Study Report

Real-world use of Breztri/Trixeo for the management of COPD in a UK primary care population

An observational, historical cohort study to evaluate the acceptability of budesonide / glycopyrrolate / formoterol (Breztri/Trixeo) for the management of chronic obstructive pulmonary disease using the OPCRD database

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Table of contents

List Of Abbreviations

Abbreviation or special term	Explanation
ADEPT	Anonymised Data Ethics & Protocol Transparency Committee
AZ	AstraZeneca
BMI	Body Mass Index
CAT	Chronic obstructive pulmonary disease Assessment Test
COPD	Chronic obstructive pulmonary disease
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FEV_1	Forced Expiratory Flow in one second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	Inhaled Corticosteroids
LABA	Long Acting β adrenoceptor Agonists
LAMA	Long-Acting Muscarinic Receptor Antagonists
MACRE	Major cardiac and respiratory events
mMRC	Modified Medical Research Council dyspnoea questionnaire
NICE	National Institute for Health and Care Excellence
OCS	Oral Corticosteroids
OPC	Optimum Patient Care
OPCRD	Optimum Patient Care Research Database
OPRI	Observational and Pragmatic Research Institute
PRO	Patient-reported outcome
SABA	Short-Acting Beta-Agonists
SAMA	Short-Acting Muscarinic Antagonist
UK	United Kingdom

1 Executive Summary

1.1 Introduction

The current, stepwise management approach of patients with stable chronic obstructive pulmonary disease (COPD) involves the use of long-acting beta-agonists (LABA), long-acting muscarinic antagonists (LAMA), and/or inhaled corticosteroids (ICS) depending on patients' disease severity and symptomatology. In particular, dual therapies, namely LAMA+LABA or ICS+LABA, are recommended for highly symptomatic patients with moderate to severe COPD. Nonetheless, some patients remain symptomatic and suffer from exacerbations despite using dual therapies. Hence, recent years have seen the emergence of triple therapies (LABA+LAMA+ICS), such as budesonide/glycopyrrolate/formoterol (Breztri/Trixeo). Following demonstration of efficacy by randomized controlled trials, Breztri/Trixeo has been approved by the United States' Food and Drug Administration on 23rd July 2020, and by the European Medicines Agency on 9th December 2020. Nevertheless, as a new medication, real-life evidence underlying the safety, acceptability, and efficacy of Breztri/Trixeo is limited. Given that findings from randomized controlled trials may only be applicable to a subset of patients in real life, this study seeks to investigate the patient acceptability and describe clinical outcomes of Breztri/Trixeo amongst patients with COPD in the early period after launch using a large general practice database in the United Kingdom.

1.2 Study objective

This study aimed to describe the acceptability and clinical outcomes of Breztri/Trixeo amongst patients with COPD.

1.3 Methods

This was a historical cohort study of COPD patients who were early adopters of Breztri/Trixeo within the OPCRD and recruited general practice. Patients' electronic medical records will be extracted from general practices from the Optimum Patient Care Research Database (OPCRD). In addition, 11 general practices which were early adopters from England National Prescribing Data in the United Kingdom (UK) were recruited as part of the targeted Breztri/Trixeo site recruitment by the Optimum Patient Care (OPC). This recruitment was done as part of the quality improvement program by OPC. Selected patient-reported outcome (PRO) data can be extracted from the data collected as part of the quality improvement program where available. The exposure was defined as at least one prescription of Breztri/Trixeo.

Patients fulfilling all of the following criteria were included: 1) received at least one prescriptions of Breztri/Trixeo from the start of data availability up to 90 days prior to the date of data extraction, which is expected to be in November 2022 by the latest; and 2) ever record with any diagnostic code for COPD; and 3) aged at least 40 years old at index date; and 4) ever recorded to be an ex-smoker or current smoker; and 5) with at least one year of continuous practice data prior to index date; and 6) had 90-day medication persistence, as defined by having received at least one further prescription of Breztri/Trixeo without any other LABA- / LAMA- / ICS-containing prescription within 90 days of the first prescription of Breztri/Trixeo. Patients who were ever recorded with any diagnostic code for other chronic lower respiratory conditions were excluded, with the exception of asthma.

The index date was the date of Breztri/Trixeo initiation. All patients were followed up until 21st October 2022 or death, whichever occurred first. The primary outcome was medication success assessed at 90 days (early medication success) after Breztri/Trixeo initiation, which was a binary, composite outcome defined as fulfilling all of the following:

1. No major cardiac and respiratory events (MACRE), defined as not having any of the below events:
    - New diagnosis of heart failure; or
    - Hospitalization for heart failure; or
    - Myocardial infarction; or
    - Hospitalization for respiratory events; or
    - Complicated COPD exacerbations, as defined by exacerbations which require hospitalization or treatment with acute doses of oral corticosteroids and/or antibiotics between 8 and 28 days after the start of the initial event (i.e., the date of coding for COPD exacerbation); or
    - All-cause mortality.
2. No pneumonia, defined as a physician diagnosed pneumonia that was confirmed with a chest radiograph or hospital admission within one month of diagnosis

Medication success was to be claimed if the proportion of patients who meet the primary outcome of medication success was demonstrated to be ≥70% (i.e., if the lower 95% confidence limit for the percentage is ≥70%), which has been considered in previous publications to be a clinically meaningful limit.

Exploratory outcomes included the following:

1. Patient demographics and clinical characteristics at Breztri/Trixeo initiation and during follow-up
2. In a subset, for patients with CAT score available at both baseline and follow-up, changes in CAT score, stratified by whether patients switched to Breztri/Trixeo from another triple therapy regimens or stepped up from non-triple therapy. Clinically meaningful changes in CAT score were defined as changes by at least 2 points in CAT score.
3. Factors associated with the primary outcome (early medication success) and with change in CAT score after 90 days
4. Medication success assessed at 180 days. The definition of medication success was the same as the above.
5. Amount of short-acting beta-agonist (SABA) use based on collected prescriptions, and calculated as $\frac{Count\ of\ inhaler\ doses\ (pack\ mg\ strength)}{duration\ of\ follow\text{-}up\ in\ days}$, and expressed as salbutamol equivalent in mg/day.
6. Acceptability of medication change, as defined by the percentage of patients receiving at least one additional prescription for Breztri/Trixeo during the follow-up period.
7. Adherence, as represented by the MPR which will be calculated as the ratio of total Breztri/Trixeo pack days (i.e., total number of days' equivalent of Breztri/Trixeo prescribed) to the number of prescription days (i.e., total number of days from Breztri/Trixeo initiation to the last day of prescription), and which was expressed as a percentage.
8. The overall number of inhalers used (fixed triple, free triple, or SABA).
9. Change in COPD control assessed at a minimum of 90 days after index date.
10. Change in exercise capacity assessed at a minimum of 90 days after index date.

Primary and exploratory outcomes were summarised as means, medians or percentages as appropriate with 95% confidence intervals. For the primary outcome, medication success was claimed if the lower 95% confidence limit for the percentage achieving success, assessed at 90 days after Breztri/Trixeo initiation, was ≥ 70%; this has been considered in previous publications to be a clinically meaningful limit. Exploratory outcomes were summarised separately for both 90 days and 180 days, unless otherwise specified. Additionally, an exploratory analysis was carried out to try to identify factors associated with the primary outcome (early medication success) and with change in CAT score at 90 days.

1.4 Results

Of the 737 patients receiving a Breztri/Trixeo prescription in OPCRD by 24 Oct 2022, 285 patients were analysed after applying the inclusion and exclusion criteria (131 males (46.0%); median age 69.8 (interquartile range 62.7-77.3) years old).

1.5 Primary outcome

At 90 days, 275 patients (96.5%, 95% confidence interval: 93.6%, 98.3%) achieved medication success. As the lower 95% confidence interval was ≥70%, overall medication success was achieved. Of the 10 patients who did not achieve 90-day medication success, one (10%; 0.4% of all patients) had a new diagnosis of heart failure, one (10%; 0.4% of all patients) had myocardial infarction, three (30%; 1.1% of all patients) had hospitalization for respiratory events, and five (50%; 1.8% of all patients) had a complicated COPD exacerbation. Subgroup analysis by prior asthma status, switching from another triple therapy vs stepping up from non-triple therapy, and by prior exacerbation history showed consistent results, with overlapping confidence intervals signifying that these factors had no meaningful impact on the proportion of patients achieving 90-day medication success.

1.6 Exploratory outcomes

1.7 Patient demographics and clinical characteristics

Patient demographics and clinical characteristics prior to Breztri/Trixeo initiation were described.

1.8 Changes in CAT score

In total, 68 patients had follow-up scores at least 90 days after Breztri/Trixeo initiation, whose baseline CAT score was recorded a median of 84.5 days prior to Breztri/Trixeo initiation, and whose follow-up score was recorded a median of 250.5 days after Breztri/Trixeo initiation. 90-day CAT score (median CAT score 24 [interquartile range: 18-30]) was significantly higher ($p<0.001$) than that at baseline (median CAT score 19 [interquartile range: 15.5-25.5]). The median change in 90-day CAT score was 3 (interquartile range: -0.5-8; 95% confidence interval of median: 1, 5). 14 patients (20.6%)

had clinically meaningful (≥2 points) decreases in CAT score, 13 (19.1%) had no clinically meaningful change (≤1 point), and 41 (60.3%) had clinically meaningful increases.

Similarly, 50 patients had follow-up scores at least 180 days after Breztri/Trixeo initiation, whose baseline CAT score was recorded a median of 65.5 days prior to Breztri/Trixeo initiation, and whose follow-up score was recorded a median of 300 days after Breztri/Trixeo initiation. 180-day CAT score (median CAT score 24 [interquartile range: 18-30]) was significantly higher (p<0.001) than baseline (median CAT score 19 [interquartile range: 16-24]). The median change in 180-day CAT score was 4 (interquartile range: -1-9; 95% confidence interval of median: 0, 6). 10 patients (20%) had clinically meaningful decreases in CAT score, 9 (18%) had no clinically meaningful change, and 31 (62%) had clinically meaningful increases.

1.9 Factors associated with the primary outcome and with changes in CAT score

Univariable logistic regression found that older age was associated with significantly higher odds of achieving 90-day medication success, while inactive asthma, evidence of asthma before age 40, higher number of acute OCS prescriptions in the baseline year, and higher average daily dose of SABA prescription in the baseline year were associated with lower odds of achieving 90-day medication success. Multivariable logistic regression with LASSO on the 200 patients with all candidate baseline variables available selected daily dose of SABA prescription in the baseline year (odds ratio per mcg/day increase: 1.00 [1.00, 1.00], p=0.007) as the only variable in the predictive model.

Univariable logistic regression found that a higher baseline CAT score was associated with larger decreases in CAT score (coefficient -0.47 [-0.67, -0.27], p<0.001). Both forward stepwise linear regression and LASSO (using any selection criterion) on the 80 patients with all candidate baseline variables available selected baseline CAT score as a predictor of changes in CAT score, with higher baseline CAT score associated with larger decreases in CAT score (coefficient -0.51 [-0.72, -0.31], p<0.001).

An additional exploratory analysis was performed to construct a multivariable logistic model predicting clinically meaningful improvements (≥2 points' decrease) in CAT score as the dependent variable. LASSO selected only baseline CAT score for the predictive model (odds ratio 1.15 [1.05, 1.25], p=0.002).

1.10 Medication success assessed at 180 days

In total, 184 of 285 patients (64.6%) completed 180-day follow-up. At 180 days, 169 patients (91.8%, 95% confidence interval: 86.9-95.4%) achieved medication success. Of the 15 patients who did not achieve 90-day medication success, two had a new diagnosis of heart failure (13.3%; 1.1% of the 184 patients who completed 180-day follow-up), two had hospitalization for respiratory events (13.3%; 1.1% of the 184 patients who completed 180-day follow-up), one had pneumonia (6.7%; 1.1% of the 184 patients who completed 180-day follow-up), and 10 had complicated COPD exacerbation (66.7%; 5.4% of the 184 patients who completed 180-day follow-up).

1.11 Amount of SABA used

The average proportions of patients who used an average SABA dose of 0<101 mcg/day, 101<201 mcg/day, 201<301 mcg/day, 301<401 mcg/day, and >401 mcg/day at 90 days were 38.3%, 0%, 13.7%, 0.4%, and 47.7%, respectively, while those at 180 days were 33.3%, 8.4%, 7.4%, 7.0%, and 43.9%, respectively.

1.12 Acceptability of medication change

The number of Breztri/Trixeo prescriptions after initiation was taken as a surrogate of the acceptability of medication change. At 90 days, 26.3% of patients had received two Breztri/Trixeo prescriptions, 34.0% had received three, 32.6% had received four, and the rest had received more. At 180 days, 10.9% of patients had received two Breztri/Trixeo prescriptions, 17.5% had received three, 12.3% had received four, 17.5% had received five, 17.2% had received six, 15.8% had received seven, and the rest had received more.

1.13 Adherence

The medication possession ratio throughout the study period was taken as a surrogate for adherence. In total, 2.5% of the patients had a medication possession ratio of 25<50%, 15.8% had a ratio of 50<75%, 30.5% had a ratio of 75<100%, 40% had a ratio of 100<125%, and the rest had higher ratios.

1.14 Overall number of inhalers used

The proportions of patients who used 0, 1-2, 3-6, 7-10, and >10 inhalers at 90 days were 33.3%, 33.3%, 29.5%, 3.5%, and 0.4%, respectively, while those at 180 days were 26.3%, 20.4%, 36.9%, 10.2%, and 6.3%, respectively.

1.15 Change in COPD control

Amongst the nine patients with available data for COPD control both before and after initiation of Breztri/Trixeo, eight (88.9%) had poor control before initiation of Breztri/Trixeo, with the same observed after initiation of Breztri/Trixeo. The two-sided sign test indicated that patients' COPD control were not significantly different following Breztri/Trixeo initiation (p=1.000).

1.16 Change in exercise capacity

Amongst the 33 patients with available data for changes in exercise capacity after initiation of Breztri/Trixeo, three (9.1%) reported that they exercised more often following Breztri/Trixeo initiation, 12 (36.4%) reported that they exercised less often, while 18 (54.6%) reported no difference. The two-sided sign test indicated that patients exercised significantly less often following Breztri/Trixeo initiation (p=0.035).

1.17 Conclusion

Breztri/Trixeo achieved overall medication success, with the vast majority of patients with COPD that were prescribed Breztri/Trixeo having early (90-day) and sustained (180-day) medication success. Baseline daily dose of SABA prescription may be a predictor of early medication success in these patients. However, CAT scores increased significantly following Breztri/Trixeo use, and patients may exercise less often after Breztri/Trixeo initiation. Larger studies with control groups are required to verify these findings.

2 Background

Chronic obstructive pulmonary disease (COPD) is a prevalent public health problem, affecting an estimated 10.3% of all people aged 30-79 years old globally in 2019 which translated to 391.9 million patients with COPD.[1] In 2010 alone, COPD incurred USD32 billion in direct costs and USD20.4 billion in indirect costs in the United Sates.[2] Current management of stable COPD takes a stepwise approach, with regimens consisting of long-acting beta-agonists (LABA), long-acting muscarinic antagonists (LAMA), and/or inhaled corticosteroids (ICS) depending on patients' disease severity as measured by the numbers of moderate exacerbation or COPD hospitalization, and symptomatology as measured by the COPD Assessment Test (CAT) or the modified Medical Research Council dyspnoea questionnaire (mMRC).[3] Dual therapies, namely a combination of LAMA+LABA or ICS+LABA, are recommended for highly symptomatic (CAT score ≥10 or mMRC ≥2) patients with at least two moderate exacerbations or any COPD hospitalization in a year.[3] The National Institute for Health and Care Excellence (NICE) guidelines largely echoed the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline in that dual therapies are to be used for more severe patients.[4]

Nonetheless, some patients remain symptomatic or continue to suffer from COPD exacerbations despite using dual therapies. Although "open triple" therapies, referring to separate prescriptions of LABA+LAMA+ICS have been used clinically by some clinicians, "fixed triple" therapies, where LABA+LAMA+ICS are available as a single medication such as budesonide/glycopyrrolate/formoterol (Breztri/Trixeo), have been explored as a potential option for these patients. In 2018, the KRONOS trial first demonstrated superiority of Breztri/Trixeo over corresponding dual therapies in terms of lung function improvement in patients with moderate to very severe COPD.[5] This was followed by the ETHOS trial in 2020 which reported significant superiority of Breztri/Trixeo over monotherapies and dual therapies in patients with moderate to very severe COPD, resulting in significantly less COPD exacerbation without significant differences in adverse events.[6] Following these, Breztri/Trixeo was approved by the United States' Food and Drug Administration for maintenance treatment of patients with COPD on 23rd July 2020,[7] followed by approval by the European Medicines Agency for maintenance treatment in adult patients with moderate to severe COPD not adequately treated by a combination of ICS and LABA or LABA+LAMA on 9th December 2020.[8] The 2023 GOLD guideline also recommended triple therapy over ICS/LABA therapy.[9]

Commented [JC1]: Inserted as per Hana's request -- please note the previous paragraph was about dual therapy and not triple

It has been shown that due to the highly controlled and experimental settings of randomized controlled trials, findings from these trials require further contextualization in real life clinical settings.[10,11] Hence, despite strong evidence from the KRONOS and ETHOS trials indicating the clinical efficacy of Breztri/Trixeo, real-life evidence of the acceptability and clinical outcomes of Breztri/Trixeo remains an important area of investigation. As a relatively new medication, real-life evidence for Breztri/Trixeo is exceedingly scarce, further highlighting the need for observational studies evaluating the acceptability and efficacy of Breztri/Trixeo.

3 Study Objectives

3.1 Primary objective

To evaluate medication success at 90 days after Breztri/Trixeo initiation.

3.2 Exploratory objectives

1. To describe patient characteristics at Breztri/Trixeo initiation and during follow-up
2. To compare CAT scores before Breztri/Trixeo use and 90 days after Breztri/Trixeo initiation in a subset of patients for whom CAT scores are available at both baseline (nearest reading in the 24 months prior to the index date) and follow-up
3. To identify factors associated with the primary outcome (early medication success) and with change in CAT score after 90 days
4. To explore medication success at 180 days after Breztri/Trixeo initiation
5. To describe the amount of short-acting beta-agonists (SABA) used during the first 90 days after Breztri/Trixeo initiation
6. To describe acceptability of medication change at 90 days after Breztri/Trixeo initiation
7. To describe adherence, as represented by the medication possession ratio (MPR), during the first 90 days after Breztri/Trixeo initiation
8. To describe the overall number of inhalers used (fixed triple, free triple, or SABA) during the first 90 days after Breztri/Trixeo initiation
9. To explore changes in COPD control assessed at a minimum of 90 days after index date
10. To explore changes in exercise capacity assessed at a minimum of 90 days after index date

4 Materials and Methods

4.1 Data source

Patients' electronic medical records were extracted from general practices from the Optimum Patient Care Research Database (OPCRD). In addition, 11 general practices which were early adopters from England National Prescribing Data in the United Kingdom (UK) were recruited as part of the targeted Breztri/Trixeo site recruitment by the Optimum Patient Care (OPC). This recruitment was done as part of the quality improvement program by OPC. Selected patient-reported outcome (PRO) data can be extracted from the data collected as part of the quality improvement program where available (**Error! Reference source not found.**).

The OPCRD comprises data extracted through the OPC Clinical Service Evaluation. At the time of writing, OPCRD contains anonymized, research-quality data for approximately 16.4 million patients across the UK. The OPCRD encodes diagnostic, prescription and procedural data using SNOMED-International codes, SNOMED-UK codes, Read codes v2 and v3, and ICD-10 codes. The OPCRD database is approved by the Health Research Authority for clinical research use (Research Ethics Committee reference: 15/EM/0150), is governed by the Anonymised Data Ethics & Protocol Transparency (ADEPT) Committee, and offers a high-quality data source that is used regularly in clinical, epidemiological and pharmaceutical research.

4.2 Study design

This was a historical cohort study of COPD patients of Breztri/Trixeo within the OPCRD and recruited general practice from the start of data availability up to 21st October 2022.

The **index date** was the date of Breztri/Trixeo initiation.

The **baseline period** encompassed the entire period available for each patient prior to the index date and was at least one year; the baseline period for FEV1, percentage predicted FEV1, FEV1:FVC ratio, mMRC score, and GOLD grouping. The most recent CAT score any time prior to the index date was used as the baseline measurement to maximise the number of patients who could be included in this analysis. Sensitivity analyses were carried out to assess the effect of only including patients with a baseline score <2 years prior to the index date.

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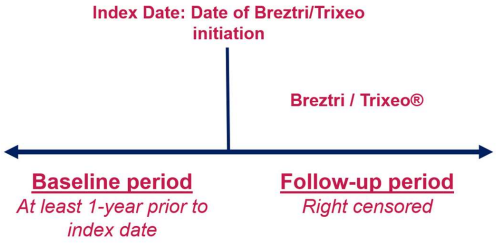
The **enrolment period** started at the date of Brexti/Trixeo launch in the UK and ended 90 days before the end of data availability. For exploratory objective 4 the enrolment period ended 180 days before the end of data availability.

The **follow-up period** started at the date of Brexti/Trixeo launch in the UK and ended at the end of data availability. The study design is briefly illustrated in Figure 1.

Figure 1 Study design



4.3 Inclusion and exclusion criteria

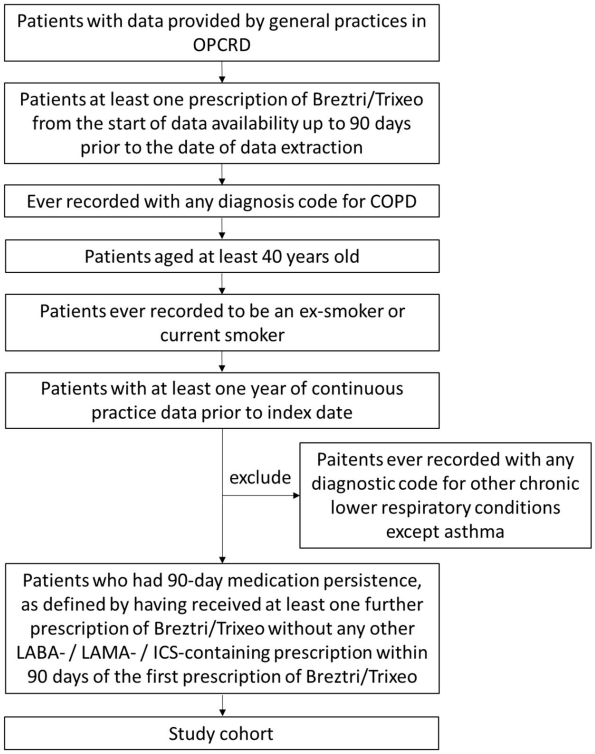
Patients fulfilling all of the following inclusion criteria were identified:

1. Received at least one prescription of Breztri/Trixeo from the start of data availability up to 90 days prior to the date of data extraction, which is expected to be in November 2022 by the latest; and
2. Ever recorded with any diagnostic code for COPD during baseline; and
3. Aged at least 40 years old at index; and
4. Ever recorded to be an ex-smoker or current smoker during baseline; and
5. With at least one year of continuous practice data prior to index date; and
6. Had 90-day medication persistence, as defined by having received at least one further prescription of Breztri/Trixeo without any other LABA- / LAMA- / ICS-containing prescription within 90 days of the first prescription of Breztri/Trixeo.

Patients who were ever recorded with any diagnostic code for other chronic lower respiratory conditions were excluded, with the exception of asthma.

The inclusion and exclusion criteria below resulted in the patient flow depicted in Figure 2.

Figure 2 Patient flow diagram



5 Outcomes

5.1 Primary outcome

The primary outcome was medication success assessed at 90 days (early medication success) after Breztri/Trixeo initiation, which was a binary, composite outcome that is defined as fulfilling all of the following:

1. No major cardiac and respiratory events (MACRE), defined as not having any of the below events:
    - New diagnosis of heart failure; or
    - Hospitalization for heart failure; or
    - Myocardial infarction; or
    - Hospitalization for respiratory events; or
    - Complicated COPD exacerbations, as defined by exacerbations which require hospitalization or treatment with acute doses of oral corticosteroids and/or

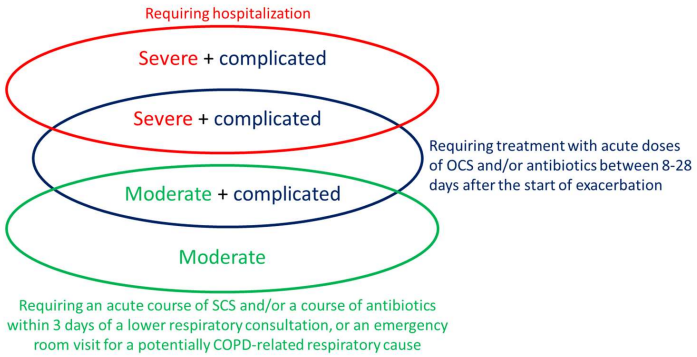
antibiotics between 8 and 28 days after the start of the initial event (i.e., the date of coding for COPD exacerbation; Figure 3); or

- All-cause mortality.

2. No pneumonia, defined as a physician diagnosed pneumonia confirmed with a chest radiograph or hospital admission within one month of diagnosis[12]

The cardiovascular component of MACRE here was a derivative and subset of the classical, core components of major adverse cardiovascular events as recommended by both the Food and Drug administration of the United States of America and the European Medicines Agency, i.e. cardiovascular mortality, myocardial infarction, and stroke.[13,14] Stroke was omitted from MACRE in this study due to a presumed lack of mechanisms via which triple therapy may influence the risk of stroke, as pointed out by the AstraZeneca team and acknowledged by the OPRI team. Multiple components of MACRE, and pneumonia may occur to the same patient, and the number of patients who experience each of these components will be described; however, as this was a primary outcome, each of these patients was only counted once when evaluating the primary outcome, regardless of how many components these patients each experienced. The definition of pneumonia included here has been used in prior work as a specific definition of pneumonia.[12]

Figure 3 Relationship between categories of COPD exacerbation severity



Medication success was to be claimed if the proportion of patients who meet the primary outcome of medication success is demonstrated to be ≥70% (i.e. if the lower 95% confidence limit for the percentage is ≥70%), which has been considered in previous publications to be a clinically meaningful limit.[15] Medication success at 90 days was termed "early medication success" and, at 180 days, "sustained medication success".

5.2 Exploratory outcomes

Exploratory outcomes were assessed at both 90 and 180 days, unless specified. These included and were defined as the following:

1. Patient demographics and clinical characteristics at Breztri/Trixeo initiation and during follow-up
2. In a subset, for patients with CAT score available at both baseline and follow-up, changes in CAT score were analysed as both a continuous variable and a categorical variable (with or without clinically meaningful changes in CAT score), stratified by whether patients switched to Breztri/Trixeo from another triple therapy regimens or stepped up from non-triple therapy. Clinically meaningful changes in CAT score were defined as changes by at least 2 points in CAT score.
3. Factors associated with the primary outcome (early medication success) and with change in CAT score after 90 days.
4. Medication success assessed at 180 days. The definition of medication success was the same as the above.
5. Amount of short-acting beta-agonist (SABA) use based on collected prescriptions, and calculated as $\frac{Count\ of\ inhaler\ doses\ (pack\ mg\ strength)}{duration\ of\ follow\text{-}u\quad in\ days}$, and expressed as salbutamol equivalent in mg/day.
6. Acceptability of medication change, as defined by the percentage of patients receiving at least one additional prescription for Breztri/Trixeo during the follow-up period.
7. Adherence, as represented by the MPR which will be calculated as the ratio of total Breztri/Trixeo pack days (i.e., total number of days' equivalent of Breztri/Trixeo prescribed) to the number of prescription days (i.e., total number of days from Breztri/Trixeo initiation to the last day of prescription), and which was expressed as a percentage.
8. The overall number of inhalers used (fixed triple, free triple, or SABA).
9. Change in COPD control assessed at a minimum of 90 days after index date. Definitions and measurements of COPD control were detailed in Appendix 1: Potential PRO data from the OPC quality improvement program.
10. Change in exercise capacity assessed at a minimum of 90 days after index date. Definitions and measurements of exercise capacity were detailed in Appendix 1: Potential PRO data from the OPC quality improvement program.

6 Study Variables

6.1 Exposures

Exposure was defined as prescription of Breztri/Trixeo.

6.2 Other Variables and Covariates

Baseline characteristics of all patients were described, as summarized in Table 1. The number of missing records was recorded for each variable for the entire cohort, as well as specifically for patients with fully characterised baseline (initiation visit) and follow-up PRO data. Additionally, the time between the date of each baseline variable availability and index date was described for all patients, expressed as median with interquartile range. Furthermore, the maintenance treatment used by patients at the time of initial CAT score assessment was described, with comparison of subgroups stratified by the maintenance regimens.

Table 1 Variables to be measured at baseline. Selected variables will also be measured on follow-up as specified.

Patient characteristics

Age	Age in years on index date, expressed as mean ± standard deviation and/or median with interquartile range. This was analysed and described as both a continuous and categorical variable, with the following categories: • 40-59 years old • 60-79 years old • 80 years old or above
Sex	Female or Male
Body Mass Index (BMI)	Defined as the ratio of weight (kg) to squared height (m^2) closest to Breztri/Trixeo initiation. This was analysed and described as both a continuous and categorical variable, with the following categories: • Underweight (BMI <18.5) • Normal weight (BMI 18.5 to <25) • Overweight (BMI 25 to <30) • Obese (BMI 30 and over)
Smoking status	The status prior to and closest to Breztri/Trixeo initiation was be used. This was analysed and described as categories, with the following categories: • Active smoker • Ex-smoker
Socioeconomic status	This was analysed and described as categories, based on the deciles of Index of Multiple Deprivation of the patient's corresponding general practice. The Index is based on

	national statistics for the postcode in which the general practice is situated.
Ethnicity	This was analysed and described as categories, with the following categories: • White • Black • Asian • Mixed / others • Unknown
Comorbidities	
Asthma	Active / inactive / never diagnosed Active asthma was defined by ongoing codes for asthma within a year before or after Breztri/Trixeo initiation. Inactive asthma was defined by ever having codes for asthma recorded, but not within a year before or after Breztri/Trixeo initiation.
Validated COPD diagnosis	This was defined as a post-bronchodilator forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio that was less than 0.7 on spirometry: yes / no
Evidence of asthma before the age of 40	Yes / no
Rhinitis	Any diagnosis, ever: yes / no
Eczema	Any diagnosis, ever: yes / no
Nasal polyps	Any diagnosis, ever: yes / no
Chronic sinusitis	Any diagnosis, ever: yes / no
Gastroesophageal reflux disease	Any diagnosis, ever: yes / no
Diabetes mellitus	Any diagnosis, ever: yes / no
Osteoporosis	Any diagnosis, ever: yes / no
Hypertension	Any diagnosis, ever: yes / no
Ischaemic heart disease	Any diagnosis, ever: yes / no
Heart failure	Any diagnosis, ever: yes / no. This was also recorded on follow-up as part of the outcomes.
Chronic kidney disease	Any diagnosis, ever: yes / no

Depression or anxiety	Any diagnosis, ever: yes / no
Sleep apnoea	Any diagnosis, ever: yes / no
Sleep disorder	Any diagnosis, ever: yes / no
Clinical characteristics	
Time since COPD diagnoses, years	The date of first validated COPD diagnosis was determined, and the time between that and Breztri/Trixeo initiation will be determined. This was analysed as a continuous variable, expressed as mean ± standard deviation and/or median with interquartile range.
FEV1	The value within 24 months prior to and closest to Breztri/Trixeo initiation was used. FEV1 in litre, expressed as mean ± standard deviation and/or median with interquartile range
Percentage predicted FEV1	The value within 24 months prior to and closest to Breztri/Trixeo initiation was used. Percentage predicted FEV1 in percent, expressed as mean ± standard deviation and/or median with interquartile range. This was analysed as a continuous variable, as well as a categorical variable according to the GOLD stage of airflow limitation: • GOLD 1 (mild): ≥80% • GOLD 2 (moderate): 50% to <80% • GOLD 3 (severe): 30% to <50% • GOLD 4 (very severe): <30%
Ratio of FEV1 to FVC <0.7	The value within 24 months prior to and closest to Breztri/Trixeo initiation was used. This was analysed as a binary variable.
mMRC score	The value within 24 months prior to and closest to Breztri/Trixeo initiation was used. This was analysed as a categorical variable, with each integer score value constituting a separate category. This was also recorded on follow-up. The definitions of individual scores of the mMRC score were detailed in Appendix 2: mMRC score.
GOLD groups[3]	The grouping within 24 months prior to and closest to Breztri/Trixeo initiation was used. This was analysed as a categorical variable, with each treatment group (A / B / C / D) constituting a separate category. Definitions of individual GOLD groups were detailed in Appendix 3: GOLD treatment groups. An alternative GOLD classification to A/D groups will be applied as a secondary one shall it arise during the protocol development.
CAT score	The value at any point prior to and closest to Breztri/Trixeo initiation was used; a sensitivity analysis was done where only values taking within the 24 months prior to Breztri/Trixeo initiation were used. This was analysed as a continuous variable, expressed as mean ± standard deviation and/or median with interquartile range. This was also recorded on follow-up as part of the outcomes. The CAT questionnaire

	and calculation of CAT score are detailed in Appendix 4: CAT questionnaire**Error! Reference source not found.**. Additionally, the number of patients with multiple CAT score assessments was recorded, as well as the number of assessments per patient. This variable was described with stratification by maintenance therapies.
Number of COPD exacerbations	This was measured in the year prior to the index date, and was analysed and described as both a continuous and categorical variable, with the following categories: • None • 1 exacerbation • 2 exacerbations • 3 exacerbations • ≥4 exacerbations Additionally, the severity of exacerbation was recorded. Complicated COPD exacerbations had been defined above as part of the outcomes. Moderate COPD exacerbations was defined by the requirement for an acute course of systemic corticosteroids and/or a course of antibiotics within 3 days of a lower respiratory consultation, or an emergency room visit for a potentially COPD-related respiratory cause. Severe COPD exacerbations was defined by COPD-related hospitalizations. Moderate and severe exacerbations were mutually exclusive, but there may be overlaps between severe and complicated exacerbations, and between moderate and complicated exacerbations (Figure 3). The respective numbers of patients with moderate, severe, and complicated COPD exacerbations were described, with multiple categories allowed for the same patient. This variable was also recorded on follow-up as part of the outcomes.
Number of acute OCS courses	This was measured in the year prior to the index date, and was analysed and described as both a continuous and categorical variable, with the following categories: • None • 1 course • 2 courses • 3 courses • ≥4 courses Acute OCS courses were short course of OCS prescriptions related to respiratory exacerbations as identified and defined by an OPRI algorithm which has been used in previous studies of OCS prescriptions. The algorithm was briefly described in Appendix 5: OPRI algorithm for acute OCS courses.
Number of antibiotic courses with lower respiratory consultations	This referred to courses of antibiotic prescriptions accompanied by consultations for lower respiratory conditions in the baseline period (year prior to index date). This was analysed and described as both a continuous and categorical variable, with the following categories: • None • 1 course • 2 courses

	• 3 courses • ≥4 courses
Average daily SABA dose, mcg/day	This was measured in the year prior to the index date, and was analysed and described as both a continuous and categorical variable, with the following categories: • No SABA use • 1-100 • 101-200 • 201-300 • 301-400 • >400
COPD-related general practice consultations	This was measured in the year prior to the index date, and was analysed and described as both a continuous and categorical variable, with the following categories: • None • 1 consultation • 2-4 consultations • 5-7 consultations • ≥8 consultations
All-cause general practice consultations	This was measured in the year prior to the index date, and was analysed and described as both a continuous and categorical variable, with the following categories: • 0-1 consultation • 2-4 consultations • 5-8 consultations • 9-13 consultations • 14-17 consultations • 18-22 consultations • ≥23 consultations
Maintenance COPD treatment immediately prior to Breztri/Trixeo initiation	This referred to the last combination of maintenance COPD treatments that was recorded in the year prior to the index date. It was analysed and described as a categorical variable, with the following categories: • LAMA only • LABA only • LABA+LAMA • ICS+LABA • ICS+LABA+LAMA as separate prescriptions (i.e., free triple) • ICS+LABA+LAMA as a single, combined prescription (i.e., fixed triple) In addition to the regimen used by patients immediately before initiating Breztri/Trixeo, the maintenance treatments used by patients during the year prior to Breztri/Trixeo initiation, and the pattern of these treatments were described.
Maintenance COPD treatments during the year prior to Breztri/Trixeo initiation	This referred to all combinations of maintenance COPD treatments observed in the year prior to the index date. The following combinations were recorded: • LAMA only • LABA only • LABA+LAMA

	• ICS+LABA • Free triple • Fixed triple The number of patients with each combination recorded during the year prior to the index date was described; a patient may have multiple combinations recorded. Additionally, the pattern of these combinations was described.
Number of SABA inhalers used	This was measured in the year prior to the index date, and was analysed and described as both a continuous and categorical variable, with the following categories: • None • 1-2 inhaler(s) • 3-6 inhalers • 7-10 inhalers • 11-16 inhalers • ≥17 inhalers
Blood eosinophil count, 10^9cells/L	This referred to the highest blood eosinophils in the year prior to index date; if no measurement is available within a year prior to index date, the closest value within the 5 years prior to index date was used. This was analysed and described as both a continuous and categorical variable, with the following categories: • <50 • 50-349 • ≥350

The above baseline variables were also described for patients who were excluded because of having had Breztri/Trixeo initiated less than 90 days before data extraction. Additionally, the proportion of patients with the following events were described for these patients:

- New diagnosis of heart failure
- Hospitalization for heart failure
- Myocardial infarction
- Hospitalization or hospital admittance for respiratory events
- Complicated COPD exacerbations
- Pneumonia
- Death

7 Feasibility Analysis

As of 10th August 2022, 449 patients in OPCRD were prescribed Breztri/Trixeo. After applying the inclusion and exclusion criteria, 198 patients were eligible for this study, with 180 days' follow-up data available for 136 patients. The median follow-up time of these 198 patients was 248 days [interquartile range 160-294 days]. Fifty of these patients had CAT

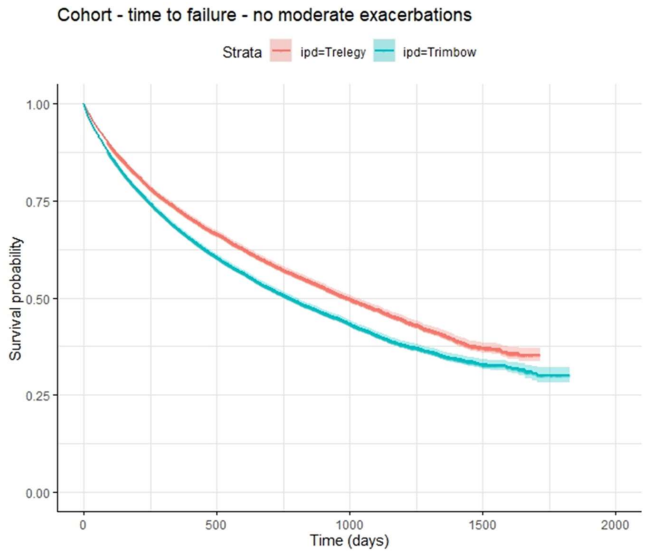
score available in the year prior to Breztri/Trixeo initiation, and 37 had CAT score available at 1-year post-initiation.

Patients using other fixed triple therapies (Trelegy and Trimbow) were analysed with the specified inclusion and exclusion criteria using data as of 17th October 2022. Of the 16,294 and 19,462 eligible patients on Trelegy and Trimbow, respectively, 14,679 (90.1%) and 17,011 (87.4%) patients achieved medication success by 90 days, respectively. Survival analysis was also performed (Figure 4), with 90.2% and 82.9% of patients on Trelegy estimated to achieve medication success by 90 and 182 days, respectively; the corresponding values for patients on Trimbow were 87.9% and 79.4%, respectively.

Commented [JC3]: Whilst the outcomes were at 180 days, the survival table in Figure 4 below listed 182 days, hence the cited figure here

As of 24th October 2022, the number of patients eligible for this study in OPCRD has increased to 285.

Figure 4 Kaplan-Meier survival curve and risk tables for medication success outcome in patients taking Trelegy and Trimbow (feasibility analysis)



Trelegy

Time	At risk	Event	Survival	lower 95% CI	upper 95% CI
90	14710	1597	0.902	0.897	0.907
182	12682	2744	0.829	0.823	0.835
365	9454	1497	0.724	0.717	0.731
720	5517	1588	0.583	0.574	0.591
1096	2523	855	0.472	0.462	0.481
1460	507	310	0.375	0.362	0.388

Trimbow

Time	At risk	Event	Survival	lower 95% CI	upper 95% CI
90	17121	2357	0.879	0.874	0.883
182	14537	3968	0.794	0.788	0.799
365	10379	2054	0.673	0.666	0.68
720	5418	1989	0.519	0.511	0.527
1096	2280	940	0.406	0.397	0.415
1460	467	250	0.336	0.325	0.348

8 Statistical Analysis

The variables listed in Table 1 were summarised as numbers of patients with data, means (standard deviation (SD)), medians (inter-quartile range (IQR)) or percentages, as appropriate, along with the number of patients with missing values for these measures. For each characteristic, the median (IQR) time since data collection and the patient's index date were also presented. Where it was specified that these were to be collected at more than one time point, each timepoint was summarised separately. Each characteristic was described with stratification by the availability of CAT data at 90 and 180 days, respectively. For all analyses, p-values <0.05 were considered significant. For all analyses, the numbers of patients excluded (due to missing data or other reasons) were also summarised.

8.1 Primary outcome

The primary outcome (early medication success) was presented as the number of patients achieving medication success at 90 days and also as a percentage of all patients included, together with a 95% confidence interval (CI). Overall medication success was to be claimed if the lower 95% confidence limit for the percentage achieving early medication success was ≥70%.

8.2 Exploratory outcomes

Exploratory outcomes were summarised separately for 90 days and 180 days as follows: (Summaries included all patients with available data for the appropriate timepoint, and percentages were of all patients with available data for the appropriate timepoint, together with the number of patients not included due to missing data).

- Acceptability of medication change (patients receiving at least one additional prescription for Breztri/Trixeo) – the number and percentage (95% confidence interval) (180 days only).
- Adherence (medication possession ratio), SABA usage (salbutamol equivalent in mg/day), and overall number of inhalers – the mean (SD), if normally distributed, or median (IQR), if non-normally distributed, was presented, along with a 95% confidence interval.
- For patients with data available, change in CAT score were assessed using a paired t-test (if normally distributed) or Wilcoxon's matched pairs test (if non-normally distributed). Change in CAT score was also summarised as the mean change (SD), if normally distributed, or median change (IQR), if non-normally distributed, together with a 95% confidence interval, and also as the number and

percentages of patients who had a clinically meaningful increase (≥2 points increase), clinically meaningful decrease (≥2 points decrease), or no clinically meaningful change (≤ 1 point change). This analysis was stratified by prior asthma status (yes / no).

- The above analyses (acceptability of medication change, adherence, and change in CAT score) were repeated for groups defined by whether the patient switched to Breztri/Trixeo from another triply therapy *vs.* stepped up from a non-triple therapy.
- Sustained medication success – this was defined as for the primary outcome but was assessed at 180 days after Breztri/Trixeo initiation. It was analysed as described for the primary outcome.
- COPD control at baseline and follow-up were summarised as the percentage of patients with control at each timepoint, and the change between baseline and follow-up was assessed using a McNemar test.
- Changes in exercise capacity were summarised as the percentage of patients in each category. The two-sided sign test, with ties excluded, is used to test the null hypothesis of there being no change in exercise capacity.

8.3 Subgroup analyses

Furthermore, subgroup / stratified analysis of the primary outcome were performed, as described above, including but not limited to for sub-groups defined by patients (a) with vs without prior asthma status; (b) who switched to Breztri/Trixeo from another triple therapy regimen *vs.* stepped up from non-triple therapy; (c) by prior exacerbation history; and (d) by prior maintenance medication adherence level.

8.4 Further exploratory analyses

Additionally, an exploratory analysis was carried out to identify factors associated with the primary outcome (early medication success) and with change in CAT score.

Associations between the primary outcome (early medication success) and baseline values of each of the variables listed in Table 1 were tested individually using logistic regression models. Considering the results from these univariable models, exploratory attempts may be made to create a multivariable prediction model using lasso and stepwise regression to identify patient characteristics independently associated with success of the Breztri/Trixeo treatment. Consideration was given to omitting variables from the multivariable model if they are highly correlated or have too many missing values. Clinical opinion was also used to

Commented [JC4]: Both were attempted

identify groups (e.g., above and below specified cut-offs) who might be expected to benefit least / most from the treatment and their effect tested using logistic regression models. This also allowed investigation of interactions between specified characteristics. The final choice of models and / or sub-groups of interest considered the distribution of patient characteristics in the sample and the total number who did not experience medication success.

A similar approach was used for change in CAT score using linear regression to identify the baseline factors most associated with change. This analysis was limited by the number of patients for whom we have data on changes in CAT scores as well as the other covariates.

8.5 Missing data

Values were imputed where possible to maximise the number of patients who could be included in each analysis using the methods detailed in Table 2.

Table 2 Missing data handling

Missing value	Rule(s)
Date (days & months)	- Imputed 15th of the month for missing days - Imputed July 1st for missing days and months
Strength from generic active ingredient read codes	- Affected < 1% observations - Imputed strength of branded/generic drug of the same active ingredient (by Read code) that is most frequently prescribed
Invalid quantity (number of units prescribed)	- Up to 35% invalid observations. Mostly quantity = 0 1. Imputed most common strength of the same drug (by strength & Read code) for the patient 2. Imputed most common quantity of drug of the same strength (by strength & Read code) prescribed for the OCS-related condition 3. Imputed based on clinical input
Dose information	- Missing dose information for Breztri/Trixeo assumed two inhalations twice daily as per the defined in the summary of product characteristics. - Missing dose information for other drug such as SABA derived using the dose text data where possible. If this was not possible, the dose was imputed using the most common quantity of drug of the same strength.
BMI	- Patients' BMI were calculated using individual height and weight measurements if available.
Patient registration details	- Missing or incorrect patient join dates (dates in the future or distant past) will utilise the first clinical or therapeutic record as a proxy start date.

8.6 Sample size calculation

The sample size calculation was based on the primary outcome of medication success. If 80% of patients had success, 285 patients would have been sufficient to achieve a 97.6% power to demonstrate a medication success rate ≥70% at the p<0.025 (one sided) level of significance.

8.7 Software

All statistical analyses were performed on Stata v14.2 (StataCorp LLC, College Station, Texas, United States of America).

9 Results

Of the 737 patients receiving a Breztri/Trixeo prescription in OPCRD by 24 Oct 2022, 285 patients were analysed after applying the inclusion and exclusion criteria (Table 3; 131 males (46.0%); median age 69.8 (interquartile range 62.7-77.3) years old).

Table 3 Patient flow

Criterion	Excluded	Remaining
Patients with data provided by general practices in OPCRD who were ever prescribed Breztri/Trixeo		737
Patients at least one prescription of Breztri/Trixeo from the start of data availability up to 90 days prior to the date of data extraction	306 (42%)	431
Ever recorded with any diagnosis code for COPD	9 (2%)	422
Patients aged at least 40 years old	4 (1%)	418
Patients ever recorded to be an ex-smoker or current smoker	13 (3%)	405
Patients with at least one year of continuous practice data prior to index date	20 (5%)	385
Patients who had 90-day medication persistence, as defined by having received at least one further prescription of Breztri/Trixeo without any other LABA- / LAMA- / ICS-containing prescription within 90 days of the first prescription of Breztri/Trixeo	91 (24%)	294
Exclusion: Patients ever recorded with any diagnostic code for other chronic lower respiratory conditions except asthma	9 (3%)	285

9.1 Primary outcome: medication success

At 90 days, 275 patients (96.5%, 95% confidence interval: 93.6%, 98.3%) achieved medication success. As the lower 95% confidence interval was ≥70%, overall medication success was achieved.

Of the 10 patients who did not achieve 90-day medication success, one (10%; 0.4% of all patients) had a new diagnosis of heart failure, one (10%; 0.4% of all patients) had

myocardial infarction, three (30%; 1.1% of all patients) had hospitalization for respiratory events, and five (50%; 1.8% of all patients) had a complicated COPD exacerbation. Meanwhile, among the 91 patients who were excluded due to not achieving medication persistence at 90 days, two (2.2%) had complicated COPD exacerbations.

9.1.1 Subgroup analysis: by prior asthma status

In total, 148 patients never had asthma, 49 had inactive asthma, and 88 had active asthma. Of those who never had asthma, 146 (98.7%) achieved 90-day / early medication success (95% confidence interval: 95.2%, 99.8%). Of those who had inactive asthma, 44 (89.8%) achieved 90-day / early medication success (95% confidence interval: 77.8%, 96.6%). Of those who had active asthma, 85 (96.6%) achieved 90-day / early medication success (95% confidence interval: 90.4%, 99.3%). The confidence intervals of the three categories overlapped substantially, but success was achieved in all subgroups i.e., irrespective of previous asthma status.

9.1.2 Subgroup analysis: switching from another triple therapy vs stepping up from non-triple therapy

In total, 172 patients stepped up from non-triple therapy, while 113 switched from another triple therapy (32 from free triple therapy, and 81 from a fixed triple therapy). 165 (95.9%) of the former achieved 90-day / early medication success (95% confidence interval: 91.8%, 98.3%), while 110 (97.4%) of the latter achieved the same (95% confidence interval: 92.4%, 99.4%). The confidence intervals of the two categories overlapped substantially.

9.1.3 Subgroup analysis: by prior exacerbation history

In total, 185 patients did not have any exacerbation in the year prior to Breztri/Trixeo initiation, 58 had one exacerbation, 20 had two exacerbations, 10 had three exacerbations, and 12 had four or more exacerbations. The numbers and proportions of patients who achieved 90-day / early medication success for each group are summarized in Table 4, with the corresponding 95% confidence intervals. The confidence intervals of the categories overlapped substantially.

Table 4 The numbers and proportions of patients who achieved 90-day / early medication success with the corresponding 95% confidence intervals, stratified by the number of COPD exacerbations in the year prior to Breztri/Trixeo initiation.

Number of COPD exacerbations in the year prior to Breztri/Trixeo initiation	Total number of patients, N	Number of patients achieving 90-day / early medication success, N	Proportion [95% confidence interval], %
0	185	182	98.4 [95.3, 99.7]
1	58	54	93.1 [83.3, 98.1]
2	20	18	90.0 [68.3, 98.8]
3	10	10	100 [69.2, 100]
≥4	12	11	91.7 [61.5. 99.8]

9.1.4 Subgroup analysis: by prior maintenance medication adherence level

In total, 70 patients had a prior maintenance therapy medication possession ratio (which was used as a surrogate of medication adherence level) of <25%, 37 had that of 25-<50%, 43 had that of 50-<75%, 55 had that of 75-<100%, and 80 had that of ≥100%. The numbers and proportions of patients who achieved 90-day / early medication success for each group are summarized in Table 5, with the corresponding 95% confidence intervals. The confidence intervals of the categories overlapped substantially.

Table 5 The numbers and proportions of patients who achieved 90-day / early medication success with the corresponding 95% confidence intervals, stratified by the maintenance therapy medication possession ratio in the year prior to Breztri/Trixeo initiation.

Prior maintenance therapy medication possession ratio	Total number of patients, N	Number of patients achieving 90-day / early medication success, N	Proportion [95% confidence interval], %
<25%	70	68	97.1 [90.1, 99.7]
25-<50%	37	36	97.3 [85.8, 99.9]
50-<75%	43	41	95.3 [84.2, 99.4]
75-<100%	55	55	100 [93.5, 100]
≥100%	80	75	93.8 [86.0. 97.9]

9.2 Exploratory outcomes

9.2.1 Patient demographics and clinical characteristics

The baseline characteristics of included patients are summarized in Table 6, as well as for those who were excluded due to not achieving medication persistence at 90 days. There appeared to be more of the patients excluded for not achieving medication persistence at 90 days who were male, current smoker, did not have prior asthma diagnosis, did not have

validated COPD diagnosis, or had poorer COPD health status, compared to the included patients. The two groups of patients were otherwise largely comparable in baseline characteristics.

Table 6 Baseline characteristics of included patients. All proportions were calculated with the number of patients with non-missing records as the denominator, with the exception of the proportion of missing records.

	Included in the study (N=285)	**Excluded for not achieving medication persistence at 90 days (N=91)**	**SMD**
Demographics			
Age			
Age (mean & SD)	69.4 (10.8)	68.7 (10.3)	-0.074
Age (median & IQR)	69.8 (62.7-77.3)	69.2 (61.9-76.6)	
Age category			
40 <60	51 (17.9%)	18 (19.8%)	0.147
60 <80	185 (64.9%)	62 (68.1%)	
80 <100	49 (17.2%)	11 (12.2%)	
Gender			
Male	131 (46.1%)	56 (61.5%)	0.156
Missing	1 (0.4%)	0 (0.0%)	
BMI			
BMI (mean & SD)	28.4 (7.3)	28.7 (8.1)	0.042
BMI Categories			
0 <18.5	18 (6.3%)	3 (3.3%)	0.153
18.5 <25	84 (29.6%)	28 (30.8%)	
25 <30	82 (28.9%)	25 (27.5%)	
30 <100	100 (35.2%)	35 (38.5%)	
Missing	1 (0.4%)	0 (0.0%)	
Smoking status			
Current	105 (36.8%)	31 (34.1%)	0.059
Ex	180 (63.2%)	60 (65.9%)	
Missing	0 (0.0%)	2 (2.2%)	
Index of Material Deprivation Decile[1]			
1	39 (14.0%)	13 (14.8%)	0.470
2	27 (9.7%)	13 (14.8%)	
3	29 (10.4%)	12 (13.6%)	
4	49 (17.6%)	9 (10.2%)	
5	24 (8.6%)	11 (12.5%)	
6	48 (17.2%)	6 (6.8%)	
7	31 (11.1%)	11 (12.5%)	
8	11 (3.9%)	3 (3.4%)	
9	10 (3.6%)	7 (8.0%)	

	Included in the study (N=285)	Excluded for not achieving medication persistence at 90 days (N=91)	SMD
10	11 (3.9%)	3 (3.9%)	
Missing	6 (2.1%)	3 (3.3%)	
Ethnicity			
White	255 (95.5%)	86 (95.6%)	0.331
Asian	4 (1.5%)	3 (3.3%)	
Mixed/Others	8 (3.0%)	1 (1.1%)	
Unknown/Missing	18 (6.3%)	1 (1.1%)	
Comorbidity			
Asthma ever	137 (48.1%)	44 (48.4%)	0.006
Active asthma (within the year prior to Breztri/Trixeo initiation)	88 (30.9%)	24 (26.4%)	0.100
Asthma prior to 40 years old	36 (12.6%)	13 (14.3%)	0.048
Validated COPD diagnosis	96 (33.7%)	31 (34.1%)	0.008
Rhinitis	61 (21.4%)	18 (19.8%)	0.040
Eczema	78 (27.4%)	30 (33.0%)	0.122
Nasal Polyps	11 (3.9%)	1 (1.1%)	0.178
Chronic Rhinosinusitis	2 (2.2%)	8 (2.8%)	0.039
Gastroesophageal reflux disease	80 (28.1%)	28 (30.8%)	0.059
Diabetes	54 (18.9%)	23 (25.3%)	0.153
Osteoporosis	42 (14.7%)	11 (12.1%)	0.078
Hypertension	125 (43.9%)	44 (48.4%)	0.090
Ischaemic heart disease	35 (12.3%)	10 (11.0%)	0.040
Heart failure	27 (9.5%)	9 (9.9%)	0.014
Chronic kidney disease	42 (14.7%)	14 (15.4%)	0.018
Depression or anxiety	167 (58.6%)	65 (71.4%)	0.272
Sleep apnoea	20 (7.0%)	4 (4.4%)	0.113
Sleep disorder	67 (23.5%)	20 (22.0%)	0.037
Clinical characteristics			
Time since first validated COPD diagnosis, years			
Time (mean and SD)	8.2 (4.8)	8.5 (4.5)	0.076
Time (median and IQR)	7.9 (4.4-11.7)	7.5 (5.0-13.5)	
missing	114 (40%)	34 (37%)	
FEV1 (within 2 years prior to Breztri/Trixeo initiation), litre			
FEV1 (mean & SD)	1.5 (0.7)	1.5 (0.7)	-0.116
FEV1 (median and IQR)	1.5 (0.9-2.0)	1.2 (0.9-1.8)	
missing	215 (75%)	73 (80%)	
FEV1 percent predicted (within 2 years prior to Breztri/Trixeo initiation)			
FEV1 % predicted (mean and SD)	54.5% (22.6)	62.3 (20.7)	0.358
FEV1 % predicted (median and IQR)	52.0% (36.0-70.0)	70.0 (48.0-75.5)	

Commented [JC5]: Is this inactive asthma?

Commented [JC6R5]: Clarified with thanks

Commented [JC7R5]: Hana commented: "Accepted; however, we are missing Inactive asthma category" Response: The inactive asthma category would just be the complementary to the active asthma category among the 137 patients ever with asthma -- meaning that the number of inactive asthma is 49 among those included, and 20 among those excluded. As this is complementary to the presented numbers it would be unnecessary and redundant to specify these numbers here

	Included in the study (N=285)	Excluded for not achieving medication persistence at 90 days (N=91)	SMD
missing	235 (82%)	78 (86%)	
GOLD stage (2022 version)			
0 <30	6 (12.0%)	1 (7.7%)	0.414
30 <50	19 (38.0%)	3 (23.1%)	
50 <80	15 (30.0%)	6 (46.2%)	
80 <110	10 (20.0%)	3 (23.1%)	
missing	235 (82.5%)	78 (85.7%)	
FEV1/FVC ratio (calculated and recorded; within 2 years prior to Breztri/Trixeo initiation)			
FEV1/FVC Ratio (mean and SD)	58.5% (15.5)	60.2% (14.4)	0.110
FEV1/FVC Ratio (median and IQR)	58.0% (46.0-69.2)	62.0% (46.5-68.8)	
missing	164 (57%)	40 (44%)	
mMRC Score (nearest and within 2 years prior to Breztri/Trixeo initiation)			
0	8 (3.0%)	0 (0.0%)	0.276
1	50 (19.0%)	21 (23.6%)	
2	95 (36.1%)	33 (37.1%)	
3	82 (31.2%)	25 (28.1%)	
4	28 (10.6%)	10 (11.2%)	
missing	22 (7.7%)	2 (2.2%)	
GOLD 2022 group			
A	9 (3.2%)	2 (2.2%)	0.154
B	26 (9.1%)	11 (12.1%)	
C	49 (17.2%)	19 (20.9%)	
D	201 (70.5%)	59 (64.8%)	
CAT score (nearest and prior to Breztri/Trixeo initiation)			
CAT score (mean and SD)	21.7 (7.8)	22.0 (8.4)	0.038
CAT score (median and IQR)	21.5 (16.0-27.0)	23.0 (16.0-30.0)	
CAT Scores (mean and SD)	2.0 (1.2)	2.0 (1.0)	0.010
Minimum CAT score	2	4	
Maximum CAT score	39	36	
missing	67 (24%)	23 (25.2%)	
CAT Scores for those with >1 score (mean and SD)	2.7 (1.1)	2.7 (0.7)	-0.047
With no or only one CAT score available	171 (60%)	56 (62%)	
Any Exacerbation (by hierarchy)			
Severe - Admission	0 (0%)	1 (1.1%)	0.48704
Complicated - OCS and Antibiotic	13 (4.6%)	8 (8.8%)	
- Antibiotic	3 (1.1%)	1 (1.1%)	
- OCS	11 (3.9%)	2 (2.2%)	

Commented [JC8]: Added as per Hana's request

		Included in the study (N=285)	Excluded for not achieving medication persistence at 90 days (N=91)	SMD
Moderate	- OCS and Antibiotic	40 (14.0%)	10 (11.0%)	
	- Antibiotic	19 (6.7%)	10 (11.0%)	
	- LR with OCS	7 (2.5%)	3 (3.3%)	
	- ER visit	7 (2.5%)	4 (4.4%)	
None		185 (65.0%)	52 (57.1%)	
Number of moderate exacerbations (within a year prior to Breztri/Trixeo initiation)				
Exacerbations (mean and SD)		0.79 (1.5)	0.81 (1.42)	0.016
Exacerbations (median and IQR)		0 (1-0)	0 (0-1)	
Exacerbations categories				
0		185 (64.9%)	53 (58.2%)	0.200
1		49 (17.19%)	22 (24.18%)	
2		20 (7.0%)	8 (8.8%)	
3		12 (4.2%)	3 (3.3%)	
4		7 (2.4%)	2 (2.2%)	
>4		12 (4.2%)	3 (3.3%)	
Number of complicated exacerbations (within a year prior to Breztri/Trixeo initiation)				
Exacerbations (mean and SD)		0.15 (0.53)	0.17 (0.63)	-0.134
Exacerbations (median and IQR)		0 (0-0)	0 (0-0)	
Exacerbations categories				
0		258 (90.5%)	80 (88.0%)	0.986
1		15 (5.3%)	9 (9.9%)	
2		9 (3.2%)	1 (1.1%)	
3		2 (0.7%)	0 (0%)	
4		1 (0.4%)	1 (1.1%)	
5		0 (0%)	0 (0%)	
Number of severe exacerbations (within a year prior to Breztri/Trixeo initiation)				
Count		0 (0%)	1 (1.1%)	Not estimable
Acute OCS prescription (within a year prior to Breztri/Trixeo initiation)				
Acute OCS prescription (mean and SD) in year prior		1.9 (3.7)	1.7 (2.6)	-0.079
Acute OCS prescription (median and IQR)		0.0 (0.0-3.0)	0.0 (0.0-2.0)	
Acute OCS prescription categories				
0		158 (55.4%)	47 (51.7%)	0.238
1		33 (11.6%)	13 (14.3%)	
2		20 (7.0%)	9 (9.9%)	
3		26 (9.1%)	4 (4.4%)	

	Included in the study (N=285)	Excluded for not achieving medication persistence at 90 days (N=91)	SMD
≥4	48 (16.8%)	18 (19.8%)	
Antibiotic prescription within 3 days of a lower respiratory tract infection (within a year prior to Breztri/Trixeo initiation)			
Antibiotic prescription (mean and SD)	0.6 (1.6)	0.5 (0.9)	-0.073
Antibiotic prescription (median and IQR)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	
Antibiotic categories			
0	204 (71.6%)	61 (67.0%)	0.243
1	44 (15.4%)	19 (20.9%)	
2	17 (6.0%)	8 (8.8%)	
3	11 (3.4%)	1 (1.1%)	
≥4	9 (3.2%)	2 (2.2%)	
EOS measurements (highest in the year prior to Breztri/Trixeo initiation; if not available: most recent within 5 years prior to Breztri/Trixeo initiation)			
EOS measurements (mean and SD)	227.9 (141.2)	196.7 (104.7)	-0.251
EOS measurements (median and IQR)	193.3 (127.5-290.9)	175 (130.0-245.0)	
EOS measurement categories			
0 <50	5 (1.9%)	0 (0.0%)	0.266
50 <350	225 (83.3%)	79 (86.8%)	
350 <10000	40 (14.8%)	8 (8.8%)	
missing	15 (5.3%)	4 (4.4%)	
Daily SABA Dose (within a year prior to Breztri/Trixeo initiation)			
Daily SABA dose (mean and SD)	395.7 (415.3)	365.7 (379.9)	-0.076
Daily SABA dose (median and IQR)	274.0 (54.8-657.5)	274.0 (0.0-602.7)	
Daily SABA dose categories			
0 <100	91 (31.9%)	29 (31.9%)	0.235
100 <200	28 (9.8%)	8 (8.8%)	
200 <300	24 (8.4%)	12 (13.2%)	
300 <400	20 (7.0%)	10 (11.0%)	
400 <3000	122 (42.8%)	32 (35.2%)	
SABA Inhalers (within a year prior to Breztri/Trixeo initiation)			
SABA Inhalers (mean and SD)	7.1 (7.1)	6.8 (7.2)	-0.041
SABA Inhalers (median and IQR)	5.0 (1.0-13.0)	5.0 (0.0-11.0)	
SABA Inhalers categories			
0	69 (24.2%)	23 (25.3%)	0.232
1-2	39 (13.7%)	10 (11.0%)	

	Included in the study (N=285)	Excluded for not achieving medication persistence at 90 days (N=91)	SMD
3-6	46 (16.1%)	22 (24.2%)	
7-10	43 (15.1%)	10 (11.0%)	
11-15	53 (18.6%)	16 (17.6%)	
≥16	35 (12.3%)	10 (11.0%)	
COPD Primary Care Consultations (within a year prior to Breztri/Trixeo initiation)			
COPD consultations (mean and SD)	2.3 (1.9)	2.0 (2.1)	-0.140
COPD consultations (median and IQR)	2.0 (1.0-3.0)	1.0 (1.0-2.0)	
COPD consultations categories			
0	26 (9.1%)	7 (7.7%)	0.447
1	85 (29.8%)	41 (45.1%)	
2-4	143 (50.2%)	36 (39.6%)	
5-6	20 (7.0%)	1 (1.1%)	
≥7	11 (3.9%)	6 (6.6%)	
All-cause consultations (within a year prior to Breztri/Trixeo initiation)			
All-cause consultations (mean and SD)	27.4 (19.1)	27.1 (17.0)	-0.012
All-cause consultations (median and IQR)	23.0 (15.0-36.0)	25.0 (17.0-38.0)	
All-cause consultation categories			
0-1	26 (9.1%)	7 (7.7%)	0.200
2-4	0 (0.0%)	4 (4.4%)	
5-8	6 (2.1%)	7 (7.7%)	
9-13	26 (9.1%)	7 (7.7%)	
14-17	31 (10.9%)	9 (9.9%)	
18-21	33 (11.6%)	57 (62.6%)	
≥22	163 (57.2%)	7 (7.7%)	
Maintenance Treatment immediately prior to Breztri/Trixeo initiation[2]			
LAMA	9 (3.2%)	1 (1.1%)	0.742
LABA	1 (0.4%)	0 (0.0%)	
LABA+LAMA	48 (16.8%)	9 (9.9%)	
ICS+LABA	53 (18.6%)	25 (27.5%)	
Free triple (separates)	81 (28.4%)	10 (11.0%)	
Fixed triple	32 (11.2%)	28 (30.8%)	
Other Separate/Combinations	14 (4.9%)	1 (1.1%)	
None	47 (16.5%)	17 (18.7%)	
Maintenance Treatment (within a year prior to Breztri/Trixeo initiation)[3]			
LAMA	3 (1.1%)	0 (0.0%)	0.284

	Included in the study (N=285)	Excluded for not achieving medication persistence at 90 days (N=91)	SMD
LABA	1 (0.4%)	0 (0.0%)	
LABA+LAMA	38 (13.3%)	6 (6.6%)	
ICS+LABA	104 (36.5%)	41 (45.1%)	
Free triple (separates)	67 (23.5%)	20 (22.0%)	
Fixed triple	92 (32.3%)	36 (39.6%)	
None	58 (20.4%)	19 (21.9%)	

[1] The Index of Multiple Deprivation (IMD), is the official measure of relative deprivation for small areas in England. The IMD combines information from the seven domains (income, emplyment, education, health, crime, housing and service, environment) to produce an overall relative measure of deprivation.
[2] The last combination of maintenance COPD treatments in the year prior to the index date, combination treatment containing separates occur on the same day (patients are only in one category).
[3] All combinations of maintenance COPD treatments in the year prior to the index date, patients receiving individual separates on the same day are classed as combinations (patients can be in multiple categories).
SMD, standardised mean difference.

BMI and smoking status at both 90 and 180 days are summarized in Supplementary Table 3 and Supplementary Table 4, respectively.

9.2.2 Changes in CAT score

In this study, the most recent CAT score any time prior to the index date was used as the baseline measurement to maximise the number of patients who could be included in this analysis. Sensitivity analyses were carried out to assess the effect of only including patients with a baseline score <2 years prior to the index date.

Commented [JC9]: Added this as Hana requested the baseline to be explicitly stated

The time between baseline CAT score recording and Breztri/Trixeo initiation is shown in Supplementary Figures
Supplementary Figure 1, and the time between Breztri/Trixeo initiation and follow-up CAT score recording is shown in Supplementary Figure 2. Altogether, 89 patients had any follow-up CAT score, whose baseline CAT score was recorded a median of 71 days prior to Breztri/Trixeo initiation, and whose follow-up score was recorded a median of 190 days after Breztri/Trixeo initiation. Specifically, 68 patients had follow-up scores at least 90 days after Breztri/Trixeo initiation, whose baseline CAT score was recorded a median of 84.5 days prior to Breztri/Trixeo initiation, and whose follow-up score was recorded a median of 250.5 days after Breztri/Trixeo initiation. Additionally, 50 patients had follow-up scores at least 180 days after Breztri/Trixeo initiation, whose baseline CAT score was recorded a median of 65.5 days prior to Breztri/Trixeo initiation, and whose follow-up score was recorded a median of 300

days after Breztri/Trixeo initiation. There was a statistically significant but weak positive correlation between changes in CAT score and the time between Breztri/Trixeo initiation and follow-up CAT score recording (R^2=0.144, p<0.001; Supplementary Figure 3).

9.2.2.1 90-day changes

In total, 68 patients had CAT score available at both baseline and after 90 days of Breztri/Trixeo initiation. 90-day CAT score (median CAT score 24 [interquartile range: 18-30]) was significantly higher (p<0.001) than that at baseline (median CAT score 19 [interquartile range: 15.5-25.5]). The median change in 90-day CAT score was 3 (interquartile range: -0.5-8; 95% confidence interval of median: 1, 5). 14 patients (20.6%) had clinically meaningful (≥2 points) decreases in CAT score, 13 (19.1%) had no clinically meaningful change (≤1 point), and 41 (60.3%) had clinically meaningful increases.

Two subgroup analyses were performed, stratifying by prior asthma diagnosis, and whether patients switched from another triple therapy or stepped up from a non-triple therapy. Among the 38 patients without asthma, 90-day CAT score (median CAT score 24 [interquartile range: 18-30]) was significantly higher (p=0.020) than baseline (median CAT score 21 [interquartile range: 16-25]). The median change in 90-day CAT score was 3 (interquartile range: -3-9; 95% confidence interval of median: 0, 6). 10 patients (26.3%) had clinically meaningful decreases in CAT score, seven (18.4%) had no clinically meaningful change, and 21 (55.3%) had clinically meaningful increases.

Among the 17 patients with inactive asthma, 90-day CAT score (median CAT score 29 [interquartile range: 17-31]) was significantly higher (p=0.027) than baseline (median CAT score 18 [interquartile range: 16-26]). The median change in 90-day CAT score was 3 (interquartile range: 0-10; 95% confidence interval of median: 0, 10). Two patients (11.8%) had clinically meaningful decreases in CAT score, six (35.3%) had no clinically meaningful change, and nine (52.9%) had clinically meaningful increases.

Among the 13 patients with active asthma, there was no statistically significant difference (p=0.069) in 90-day CAT score (median CAT score 22 [interquartile range: 17-27]), as compared to baseline (median CAT score 18 [interquartile range: 13-22]). The median change in 90-day CAT score was 4 (interquartile range: 2-7; 95% confidence interval of median: 2, 8). Two patients (15.4%) had clinically meaningful decreases in CAT score, and 11 (84.6%) had clinically meaningful increases.

Among the 50 patients who stepped up from non-triple therapies, 90-day CAT score (median CAT score 25.5 [interquartile range: 18-31]) was significantly higher (p<0.001) than baseline (median CAT score 21 [interquartile range: 15-26]). The median change in 90-day CAT score was 4 (interquartile range: -1-9; 95% confidence interval of median: 2, 6). 11 patients (22%) had clinically meaningful decreases in CAT score, six (12%) had no clinically meaningful change, and 33 (66%) had clinically meaningful increases.

Among the 18 patients who switched from other triple therapies, there was no significant difference (p=0.171) in 90-day CAT score (median CAT score 21 [interquartile range: 17-29]), as compared to baseline (median CAT score 19 [interquartile range: 17-23]). The median change in 90-day CAT score was 0.5 (interquartile range: 0-5; 95% confidence interval of median: 0, 5). Three patients (16.7%) had clinically meaningful decreases in CAT score, seven (38.9%) had no clinically meaningful change, and eight (44.4%) had clinically meaningful increases.

When the above analyses were restricted to patients with baseline CAT scores within 2 years of Breztri/Trixeo initiation, there were no appreciable changes in any of the reported medians or percentages, although the comparison of 90-day change (increase) in the active asthma group was statistically significant (p=0.018) (median at baseline = 18 (IQR 13-22), median at follow-up = 22 (IQR 19-31), median change = 4 (IQR 2-8), N=11).

9.2.2.2 180-day changes

In total, 50 patients had CAT score available at both baseline and after 180 days of Breztri/Trixeo initiation. 180-day CAT score (median CAT score 24 [interquartile range: 18-30]) was significantly higher (p<0.001) than baseline (median CAT score 19 [interquartile range: 16-24]). The median change in 180-day CAT score was 4 (interquartile range: -1-9; 95% confidence interval of median: 0, 6). 10 patients (20%) had clinically meaningful decreases in CAT score, 9 (18%) had no clinically meaningful change, and 31 (62%) had clinically meaningful increases.

Two subgroup analyses were performed, stratifying by prior asthma diagnosis, and whether patients switched from another triple therapy or stepped up from a non-triple therapy. Among the 28 patients without asthma, there was no statistically significant different (p=0.064) in 180-day CAT score (median CAT score 23.5 [interquartile range: 18-30]), as compared to baseline (median CAT score 21 [interquartile range: 16.5-25.5]). The median change in 180-day CAT score was 3.5 (interquartile range: -3-10; 95% confidence interval of median: -1, 7).

Eight patients (28.6%) had clinically meaningful decreases in CAT score, five (17.9%) had no clinically meaningful change, and 15 (53.6%) had clinically meaningful increases.

Among the 11 patients with inactive asthma, there was no statistically significant difference (p=0.082) in 180-day CAT score (median CAT score 29 [interquartile range: 16-32]), as compared to baseline (median CAT score 18 [interquartile range: 16-24]). The median change in 180-day CAT score was 4 (interquartile range: -1-15; 95% confidence interval of median: -1, 18). One patient (9.1%) had clinically meaningful decreases in CAT score, four (36.4%) had no clinically meaningful change, and six (54.6%) had clinically meaningful increases.

Among the 11 patients with active asthma, 180-day CAT score (median CAT score 22 [interquartile range: 19-31]) was significantly higher (p=0.018) than baseline (median CAT score 18 [interquartile range: 13-22]). The median change in 180-day CAT score was 4 (interquartile range: 2-8; 95% confidence interval of median: 2, 8). One patient (9.1%) had clinically meaningful decreases in CAT score, and 10 (90.9%) had clinically meaningful increases.

Among the 36 patients who stepped up from non-triple therapies, 180-day CAT score (median CAT score 24.5 [interquartile range: 18-31]) was significantly higher (p=0.001) than baseline (median CAT score 20 [interquartile range: 14.5-25.5]). The median change in 180-day CAT score was 4.5 (interquartile range: -0.5-10; 95% confidence interval of median: 1, 8). Seven patients (19.4%) had clinically meaningful decreases in CAT score, five (13.9%) had no clinically meaningful change, and 24 (66.7%) had clinically meaningful increases.

Among the 14 patients who switched from other triple therapies, there was no significant difference (p=0.282) in 180-day CAT score (median CAT score 21.5 [interquartile range: 19-29]), as compared to baseline (median CAT score 19 [interquartile range: 17-23]). The median change in 180-day CAT score was 1.5 (interquartile range: -1-7; 95% confidence interval of median: -6, 10). Three patients (21.4%) had clinically meaningful decreases in CAT score, four (28.6%) had no clinically meaningful change, and seven (50.0%) had clinically meaningful increases.

When the above analyses were repeated restricted to patients with baseline CAT scores within 2 years of Breztri/Trixeo initiation, there were no appreciable changes in any of the reported medians or percentages or the statistical significance of the changes.

9.2.2.3 Post hoc analyses

Three *post hoc* analyses were performed to explore changes in CAT score within 90, 120, and 180 days.

In total, 21 patients had CAT score available at both baseline and within 90 days of Breztri/Trixeo initiation. CAT score within 90 days (median CAT score 22 [interquartile range: 17-25]) was not significantly different (p=0.689) as compared to baseline (median CAT score 25 [interquartile range: 20-27]). The median change in 180-day CAT score was -1 (interquartile range: -5-6; 95% confidence interval of median: -5, 6). Nine patients (42.9%) had clinically meaningful decreases in CAT score, five (23.8%) had no clinically meaningful change, and seven (33.3%) had clinically meaningful increases.

In total, 31 patients had CAT score available at both baseline and within 120 days of Breztri/Trixeo initiation. CAT score within 120 days (median CAT score 22 [interquartile range: 17-28]) was not significantly different (p=0.731) as compared to baseline (median CAT score 24 [interquartile range: 16-26]). The median change in 180-day CAT score was 1 (interquartile range: -5-6; 95% confidence interval of median: -3, 4). 11 patients (35.5%) had clinically meaningful decreases in CAT score, seven (22.6%) had no clinically meaningful change, and 13 (41.9%) had clinically meaningful increases.

In total, 39 patients had CAT score available at both baseline and within 180 days of Breztri/Trixeo initiation. CAT score within 180 days (median CAT score 22 [interquartile range: 17-29]) was not significantly different (p=0.459) as compared to baseline (median CAT score 24 [interquartile range: 16-27]). The median change in 180-day CAT score was 1 (interquartile range: -4-6; 95% confidence interval of median: -3, 4). 13 patients (33.3%) had clinically meaningful decreases in CAT score, nine (23.1%) had no clinically meaningful change, and 17 (43.6%) had clinically meaningful increases.

9.2.3 Factors associated with the primary outcome and with changes in CAT score

Results of univariable logistic regression for associations between baseline patient characteristics and the primary outcome (90-day medication success) are summarized in Supplementary Table 1. Older age was associated with significantly higher odds of achieving 90-day medication success (odds ratio per year increase: 1.06 [1.00, 1.12], p=0.034), while inactive asthma (odds ratio 0.12 [0.02, 0.64], p=0.013), evidence of asthma before age 40 (odds ratio 0.13 [0.03, 0.46], p=0.002), higher number of acute OCS prescriptions in the

baseline year (odds ratio per prescription increase: 0.91 [0.82, 1.00], p=0.047), and higher average daily dose of SABA prescription in the baseline year (odds ratio per mcg/day increase: 1.00 [1.00, 1.00], p=0.006) were associated with lower odds of achieving 90-day medication success.

To identify risk factors associated with the primary outcome, multivariable logistic regression with LASSO using Akaike's information criterion (AIC) as the selection criterion was performed separately on the 200 patients with all candidate baseline variables available. Forward stepwise logistic regression could not be performed due to insufficient information. Only average daily dose of SABA prescription in the baseline year (odds ratio per mcg/day increase: 1.00 [1.00, 1.00], p=0.007) was selected for the model.

Results of univariable linear regression for associations between baseline patient characteristics and changes in CAT score are summarized in Supplementary Table 2. A higher baseline CAT score was associated with larger decreases in CAT score (coefficient -0.47 [-0.67, -0.27], p<0.001).

Both forward stepwise linear regression and LASSO (using any selection criterion) on the 82 patients with all candidate baseline variables available selected baseline CAT score as a predictor of changes in CAT score, with higher baseline CAT score associated with larger decreases in CAT score (coefficient -0.51 [-0.72, -0.31], p<0.001).

A *post hoc* exploratory analysis was performed on the 82 patients with all candidate baseline variables available to construct a multivariable logistic model predicting clinically meaningful improvements (≥2 points' decrease) in CAT score as the dependent variable. While forward stepwise regression could not be performed due to insufficient data, LASSO any selection criterion selected only baseline CAT score for the model. In agreement with the above analyses, a higher baseline CAT score was associated with significantly higher odds of clinically meaningful improvement in CAT score (odds ratio 1.15 [1.05, 1.25], p=0.002).

When the above analyses were repeated including only patients with a baseline CAT score within 2 years of the index date, baseline CAT score was still the only factor significantly associated with changes in CAT score.

9.2.4 Medication success assessed at 180 days

In total, 184 of 285 patients (64.6%) completed 180-day follow-up. At 180 days, 169 patients (91.8%, 95% confidence interval: 86.9-95.4%) achieved medication success. Of the 15 patients who did not achieve 90-day medication success, two had a new diagnosis of heart

failure (13.3%; 1.1% of the 184 patients who completed 180-day follow-up), two had hospitalization for respiratory events (13.3%; 1.1% of the 184 patients who completed 180-day follow-up), one had pneumonia (6.7%; 0.5% of the 184 patients who completed 180-day follow-up), and 10 had complicated COPD exacerbation (66.7%; 5.4% of the 184 patients who completed 180-day follow-up).

Meanwhile, among the 54 patients who were excluded due to not achieving medication persistence at 90 days but had available 180-day follow-up data, one (1.9%) had myocardial infarction, five (9.3%) had complicated COPD exacerbations, and one (1.9%) died.

9.2.5 Amount of SABA used

The average daily dose of SABA used at baseline (the year prior to Breztri/Trixeo initiation), and at 90 and 180 days are shown in Table 7.

Table 7 Average daily dose of SABA used at baseline, and 90 and 180 days. Data was available for all patients.

Average daily SABA use, mcg/day	Baseline, N (%)	90-day, N (%)	180-day, N (%)
0 <101	91 (31.9)	109 (38.3)	95 (33.3)
101 <201	28 (9.8%)	0 (0)	24 (8.4)
201 <301	24 (8.4%)	39 (13.7)	21 (7.4)
301 <401	20 (7.0%)	1 (0.4)	20 (7.0)
>401	122 (42.8%)	136 (47.7)	125 (43.9)

9.2.6 Acceptability of medication change

The number of Breztri/Trixeo prescriptions after initiation was taken as a surrogate of the acceptability of medication change, as summarized in Table 8.

Table 8 Number of Breztri/Trixeo prescriptions after initiation at 90' and 180 days. Data was available for all patients.

Number of Breztri/Trixeo prescriptions, N	90-day, N (%)	180-day, N (%)
2	75 (26.3)	31 (10.9)
3	97 (34.0)	50 (17.5)
4	93 (32.6)	35 (12.3)
5	18 (6.32)	50 (17.5)
6	0 (0)	49 (17.2)
7	1 (0.4)	45 (15.8)
8	1 (0.4)	18 (6.3)
9	0 (0)	5 (1.8)
≥10	0 (0)	2 (0.7)

9.2.7 Adherence

The medication possession ratio throughout the study period is summarized in Table 9 as a surrogate for adherence.

Table 9 Medication possession ratio throughout the study period. Data was available for all patients.

Medication possession ratio, %	Number of patients (%)
25<50	7 (2.5)
50<75	45 (15.8)
75<100	87 (30.5)
100<125	114 (40)
125<150	27 (9.5)
≥150	5 (1.8)

9.2.8 Overall number of inhalers used

The overall numbers of inhalers used at 90 and 180 days are shown in Table 10.

Table 10 Overall numbers of inhalers used at 90 and 180 days. Data was available for all patients.

Number of inhalers used, N	90-day, N (%)	180-day, N (%)
0	95 (33.3)	75 (26.3)
1-2	95 (33.3)	58 (20.4)
3-6	84 (29.5)	105 (36.9)
7-10	10 (3.5)	29 (10.2)
>10	1 (0.4)	18 (6.3)

9.2.9 Change in COPD control

In total, nine patients had data for COPD control available both before and after initiation of Breztri/Trixeo. Eight (88.9%) had poor control before initiation of Breztri/Trixeo, with the same observed after initiation of Breztri/Trixeo. The two-sided sign test indicated that patients' COPD control were not significantly different following Breztri/Trixeo initiation (p=1.000).

9.2.10 Change in exercise capacity

Data for changes in exercise capacity after initiation of Breztri/Trixeo were available for 33 patients. Supplementary Figure 4 summarizes the time between Breztri/Trixeo initiation and the time of follow-up exercise capacity assessment. Three patients (9.1%) reported that they exercised more often following Breztri/Trixeo initiation, 12 (36.4%) reported that they exercised less often, while 18 (54.6%) reported no difference. The two-sided sign test indicated that patients exercised significantly less often following Breztri/Trixeo initiation (p=0.035).

10 Summary and Discussion

This real-world historical cohort showed that Breztri/Trixeo achieved the pre-specified primary outcome of medication success, with the vast majority of patients having early (90-day) and sustained (180-day) medication success. However, CAT score increased significantly following Breztri/Trixeo initiation, accompanied by significantly lower exercise frequency.

Findings for the primary outcome echoed those of the ETHOS trial, which reported significant superiority of Breztri/Trixeo over monotherapies and dual therapies in patients with moderate to very severe COPD, resulting in significantly less COPD exacerbation.[6] These findings further reinforces the efficacy of Breztri/Trixeo in the real world, with subgroup analyses showing that the efficacy was not affected by asthma status, whether patients stepped up from non-triple therapy or switched from another triple therapy, or the number of COPD exacerbations prior to initiating Breztri/Trixeo.

Nonetheless, we observed significantly higher CAT score and lower exercise frequency after Breztri/Trixeo initiation than baseline. Whilst this might seem to be at odds with the primary outcome, several factors meant that this finding should be interpreted with caution and taken as exploratory / hypothesis-generating only. First, as Breztri/Trixeo remains a novel inhaler for patients with COPD, the number of patients receiving Breztri/Trixeo has remained relatively low. To maximize statistical power, we aggregated data with considerable variations in the duration between Breztri/Trixeo initiation and data recording. This disregarded any potential time-dependency of treatment effects, which could have significantly affected the results. Indeed, we observed a weak but statistically significant positive correlation between the time between Breztri/Trixeo initiation and follow-up CAT score measurement. This was consistent with COPD worsening gradually over time, which was expected as the study population generally had advanced COPD with poor control at

baseline (78% with mMRC score of 2 or above, median CAT score of 21.5, 50% with <50% predicted FEV1 post-bronchodilator, and 37% active smokers).

Additionally, although Breztri/Trixeo was found to have high acceptability, it was unclear whether the patients continued using Breztri/Trixeo up to the point of CAT score / other patient-related outcome data reporting. This was particularly important for timepoint-non-specific outcomes such as exercise capacity, as patients who were no longer receiving Breztri/Trixeo at the time of data reporting may have worse outcomes either from treatment discontinuation, or from any adverse event that necessitated treatment discontinuation. Furthermore, initiation of Breztri/Trixeo per se may indicate recent worsening of clinical state, and any change in treatment may heighten patients' awareness of adverse effects and changes in physical state. Both of these may fictitiously lead to worse clinical outcomes, especially in the absence of a control group whose treatment is also changed in some way. As such, further studies with regular, prospective data collection and careful control group selection are required to clearly delineate the changes in CAT score or other patient-reported outcomes over time after Breztri/Trixeo initiation. Our findings also highlight the need for practices to better utilize CAT score and other patient-reported tools to monitor responses to therapy.

11 Strengths and Limitation(s)

This study used all eligible new users of Breztri/Trixeo in a large real-world database. The real-life design of this study provided high generalisability of the results to primary care patients managed in actual primary care practice. Additionally, the availability of patient-reported outcomes allowed in-depth exploration of disease state.

It was worth noting the caveat that the time that elapsed between Breztri/Trixeo initiation and CAT score and patient-reported outcome data recording / collection varied considerably between patients, limiting interpretability and real-world applicability of the analytic results. Also, patient-reported outcome data was missing for some patients, potentially predisposing to selection bias, e.g., patients who were more health-conscious may have been more willing to provide such data, which may have confounded the study results. Moreover, the primary outcome, medication success, was novel and not necessarily well-validated, possibly requiring further evaluation. Additionally, no control group was included in this study, meaning that no conclusion may be made as to whether Breztri/Trixeo provided incremental benefits to patients with COPD, compared to or on top of standard therapies. Furthermore, the observational nature of this study predisposed to residual and unmeasured confounders.

This was partially mitigated by using a pre-post design for some exploratory outcomes. Lastly, the dataset represented information collected for clinical and routine use rather than specifically for research purposes.

12 Conclusion

Breztri/Trixeo achieved overall medication success, with the vast majority of patients with COPD that were prescribed Breztri/Trixeo having early (90-day) and sustained (180-day) medication success. Baseline daily dose of SABA prescription may be a predictor of early medication success in these patients. However, CAT scores increased significantly following Breztri/Trixeo use, and patients may exercise less often after Breztri/Trixeo initiation. Larger studies with control groups are required to verify these findings.

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16 Appendices

16.1 Appendix 1: Potential PRO data from the OPC quality improvement program

The OPC quality improvement program is a free service provided by OPC to participating general practices. As part of the program, some patients may have completed the OPC questionnaire (Appendix Table 1), which includes assessment of the CAT score. Treatment satisfaction may be assessed by relevant measures as part of the quality improvement program as well.

Appendix Table 1. Domains of the OPC Questionnaire.

OPC Questionnaire Domains	Number of Questions
CAT	8
Cough Severity	1
Sputum	1
Breathing Problems	1
Breathlessness/ mMRC	5
Physical Activity	1
Exacerbation QOF	2
Flare-up treatment	3
Hospital Admittance	2
Reliever Inhaler	1
Maintenance Medication	1
Medication Adherence	1
Inhaler technique	1
Smoking	3
Action Plan	1
Rescue Pack	2
Goal Setting	2
TOTAL	**36**

Specifically, responses to the question for the domain “physical activity” constitute the outcome data for exploratory outcome 10 (exercise capacity). Patients are asked to respond to the question “thinking about exercise, how much time do you spend doing exercise or

activities per day (e.g., walking)" with one of the following categories which thus constitute the nominal categories for exploratory outcome 10:

- None
- 15 minutes
- 30 minutes
- 45 minutes
- 1 hour
- 2 hours
- 3 hours or more

Additionally, where possible, we determined COPD control from CAT scores, which constituted the outcome data for exploratory outcome 9 (COPD control). The COPD control tool was developed and validated to help define the current clinical situation of a patient and therefore support individualized evaluation and management.[16–18] To be considered to have good control ('controlled'), patients were required to have low impact and good stability (Figure 5).[18] Patients not fulfilling both of these requirements were considered 'not controlled'.[18] These categories ('controlled' and 'not controlled') thus constitute the data categories for the binary exploratory outcome 9.

Figure 5 The COPD control tool

CAT ASSESSMENT	
Low Impact	
- CAT	0-10 if FEV1 ≥ 50% 0-16 if FEV1 < 50%
Stability	
- Changes in CAT	≤ 2 points
Control	Low impact + Stability

16.2 Appendix 2: mMRC score

The mMRC score is measured in a scale of 0-4:

0 - Dyspnea only with strenuous exercise

1 - Dyspnea when hurrying or walking up a slight hill

2 - Walks slower than people of the same age because of dyspnea or has to stop for breath when walking at own pace

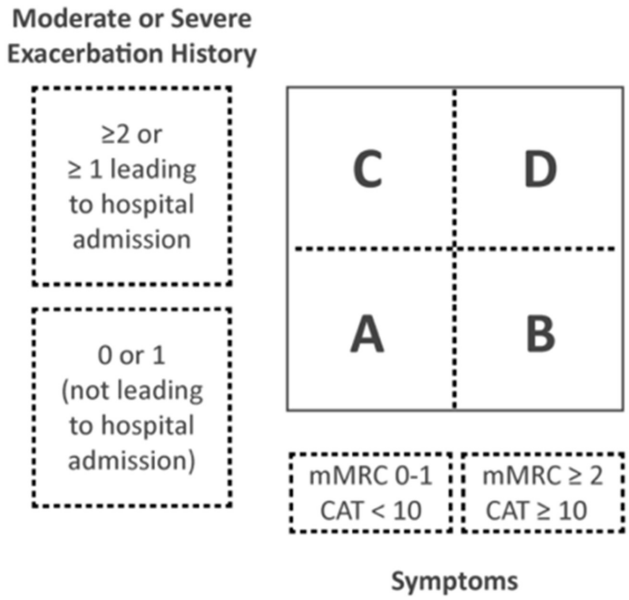
3 - Stops for breath after walking 100 yards (91 m) or after a few minutes

4 - Too dyspneic to leave house or breathless when dressing

16.3 Appendix 3: GOLD treatment groups

Definitions of GOLD treatment groups are summarized in Figure 6.

Figure 6 Definition of GOLD treatment groups



16.4 Appendix 4: CAT questionnaire

The CAT questionnaire contains 8 items, each of which adopts a Likert-type scale of 0-5 scores. The items are as follows (bracketed number indicates the corresponding score):

1. “I never cough” (0) to “I cough all the time” (5)
2. “I have no phlegm (mucus) in my chest at all” (0) to “My chest is completely full of phlegm (mucus)” (5)
3. “My chest does not feel tight at all” (0) to “My chest feels very tight” (5)
4. “When I walk up a hill for one flight of stairs I am not breathless” (0) to “When I walk up a hill or one flight of stairs I am very breathless” (5)
5. “I am not limited doing any activities at home” (0) to “I am very limited doing activities at home” (5)
6. “I am confident leaving my home despite my lung condition” (0) to “I am not at all confident leaving my home because of my lung condition” (5)
7. “I sleep soundly” (0) to “I don’t sleep soundly because of my lung condition” (5)

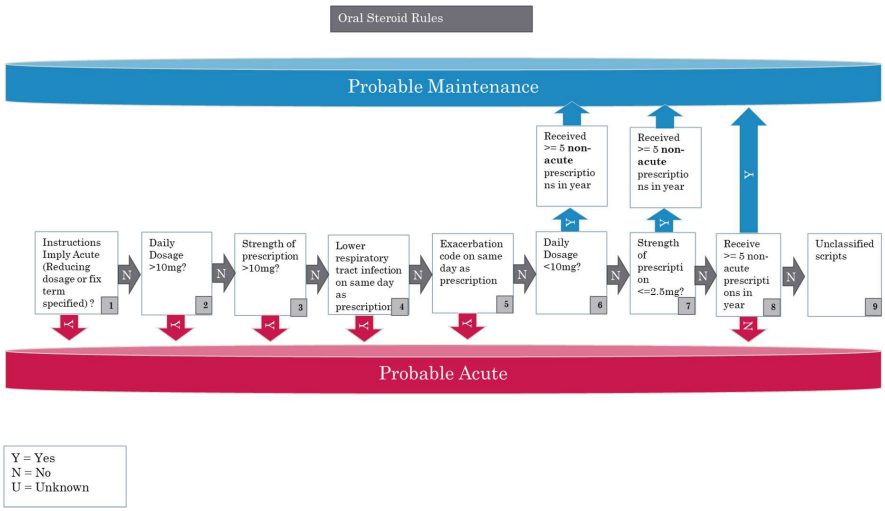
8. "I have lots of energy" (0) to "I have no energy at all" (5)

The CAT score is calculated as a sum of the score from all 8 items above.

16.5 Appendix 5: OPRI algorithm for acute OCS courses

Acute courses of OCS prescriptions are identified and defined using the algorithm depicted in Figure 7.

Figure 7 OPRI algorithm for acute OCS courses



16.6 Supplementary Tables

Supplementary Table 1 Results of univariable logistic regression for associations between baseline patient characteristics and the primary outcome (90-day medication success).

Variable	Sample size	Odds ratio [95% confidence interval]	p value
Age in years	285	1.06 [1.00, 1.12]	0.034
Age categories, years	285		
40<60		1 (reference)	
60<80		4.92 [1.27, 19.05]	0.021
80<100		5.22 [0.59, 46.38]	0.138
Female	284	0.49 [0.12, 1.93]	0.307
BMI in kg/m^2	284	1.03 [0.94, 1.13]	0.542
BMI categories, kg/m^2	284		
0<18.5		1 (reference)	
18.5<25		1.18 [0.12, 11.20]	0.888
25<30		2.35 [0.20, 27.45]	0.495
30<100		1.90 [0.19, 19.38]	0.587
Smoking status	285		

Current smoker		1 (reference)	
Ex-smoker		1.15 [0.32, 4.17]	0.833
Index of multiple deprivation decile	279	1.02 [0.79, 1.32]	0.875
Ethnicity	285	Not estimable	
Asthma	285		
Never diagnosed		1 (reference)	
Inactive asthma		0.12 [0.02, 0.64]	0.013
Active asthma		0.39 [0.06, 2.37]	0.305
Validated COPD diagnosis	285	0.63 [0.16, 2.50]	0.514
Evidence of asthma before age 40	285	0.13 [0.03, 0.46]	0.002
Rhinitis	285	2.51 [0.31, 20.22]	0.387
Eczema	285	0.36 [0.10, 1.28]	0.116
Nasal polyp	285	Not estimable	
Sinusitis	285	Not estimable	
Gastroesophageal reflux disease	285	1.58 [0.33, 7.62]	0.566
Diabetes mellitus	285	0.53 [0.13, 2.12]	0.371
Osteoporosis	285	1.58 [0.19, 12.78]	0.670
Hypertension	285	1.86 [0.47, 7.35]	0.376
Ischaemic heart disease	285	0.31 [0.08, 1.25]	0.099
Heart failure	285	0.94 [0.11, 7.71]	0.954
Chronic kidney disease	285	Not estimable	
Depression or anxiety	285	0.34 [0.07, 1.64]	0.181
Sleep apnoea	285	0.67 [0.08, 5.55]	0.709
Sleep disorder	285	1.24 [0.26, 5.98]	0.790
Time since first validated COPD diagnosis, years	171	0.98 [0.84, 1.14]	0.765
FEV1, litre	70	0.12 [0.01, 2.68]	0.182
Percentage predicted FEV1, %	50	1.49 [0.64, 3.50]	0.355
FEV1/FVC ratio	121	0.98 [0.92, 1.03]	0.388
FEV1/FVC ratio <0.7	121	0.96 [0.10, 8.97]	0.970
mMRC score	263	0.70 [0.36, 1.36]	0.290
GOLD group	285		
A		1 (reference)	
B		1.50 [0.12, 18.84]	0.735
C		Not estimable	
D		3.46 [0.38, 31.62]	0.271
CAT score	218	1.00 [0.92, 1.09]	0.955
Number of COPD exacerbations	285	0.70 [0.46, 1.07]	0.103
Number of COPD exacerbations in categories	285		
0		1 (reference)	
1		0.22 [0.05, 1.03]	0.054
2		0.15 [0.02, 0.95]	0.044
3		Not estimable	
≥4		0.18 [0.02, 1.89]	0.153
Number of acute oral corticosteroid prescriptions	285	0.91 [0.82, 1.00]	0.047
Number of acute oral corticosteroid prescriptions in categories	285		
0		1 (reference)	
1		Not estimable	
2		Not estimable	
3		0.23 [0.04, 1.46]	0.120
≥4		0.17 [0.04, 0.72]	0.017
Antibiotic prescription within 3 days of a lower respiratory condition	285	0.92 [0.71, 1.21]	0.560
Antibiotic prescription within 3 days of a lower respiratory condition in categories	285		
0		1 (reference)	
1		0.53 [0.10, 2.81]	0.454
2		0.19 [0.03, 1.05]	0.057
3		0.10 [0.01, 1.07]	0.057

≥4		Not estimable	
Average daily dose of short-acting beta-agonists, mcg/day	285	1.00 [1.00, 1.00]	0.006
Average daily dose of short-acting beta-agonists in categories, mcg/day	285		
0		1 (reference)	
1<100		Not estimable	
100<200		Not estimable	
200<300		0.69 [0.06, 7.93]	0.763
300<400		Not estimable	
≥400		0.49 [0.10, 2.43]	0.383
COPD consultations	285	1.10 [0.75, 1.62]	0.612
COPD consultations in categories	285		
0		1 (reference)	
1		1.07 [0.11, 10.09]	0.956
2-4		1.45 [0.16, 13.11]	0.739
5-7		Not estimable	
≥8		Not estimable	
Consultations	285	0.99 [0.96, 1.02]	0.693
Consultations in categories	285		
0-1		1 (reference)	
5-8		0.19 [0.02, 1.90]	0.158
9-13		0.96 [0.11, 8.27]	0.967
14-17		1.15 [0.13, 9.87]	0.901
18-22		1.22 [0.14, 10.51]	0.854
≥23		Not estimable	
Maintenance COPD treatment immediately prior to Breztri/Trixeo initiation	285		
None		1 (reference)	
ICS		0.26 [0.02, 4.48]	0.354
ICS+LABA		0.36 [0.04, 3.61]	0.387
ICS+LABA+LAMA		0.80 [0.08, 7.86]	0.846
LABA		Not estimable	
LABA+LAMA		0.50 [0.04, 5.71]	0.577
LAMA		Not estimable	
Other		Not estimable	
LAMA use only	285	Not estimable	
LABA use only	285	Not estimable	
LABA+LAMA	285	1.40 [0.17, 11.37]	0.753
ICS+LABA	285	0.86 [0.24, 3.11]	0.815
Free triple therapies	285	0.71 [0.18, 2.82]	0.624
Fixed triple therapies	285	1.12 [0.28, 4.42]	0.875
Number of SABA inhalers used	285	0.93 [0.87, 1.00]	0.050
Number of SABA inhalers used in categories	285		
0		1 (reference)	
1-2		Not estimable	
3-6		1.34 [0.12, 15.26]	0.812
7-10		1.25 [0.11, 14.26]	0.855
11-16		0.50 [0.08, 3.09]	0.454
≥17		0.32 [0.05, 2.00]	0.222
Blood eosinophil count, cells/µL	270	1.01 [1.00, 1.01]	0.097
Blood eosinophil count in categories, cells/µL	270		
0<50		1 (reference)	
50<350		Not estimable	
≥350		Not estimable	

Supplementary Table 2 Results of univariable logistic regression for associations between baseline patient characteristics and changes in CAT score.

Variable	Sample size	Coefficient [95% confidence interval]	p value
Age in years	89	-0.00 [-0.16, 0.16]	0.999
Age categories, years	89		
40<60		0 (reference)	
60<80		-1.28 [-5.73, 3.17]	0.570
80<100		-1.08 [-6.74, 4.59]	0.706
Female	89	1.91 [-1.40, 5.23]	0.254
BMI in kg/m^2	89	-0.14 [-0.38, 0.09]	0.237
BMI categories, kg/m^2	89		
0<18.5		0 (reference)	
18.5<25		3.35 [-6.33, 13.02]	0.493
25<30		0.93 [-8.67, 10.52]	0.848
30<100		1.61 [-7.86, 11.08]	0.736
Smoking status	89		
Current smoker		0 (reference)	
Ex-smoker		0.85 [-2.73, 4.43]	0.638
Index of multiple deprivation decile	89	-0.32 [-1.10, 0.46]	0.415
Ethnicity	89		
White		0 (reference)	
Mixed/others		2.25 [-7.02, 11.52]	0.631
Unknown/missing		-0.55 [-7.82, 6.71]	0.880
Asthma	89		
Never diagnosed		0 (reference)	
Inactive asthma		-1.01 [-5.13, 3.11]	0.628
Active asthma		-2.10 [-6.22, 2.02]	0.313
Validated COPD diagnosis	89	-0.99 [-4.65, 2.66]	0.591
Evidence of asthma before age 40	89	2.08 [-3.42, 7.58]	0.455
Rhinitis	89	-1.37 [-5.93, 3.19]	0.552
Eczema	89	-0.80 [-4.46, 2.85]	0.664
Nasal polyp	89	-0.14 [-9.36, 9.09]	0.977
Sinusitis	89	2.23 [-13.55, 18.01]	0.780
Gastroesophageal reflux disease	89	1.70 [-2.20, 5.60]	0.390
Diabetes mellitus	89	-1.20 [-5.53, 3.13]	0.582
Osteoporosis	89	4.62 [-0.56, 9.80]	0.079
Hypertension	89	-1.86 [-5.18, 1.46]	0.269
Ischaemic heart disease	89	-1.46 [-6.02, 3.11]	0.528
Heart failure	89	3.32 [-1.51, 8.14]	0.175
Chronic kidney disease	89	-0.13 [-4.47, 4.20]	0.951
Depression or anxiety	89	-1.42 [-4.81, 1.98]	0.409
Sleep apnoea	89	0.85 [-6.38, 8.08]	0.816
Sleep disorder	89	-1.17 [-5.08, 2.74]	0.554
Time since first validated COPD diagnosis, years	63	-0.11 [-0.49, 0.26]	0.541
FEV1, litre	18	-3.95 [-9.69, 1.79]	0.164
Percentage predicted FEV1, %	17	-0.00 [-0.18, 0.18]	0.981
FEV1/FVC ratio	49	-0.09 [-0.23, 0.04]	0.166
FEV1/FVC ratio <0.7	49	1.68 [-2.89, 6.24]	0.461
mMRC score	87	-1.19 [-3.06, 0.69]	0.211
GOLD group	89		
A		0 (reference)	
B		-3.63 [-14.29, 7.04]	0.501
C		-2.22 [-12.05, 7.60]	0.654
D		-0.63 [-9.96, 8.69]	0.893
CAT score	89	-0.47 [-0.67, -0.27]	<0.001
Number of COPD exacerbations	89	-0.21 [-2.17, 1.75]	0.832
Number of COPD exacerbations in categories	89		

0		0 (reference)	
1		1.82 [-1.78, 5.42]	0.318
2		1.38 [-7.72, 10.47]	0.764
3		7.21 [-3.83, 18.25]	0.198
≥4		-11.29 [-22.33, -0.25]	0.045
Number of acute oral corticosteroid prescriptions	89	0.18 [-0.44, 0.79]	0.573
Number of acute oral corticosteroid prescriptions in categories	89		
0		0 (reference)	
1		7.09 [2.84, 11.35]	0.001
2		-1.19 [-7.67, 5.29]	0.716
3		-0.40 [-6.12, 5.332]	0.890
≥4		3.18 [-1.28, 7.63]	0.160
Antibiotic prescription within 3 days of a lower respiratory condition	89	0.60 [-1.24, 2.44]	0.519
Antibiotic prescription within 3 days of a lower respiratory condition in categories	89		
0		0 (reference)	
1		2.46 [-1.47, 6.39]	0.217
2		1.38 [-7.66, 10.41]	0.763
3		-11.29 [-22.27, -0.31]	0.044
≥4		7.21 [-3.77, 18.19]	0.195
Average daily dose of short-acting beta-agonists, mcg/day	89	0.00 [-0.00, 0.00]	0.851
Average daily dose of short-acting beta-agonists in categories, mcg/day	89		
0		0 (reference)	
1<100		2.57 [-3.41, 8.54]	0.395
100<200		6.33 [0.51, 12.16]	0.033
200<300		2.25 [-5.05, 9.55]	0.542
300<400		8.18 [1.27, 15.09]	0.021
≥400		1.40 [-3.17, 5.96]	0.544
COPD consultations	89	-0.19 [-0.92, 0.55]	0.614
COPD consultations in categories	89		
0		0 (reference)	
1		3.65 [-4.66, 11.97]	0.385
2-4		4.98 [-3.08, 13.04]	0.223
5-7		4.20 [-6.19, 14.59]	0.424
≥8		-1.71 [-11.42, 7.99]	0.726
Consultations	89	-0.05 [-0.15, 0.05]	0.339
Consultations in categories	89		
0-1		0 (reference)	
5-8		5.00 [-8.57, 18.57]	0.466
9-13		4.00 [-5.59, 13.59]	0.409
14-17		5.60 [-3.67, 14.87]	0.233
18-22		7.25 [-1.79, 16.29]	0.115
≥23		2.89 [-5.24, 11.01]	0.482
Maintenance COPD treatment immediately prior to Breztri/Trixeo initiation	89		
None		0 (reference)	
ICS		-0.44 [-12.44, 11.57]	0.942
ICS+LABA		-1.70 [-7.28, 3.87]	0.545
ICS+LABA+LAMA		-0.77 [-5.75, 4.22]	0.761
LABA+LAMA		-1.85 [-7.11, 3.41]	0.487
LAMA		-2.94 [-13.01, 7.13]	0.563
LABA+LAMA	89	-1.15 [-5.20, 2.91]	0.575
ICS+LABA	89	1.26 [-2.25, 4.77]	0.477
Free triple therapies	89	0.67 [-3.47, 4.81]	0.748
Fixed triple therapies	89	-0.57 [-4.12, 2.98]	0.750

Number of SABA inhalers used	89	0.02 [-0.22, 0.26]	0.874
Number of SABA inhalers used in categories	89		
0		0 (reference)	
1-2		4.64 [-0.65, 9.93]	0.085
3-6		5.06 [-0.38, 10.51]	0.068
7-10		2.60 [-3.15, 8.35]	0.372
11-16		-0.56 [-6.01, 4.88]	0.838
≥17		3.75 [-2.46, 9.96]	0.233
Blood eosinophil count, cells/µL	84	-0.00 [-0.01, 0.01]	0.968
Blood eosinophil count in categories, cells/µL	84		
0<50		0 (reference)	
50<350		-2.44 [-18.51, 13.63]	0.763
≥350		-2.00 [-18.48, 14.48]	0.810

Supplementary Table 3 90-day and 180-day BMI categories, tabulated against baseline BMI

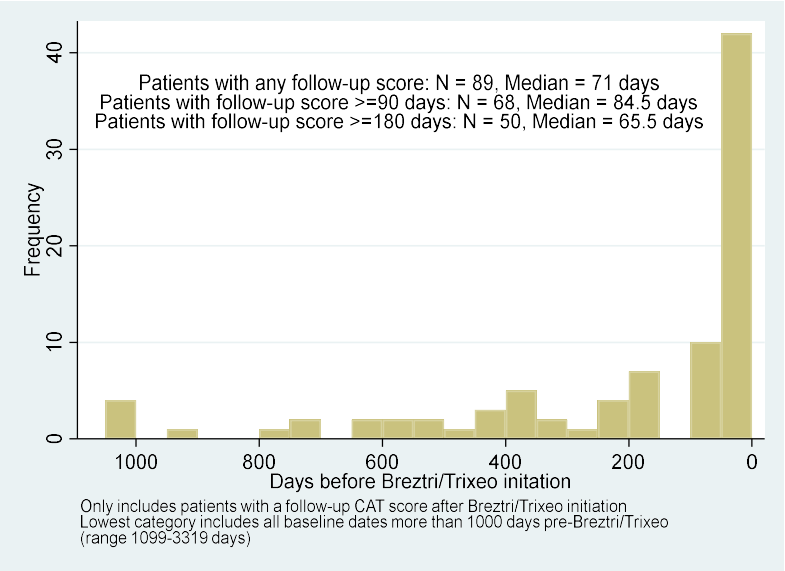
Baseline BMI (kg/m^2)	90-day BMI (kg/m^2)					180-day BMI (kg/m^2)				
Categories	0 <18.5	18.5 <25	25 <30	30 <100	Total	0 <18.5	18.5 <25	25 <30	30 <100	Total
0 <18.5	6	0	0	0	6	10	0	0	0	10
18.5 <25	0	17	0	0	17	0	24	0	0	24
25 <30	0	1	13	0	14	0	2	19	0	21
30 <100	0	0	1	30	31	0	0	2	46	48
Total	6	18	14	30	68	10	26	21	46	103

Supplementary Table 4 90-day and 180-day smoking status, tabulated against baseline smoking status

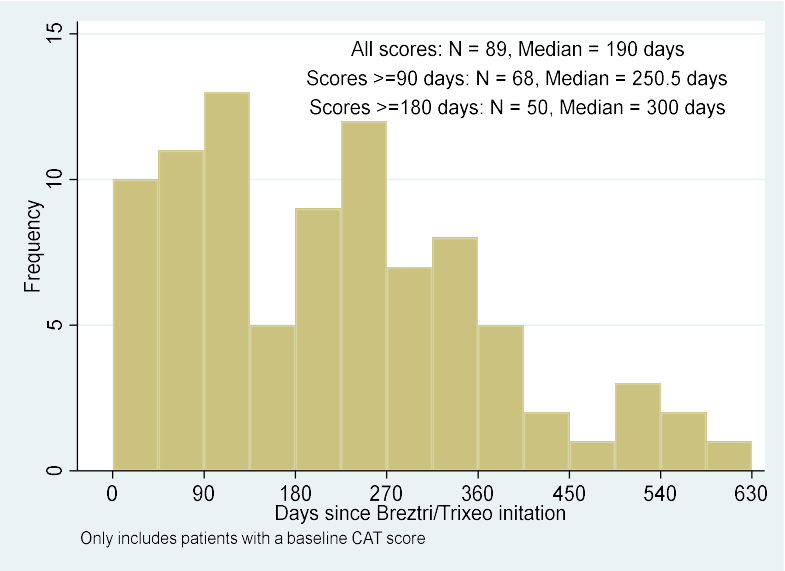
Baseline smoking status	90-day smoking status			180-day smoking status		
Categories	Current	Ex	Total	Current	Ex	Total
Current	3	1	4	4	2	6
Ex	0	1	1	0	3	3
Total	3	2	5	4	5	9

16.7 Supplementary Figures

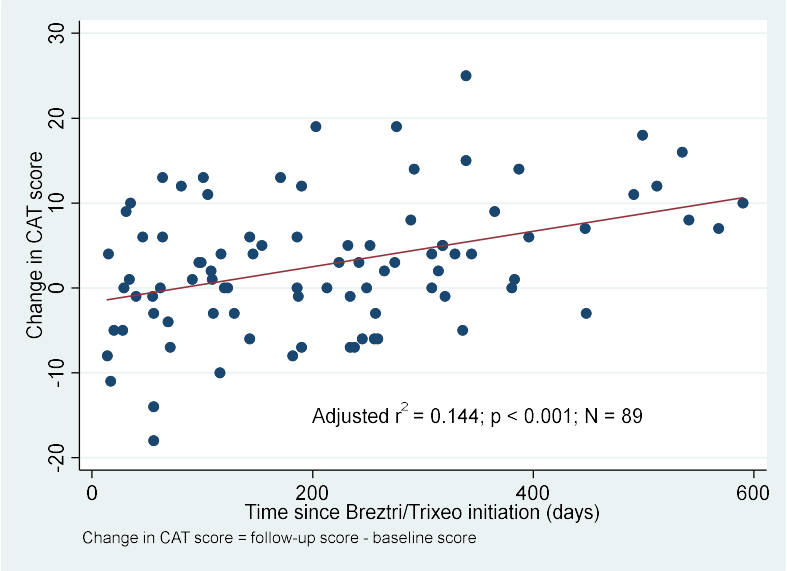
Supplementary Figure 1 Distribution of time between baseline CAT score recording and Breztri/Trixeo initiation



Supplementary Figure 2 Distribution of time between Breztri/Trixeo initiation and follow-up CAT score recording



Supplementary Figure 3 Scatter plot exploring the potential association between change in CAT score and the time between Breztri/Trixeo initiation and the time of follow-up CAT score recording



Supplementary Figure 4 Distribution of time between Breztri/Trixeo initiation and follow-up exercise capacity assessment