COMP-AIR

COMParative clinical effectiveness of Fost**AIR** (extrafine beclomethasone/formoterol) versus Symbicort (budesonide/formoterol) as maintenance and reliever therapies in adult patients with asthma

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LIST OF ABBREVIATIONS

Abbreviation or special term	**Explanation**
ACS	American Thoracic Society
A&E	Accident and Emergency
CO2	Carbon dioxide
COPD	Chronic Obstructive Pulmonary Disease
DPI	Dry powder inhaler
ERS	European Respiratory Society
GINA	Global Initiative for Asthma (guidelines)
ICS	Inhaled corticosteroids
LABA	Long-acting beta-2 agonist
LRTI	Lower respiratory tract infection
MART	Maintenance And Reliever Therapy
OPCRD	Optimum and Pragmatic Research Institute
OPRI	Observational and Pragmatic Research Institute
pMDI	Pressurised metered-dose inhaler
SABA	Short-acting beta-2 agonist

1. BACKGROUND & RATIONALE

Asthma is a common long-term health condition, characterized by airflow obstruction, bronchial hyper-responsiveness and inflammation, that accounts for substantial burden of disease, healthcare costs and loss-of-work productivity (1,2).

People with asthma typically require treatment with both high doses of inhaled corticosteroids (ICS) and another controller (and/or systemic corticosteroids) to help with asthma control. Guidelines from the Global Initiative for Asthma (GINA) recommend that moderate-to-severe asthma patients on steps 3 and 4 receive combined therapies that include both ICS and formoterol as both maintenance and reliever therapy (MART) to reduce risk of severe exacerbations (3). ICS has a preventative role by reducing inflammation in asthma patients whereas formoterol is a long-acting β2-receptor agonist (LABA) that is designed to relax the muscles in the airways to give rapid relief of asthma symptoms. Formoterol is typically preferred over other LABAS as it acts as rapidly as short-acting β2-receptor agonists (SABAs) so has the potential to replace them (SABA) (4). Indeed, ICS-formoterol has been found to be safer and more effective than SABA therapies alone (5). Moreover, combined ICS-formoterol inhalers, such as Fostair® 100/6 (beclomethasone diproprionate/formoterol) and Symbicort® (budesonide/formoterol) are preferred over individual ICS and LABA therapies as they require only one inhaler which simplifies the asthma regime and improves patient adherence to the treatment. There is extensive evidence to suggest that patients treated with MART have lower exacerbation rates, oral corticosteroid burden, and emergency/hospital admissions when compared with ICS-based treatment approaches plus as-needed SABA as a reliever therapy (14,15).

Given the rapid adoption of combined ICS-formoterol inhalers, it is crucial that we understand the comparative efficacy of different ICS when combined with formoterol. Fostair®, for example, contains an extra-fine particle formulation of beclomethasone, which results in a more potent effect and equivalent efficacy at lower steroid doses than other ICSs. Therefore, this treatment has the potential to be cheaper and have a more favourable adverse event profile. However, whilst Fostair® has been shown to be comparable to Symbicort® with fixed dose maintenance therapy (6–8), there are no equivalent studies to compare their use as

MART. The current study will provide crucial information on the comparative efficacy of Fostair® and Symbicort® as MART in adults with asthma and generate knowledge in relation to the impact of Fostair® on SABA use. A further novel component of this study is to assess the environmental impact of Fostair® as MART compared with prior SABA use, using information on greenhouse gas emissions for different inhalers (9).

2. STUDY AIMS AND OBJECTIVES

2.1. Study aims

The primary aim of this study is to:

(1) Determine whether Fostair® is comparable (non-inferior) to Symbicort® for MART for exacerbation prevention in adults with asthma.

Secondary aims are to:

(2) Determine whether Fostair® is comparable (non-inferior) to Symbicort® for MART for asthma control (see below definition) in adults with asthma.
(3) Do an exploratory investigation of:
   - the carbon footprint (greenhouse gas emissions) of inhaler use before and after initiation of Fostair® as MART.
   - asthma control (using an alternative UK definition that is not available for all patients) before and after initiation of Fostair® as MART, as measured using the Royal College of Physicians' (RCP) 3 questions (RCP3Qs) (16).

3. STUDY DESIGN

This is a collaborative study between Chiesi (Australia) and OPRI. We will use a retrospective cohort design to compare people taking Fostair® and Symbicort®. Individuals will be weighted

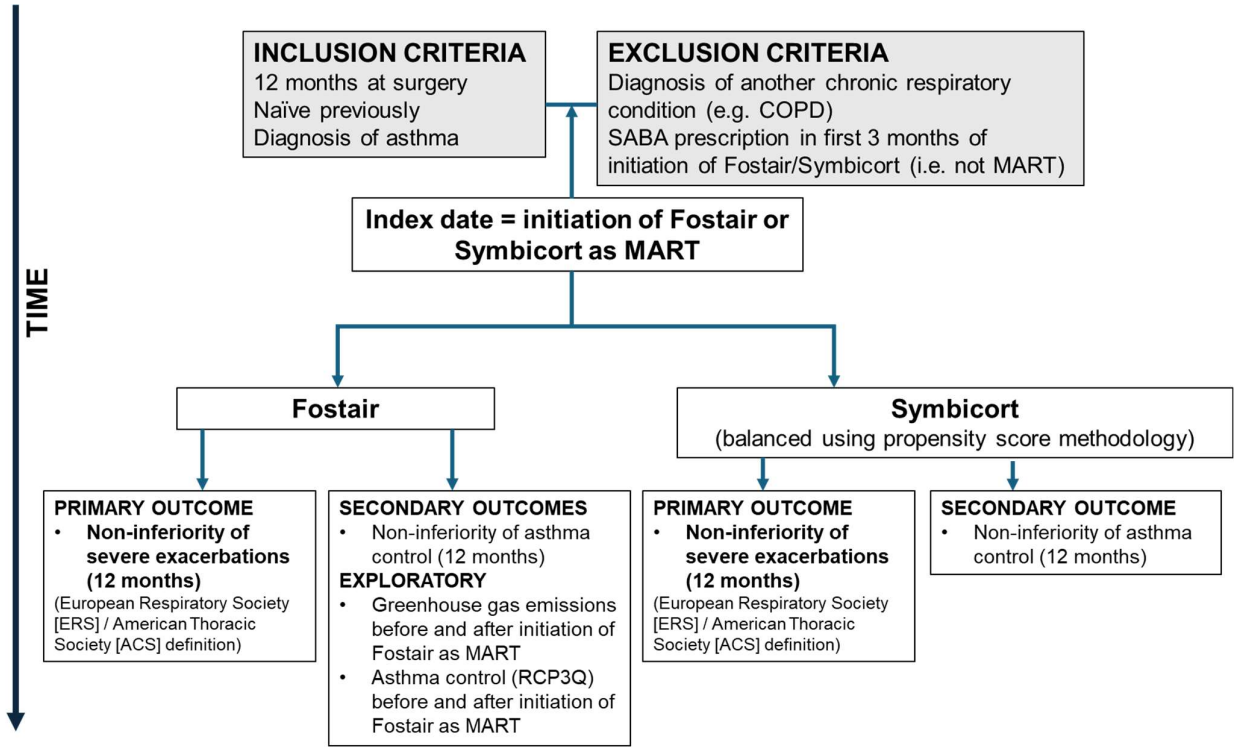
using propensity score methods to balance characteristics in the study (Fostair®) (pMDI, DPI) and comparison (Symbicort®) (pMDI, DPI) populations.

4. STUDY POPULATION

4.1. Data sources

This is a retrospective cohort study using the Optimum Patient Care Research Database (OPCRD). The OPCRD has been described in detail previously (10) but, briefly, is an electronic primary care record database covering more than 1,000 GP surgeries across England, Scotland, Wales and Northern Ireland. All adults (≥18 years) with a diagnosis of asthma and no other additional chronic respiratory condition who initiated Fostair® or Symbicort® as MART for the first time from July 2012 (following the approval of Fostair® for MART in the UK see **Figure 1**) will be selected. Index date will be the date of initiating Fostair® or Symbicort. Individuals will be propensity score weighted (11) such that the chosen characteristics of the individuals are the same in each of the treatment groups (see covariates).

Figure 1: Study design



4.1.2. Eligibility criteria

Inclusion criteria

- Adults (≥18 years) at index date
- 12 months registration at the participating GP surgery prior to index date
- An asthma diagnosis prior to index date
- Initiating Fostair® as MART or Symbicort® as MART for the first time from July 2012

Exclusion criteria

- Diagnosis of another chronic respiratory condition (e.g. COPD) other than asthma
- Symbicort® use prior to July 2012 (i.e. before Fostair® could have been prescribed)

- Prescription for SABA within first 3 months of initiation of Fostair® or Symbicort® - to align with MART definition (i.e. no SABA).

5. STUDY VARIABLES AND STUDY OUTCOME DEFINITIONS

5.1. Outcomes

5.1.1. Primary outcome (Aim 1)

Non-inferiority of severe exacerbation rates (primary aim) is defined as inferiority of no more than 10% worse (relative difference) at the 2.5% (one-sided) level of probability. Severe exacerbation rates will be measured by number of severe exacerbations in the 12 months following treatment initiation in the Fostair® MART and Symbicort® MART group. Severe exacerbations will be defined using definitions from the European Respiratory Society [ERS] / American Thoracic Society [ACS] as:

- An asthma-related hospital attendance/admission and/or
- Asthma-related accident and emergency (A&E) attendance and/or
- Primary care consultation with an acute oral corticosteroid course of ≥3 days

5.1.2. Secondary outcomes (Aim 2)

Non-inferiority of overall asthma control is defined as inferiority of no more than 15% worse (relative difference) at the 2.5% (one-sided) level of probability. Asthma control is defined as:

- No asthma-related hospitalisation
- No acute oral steroid use
- No lower respiratory tract infection (LRTI)

And

- Average salbutamol-equivalent SABA dosage ≤200 µg/day (13)

Exploratory components

- We will compare rates, number and timing of inhalers and total greenhouse gases associated with each inhaler in the 12-month period pre- and 9-month period post-initiation of Fostair® MART (i.e. excluding 3-month SABA exclusion period) using estimates of carbon dioxide (CO_2) per device, broken down by decide type (pMDI or DPI) (9).
- We will investigate asthma control using a different definition for asthma control before and after initiation of Fostair® MART using the Royal College of Physicians (RCP) 3 questions (RCP3Qs) (16) for those patients who attended an asthma clinic with a specialist nurse.

5.2. Exposure

Combined inhaler use with either Fostair® or Symbicort®.

5.3. Covariates

Propensity scores will be generated based on characteristics associated with the exposure (i.e. Fostair® use vs Symbicort® use) and primary outcome (exacerbation): age, gender, index year and baseline asthma-related factors: body mass index (BMI, smoking status, index of multiple deprivation (IMD), asthma maintenance therapy, blood eosinophil count, exacerbations, antibiotic prescriptions, QRISK score, non-emergency asthma consultations, total consultations, vaccinations (influenza, COVID, pneumococcal), comorbidities and other medications. These covariates will also be used for the analysis of asthma control (secondary outcome).

6. STATISTICAL ANALYSIS

The baseline characteristics of the study (Fostair®) and control (Symbicort®) populations will be described in accordance with the inclusion/exclusion criteria before and after probability score balancing methods. Standardised mean differences will be used to compare differences

between characteristics of individuals in the study population and control population (any values of 0.1 will be used to denote imbalance between groups).

Standardised mean differences (SMD) will be used to quantify differences between treatment groups. Propensity scores for treatment with Fostair® (pMDI or DPI) vs Symbicort (pMDI or DPI) MART will be calculated based on sex, age, baseline asthma related factors, including acute courses of oral corticosteroids, average daily SABA dose, non-emergency asthma consultations, year of initiation and calendar quarter of initiation. Inverse probability of treatment weights (IPTW) or other propensity score methods (depending on the balance of covariates) will be used in regression analyses to improve balance between the two groups. The final choice of weighting method will be whichever gives the most balance between groups. Baseline patient characteristics which still show imbalance will be added to the regressions as covariates. Binary outcomes (asthma control) will be compared using logistic regression and exacerbation rates using negative binomial regression.

Non-inferiority will be declared if Fostair® MART is no more than 10% (relative) worse than Symbicort® MART at the 2.5% (one-sided) level of probability, shown by the relevant 95% confidence limit. This will be judged from the upper 95% confidence limit for the incidence rate ratio for exacerbations, and from the lower 95% confidence limit for the odds ratio for the overall asthma control.

The RCP3Q scores pre- and post- initiation of Fostair® will be compared using a Wilcoxon matched pairs signed rank test.

Estimates of greenhouse gas emissions before and after initiation of Fostair as MART will be derived from the number and dates of SABA and Fostair inhalers used and will be descriptive only. The assessment of asthma control using the RCP3Q measure before and after initiation of Fostair as MART will also use descriptive statistics.

6.1. Sample size

With sample sizes of 16,165 Symbicort® patients and 26,607 Fostair® patients (see section on feasibility counts below), the study will have 97% power to demonstrate non-inferiority in

follow-up exacerbation rates with a non-inferiority margin of 10% and a one-sided probability of 0.025 (i.e. 2.5% significance level), assuming a mean exacerbation rate of 1.0 per year in the Symbicort® patients and that the two products are equally effective. The study power remains at >90% when the probability is lowered to 0.005 (i.e. 0.5% significance level for a one-sided test).

6.2. Feasibility counts

We have identified 26,607 adults that meet the eligibility criteria initiating Fostair as MART during the observation period and 16,165 initiating Symbicort (as at: 19 Nov 2024). Please see **Figure 2** for the feasibility count diagram.

Figure 2: Feasibility count on OPCRD to November 2024 * see Appendix 12.1 for MART algorithm

	Number of patients					
	Fostair	%	Symbicort	%	Overall	%
MART Prescriptions	105,546	100.00%	153,544	100.00%	259,090	100.00%
First prescription from 01 July 2012	93,782	88.85%	68,842	44.84%	162,624	62.77%
Asthma diagnosis prior to index date	79,385	75.21%	55,926	36.42%	135,311	52.23%
Aged at least 18 at index date	78,692	74.56%	49,971	32.55%	128,663	49.66%
12 months baseline data available	62,124	58.86%	35,028	22.81%	97,152	37.50%
No diagnosis of COPD or other respiratory conditions (in the 2 years prior to index and 1 year post index)	41,949	39.74%	22,854	14.88%	64,803	25.01%
No SABA use at follow-up	26,607	25.21%	16,165	10.53%	42,772	16.51%

6.3. Software

A combination of SQL Management Studio and Stata v15.1 (12) will be used for this analysis.

7. REGULATORY AND ETHICAL COMPLIANCE

This work requires ADEPT approval for use of OPCRD data.

8. DATA DISSEMINATION

Preliminary findings from this study will be presented at the European Respiratory Society (ERS) Conference in February 2025. The work will be published in a peer-reviewed journal in August 2025 (see Timelines).

9. TIMELINES

Action	Timeline
Protocol finalised	31 October 2024
Protocol sign-off by Directors, and sent to Chiesi AU	15 November 2024/16 November 2024
Dataset Creation	18th November 2024
Baseline characteristics (demographics)	29 November 2024
Dataset delivery + ADEPT (if OPCRD or ISAR data is used) approval	15 Dec 2024
Abstract for exploratory analysis for submission to REG	5 Jan 2025
Interim results slide deck (severe exacerbations)	15 Jan 2025
Full Results Slide deck	30 Jan 2025
Final study report	01 March 2025
Study report sign-off+ sent	30 March 2025
Conference abstract	ERS: February 2025
Publication	August 2025

10. VERSION HISTORY

Version	Date	Authors

1.0	16 Oct 2024	Freya Tyrer
1.1	29 Oct 2024	Freya Tyrer, Shelly Pathak
1.2	31 Oct 2024	Comments from David Price, John Townend, Victoria Carter
2.0	6 Nov 2024	Internal sign-off of protocol for wider circulation
2.1	14 Nov 2024	Freya Tyrer, Shelly Pathak, Alexander Roussos, Cono Ariti, John Townend, Victoria Carter, David Price
2.2	18 Nov 2024	John Townend, Ravina, Ravi, Coni Ariti, Maureen Tham

11. REFERENCES

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020; 396(10258):1204–22.
2. Global Asthma Network. The global asthma report. 2022.
3. Levy ML, Bacharier LB, Bateman E, Boulet LP, Brightling C, Buhl R, et al. Key recommendations for primary care from the 2022 Global Initiative for Asthma (GINA) update. NPJ Prim Care Respir Med. 2023; 33(1):7.
4. Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, et al. Global Initiative for Asthma Strategy 2021: Executive Summary and Rationale for Key Changes. Am J Respir Crit Care Med. 2022; 205(1):17–35.
5. Beasley R, Bruce P, Houghton C, Hatter L. The ICS/Formoterol Reliever Therapy Regimen in Asthma: A Review. J Allergy Clin Immunol Pract. 2023; 11(3):762-772.e1.
6. Kardos P. Budesonide/formoterol maintenance and reliever therapy versus free-combination therapy for asthma: a real-life study. Pneumologie. 2013; 67(8):463–70.
7. Zhong N, Lin J, Mehta P, Ngamjanyaporn P, Wu TC, Yunus F. Real-life effectiveness of budesonide/formoterol maintenance and reliever therapy in asthma patients across Asia: SMARTASIA study. BMC Pulm Med. 2013; 13(1):22.

8. Tunceli O, Williams SA, Kern DM, Elhefni H, Pethick N, Wessman C, et al. Comparative Effectiveness of Budesonide-Formoterol Combination and Fluticasone-Salmeterol Combination for Asthma Management: A United States Retrospective Database Analysis. J Allergy Clin Immunol Pract. 2014; 2(6):719-726.e6.

9. Alzaabi A, Bell JP, Montero-Arias F, Price DB, Jackson DJ, Wang HC, et al. Greenhouse Gas Emissions from Respiratory Treatments: Results from the SABA CARBON International Study. Adv Ther. 2023; 40(11):4836–56.

10. Lynam A, Curtis C, Stanley B, Heatley H, Worthington C, Roberts EJ, et al. Data-Resource Profile: United Kingdom Optimum Patient Care Research Database. Pragmat Obs Res. 2023; 14:39–49.

11. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015; 34(28):3661–79.

12. Stata Statistical Software: Release 15.1. StataCorp. College Station,TX; 2017.

13. Colice G, Chisholm A, Dima AL, Reddel HK, Burden A, Martin RJ, Brusselle G, Popov TA, von Ziegenweidt J, Price DB. Performance of database-derived severe exacerbations and asthma control measures in asthma: responsiveness and predictive utility in a UK primary care database with linked questionnaire data. Pragmat Obs Res. 2018; 9:29–42.

14. Jenkins CR, Bateman ED, Sears MR, O'Byrne PM. What have we learnt about asthma control from trials of budesonide/formoterol as maintenance and reliever? Respirology. 2020; 25(8):804-815.

15. Sobieraj DM, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, et al. Association of Inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma. JAMA. 2018; 319:1485-1496.

16. Thomas M, Gruffydd-Jones K, Stonham C, Ward S, Macfarlane TV. Assessing asthma control in routine clinical practice: use of the Royal College of Physicians '3 questions'. Prim Care Respir J. 2009;18(2):83-88. doi:10.3132/pcrj.2008.00045

12. APPENDICES

12.1. Definition of MART

MART is derived by the clinical and database team at OPRI. This involves:

- A review all ICS-LABA prescriptions that have been licensed for SMART/MART regimen use with a focus on the text dosage (free text field) to indicate if they were prescribed as a MART/SMART regimen.
- Allocating a flag to each regimen to indicate the level of certainty based on text dosage:
    - 1. Definitely MART: text dosage and regimen reviewed by clinician who has indicated that this is a MART/SMART prescription
    - 2. Very probably MART: SMART/MART is explicitly stated in the free text instructions given by the clinician
    - 3. Probably MART: prescription states a defined regimen (e.g. take 2 puffs each morning) but also refers to increasing the regimen to reduce exacerbation of symptoms