.00	Closest to IPD
ba_FEV1_Prac_Pred	Practice recorded FeV_1 predicted value - Read Code = 339P.00	Closest to IPD
ba_FEV1_Pred	Calculated FeV_1 predicted value based on Roberts formula	Closest to IPD
ba_FEV1_Perc	Calculated FeV_1 percent of value over predicted	Closest to IPD
ba_FEV1_Severity	COPD severity based on FeV_1 percent – using NICE[28] definitions – 1 = 50-80%, 2 = 30-49%, 3 < 30, 0 > 80%, -1 Please Note: Calculated severity taken first, if not available and a practice recorded COPD severity has been entered, then this is used	Closest to IPD
ba_Severity_Date	Date of COPD Severity if recorded by practice - Read Code = H36..00 AS Mild, H37..00 as Moderate, H38..00 as Severe	Last recorded prior to & incl IPD
ba_Severity_Recorded	COPD Severity if recorded by practice - 1 = Mild, 2 = Moderate, 3 - Severe, -1 - not recorded	Last recorded prior to & incl IPD
ba_SABA_Costs	Total 2013/14 costs for SABA scripts in baseline period	1 Year Prior IPD
out_SABA_Costs	Total 2013/14 costs for SABA scripts in baseline period	1 Year After IPD(incl IPD)
ba_ICS_Cost_Rx	Total number of separate ICS scripts prescribed to patient in period	1 Year Prior IPD
ba_ICS_Cost_Inh	Total number of separate ICS inhalers prescribed to patient in period	1 Year Prior IPD
ba_ICS_Costs	Total 2013/14 costs for separate ICS inhalers prescribed to patient in period	1 Year Prior IPD
out_ICS_Cost_Rx	Total number of separate ICS scripts prescribed to patient in period	1 Year After IPD (incl IPD)
out_ICS_Cost_Inh	Total number of separate ICS inhalers prescribed to patient in period	1 Year After IPD (incl IPD)
out_ICS_Costs	Total 2013/14 costs for separate ICS inhalers prescribed to patient in period	1 Year After IPD (incl IPD)
ba_COMBO_Inhalers	Total number of ICS/LABA combination scripts prescribed to patient in period	1 Year Prior IPD
out_COMBO_Inhalers	Total number of ICS/LABA combination scripts prescribed to patient in period	1 Year After IPD (incl IPD)

[28] http://www.nice.org.uk/ The National Institute for Health and Care Excellence.

ba_COMBO_Costs	Total 2013/14 costs for ICS/LABA combination inhalers prescribed to patient in period	1 Year Prior IPD
out_COMBO_Costs	Total 2013/14 costs for ICS/LABA combination inhalers prescribed to patient in period	1 Year After IPD (incl IPD)
ba_LABA_Inhalers	Total number of separate LABA inhalers prescribed to patient in period	1 Year Prior IPD
out_LABA_Inhalers	Total number of separate LABA inhalers prescribed to patient in period	1 Year After IPD (incl IPD)
ba_LABA_Costs	Total 2013/14 costs for separate LABA inhalers prescribed to patient in period	1 Year Prior IPD
out_LABA_Costs	Total 2013/14 costs for separate LABA inhalers prescribed to patient in period	1 Year After IPD (incl IPD)
ba_THEO_Costs	Total 2013/14 costs for Theophylline scripts prescribed to patient in period	1 Year Prior IPD
out_THEO_Costs	Total 2013/14 costs for Theophylline scripts prescribed to patient in period	1 Year After IPD (incl IPD)
ba_SAMA_Inhalers	Total number of SAMA inhalers prescribed to patient in period	1 Year Prior IPD
ba_SAMA_Costs	Total 2013/14 costs for SAMA inhalers prescribed to patient in period	1 Year Prior IPD
out_SAMA_Inhalers	Total number of SAMA inhalers prescribed to patient in period	1 Year After IPD (incl IPD)
out_SAMA_Costs	Total 2013/14 costs for SAMA inhalers prescribed to patient in period	1 Year After IPD (incl IPD)
ba_LAMA_Inhalers	Total number of LAMA inhalers prescribed to patient in period	1 Year Prior IPD
ba_LAMA_Costs	Total 2013/14 costs for LAMA inhalers prescribed to patient in period	1 Year Prior IPD
out_LAMA_Inhalers	Total number of LAMA inhalers prescribed to patient in period	1 Year After IPD (incl IPD)
out_LAMA_Costs	Total 2013/14 costs for LAMA inhalers prescribed to patient in period	1 Year After IPD (incl IPD)
ba_All_Other_Drug_Costs	Total 2013/14 cost for all other drugs given to patient in period	1 Year Prior IPD
out_All_other_Drug_Costs	Total 2013/14 cost for all other drugs given to patient in period	1 Year After IPD (incl IPD)