Final report

Real-life effectiveness evaluation of budesonide/formoterol (BF) DuoResp® Spiromax® for the management of asthma and COPD

Post-marketing historical, observational study to compare clinical and cost outcomes before and after switching to Duoresp Spiromax (phase 3) and between patients who switched to Duoresp Spiromax and who remained on Symbicort Turbohaler (phase 4)

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Contents

Index of tables

Index of figures

List of abbreviations

AE	Adverse Event
A&E	Accident and Emergency
BDP/FOR	Beclometasone/Formoterol
BMI	Body Mass Index
BUD/FOR	Budesonide/Formoterol
CCI	Charlson Comorbidity Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
DPI	Dry Powder Inhaler
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GERD	Gastroesophageal Reflux Disease
GP	General Practitioner
FDC	Fixed Dose Combination
HES	Hospital Episode Statistics
ICS	Inhaled Corticosteroid
IQR	Interquartile Range
LABA	Long-Acting Beta-Agonist
LAMA	Long-Acting Muscarinic Antagonist
LRTI	Lower Respiratory Tract Infection
LTRA	Leukotriene receptor antagonist
MART	Maintenance and reliever therapy
MDI	Metered Dose Inhaler
MHRA	Medicines and Healthcare products Regulatory Agency
ONS	Office of National Statistics
OR	Odds Ratio
QOF	Quality and Outcomes Framework
RR	Rate Ratio
SABA	Short-Acting Beta2 Agonist
SAE	Serious Adverse Event
SAMA	Short-Acting Muscarinic Antagonist
THEO	Theophylline

1.0 Executive summary

1.1 Introduction

Patients with asthma and/or chronic obstructive pulmonary disease (COPD) suffer greatly when their symptoms are not controlled. Disease control depends not only on effective inhaled treatment, but also on the quality of the inhaler device that delivers the treatment. Increasing evidence has shown that many patients fail to use their inhaler devices correctly and this leads to poorer outcomes. Enhancing the usability of devices has therefore become a vital element of developing treatment, and devices such as Spiromax® have been designed with features to reduce common inhaler errors. Clinicians have a growing number of devices to choose from when prescribing treatment, and evidence of the benefit of individual devices is important to allow optimal choices to be made. Evidence from a real-life setting is particularly relevant, as it demonstrates what is observed when patients use their inhalers as normal, in their everyday lives.

1.2 Study aims and objectives

The aim of phase 3 of this study was to evaluate the real-life effectiveness of DuoResp Spiromax – in terms of clinical and cost-effectiveness outcomes – by comparing asthma and COPD cohorts before and after patients switched to DuoResp Spiromax, from other ICS/LABA FDC.

The aim of phase 4 of the study was to evaluate the effectiveness of DuoResp Spiromax, this time comparing outcomes of patients who had switched to DuoResp Spiromax to those who had remained on another ICS/LABA FDC.

1.3 Methods

DuoResp Spiromax will be abbreviated as *DuoResp*, Seretide Turbohaler as *Turbohaler* and Seretide Accuhaler as *Accuhaler.*

Phases 3 and 4 were both historic cohort studies. Two primary care databases – the Optimum Patient Care Research Database and the Clinical Practice Research Datalink – were used to identify prescriptions of DuoResp, Turbohaler and Accuhaler in adult patients (≥18 years) with asthma and/or COPD, as identified by a diagnostic Read code. Patients had to have at least 2 years of continuous data, comprising a one-year baseline and one-year outcome period. In addition, patients prescribed DuoResp had to be registered at practices considered to have a policy of DuoResp adoption.

Phase 3 was a single-arm study, including only patients who switched to DuoResp. Non-inferiority of the primary outcome, risk domain control, was assessed using conditional logistic regression to

compare risk domain control before and after the switch, adjusting for relevant confounders. Conditional Poisson and logistic regression models were used to compare secondary outcomes, including: exacerbation rates, hospitalisation rates, treatment stability and short-acting beta agonist (SABA) use. Adjusted differences in healthcare costs were estimated using generalised linear models.

Phase 4 was a matched study, including patients who had switched to DuoResp and patients who had remained on Turbohaler or Accuhaler. A baseline year of data was used to characterise patients and to match those who switched to DuoResp to those who remained on Turbohaler/Accuhaler. Exact 3:1 matching with nearest neighbor methods were used. Outcomes during one year of follow-up were then compared between the matched cohorts for non-inferiority. In case non-inferiority was met, superiority was tested for. As in phase 3, the primary outcome was risk domain control and several secondary outcomes were investigated. Similar methods to those used in phase 3 were used to compare all outcomes.

1.4 Results

After applying inclusion and exclusion criteria, 410 patients (262 in the asthma group and 148 in the COPD group) were included in the study, who had switched from Turbohaler to DuoResp. In phase 4, 385 of these patients were matched to 1,091 patients (743 asthma and 348 COPD) who had remained on Turbohaler. Accuhaler users were found to be low in number, and differed widely in terms of clinical characteristics. Besides this, Accuhaler contains other active substances that differ in PK/PD profile, what would make the study's focus on the impact of inhaler type less profound. The decision was made to focus on baseline Turbohaler users only.

The phase 3 study showed the difference in the percentage of patients achieving risk domain control between the baseline and the follow-up period to be 3.1% (95% confidence interval [CI], -5.9-12.1), showing non-inferiority of outcomes after the switch to DuoResp to outcomes before the switch (being on Turbohaler) at the -10% level. The switch from Turbohaler to DuoResp resulted in a significant increase in the average daily dose of inhaled corticosteroids in the COPD group (p=0.0010).

In phase 4, patient cohorts were matched on: age (mean [SD], 56 [15] in asthma; 70 [8] in COPD); gender (44% male in asthma; 50-53% male in COPD); baseline GINA control (8% uncontrolled, asthma only); baseline GOLD risk (35-39% in group A, COPD only); number of baseline exacerbations (20-21% ≥1 event in asthma; 55-59% ≥1 event in COPD); risk domain control (26-28% uncontrolled in asthma; 55-60% uncontrolled in COPD); number of baseline antibiotic courses (15-16% ≥1 in asthma; 43-44% ≥1 in COPD) and number of baseline acute oral corticosteroid courses (20-21% ≥1, matched in asthma only). Patients in the COPD group were also matched on

combination of drug therapy and ICS dose. In the outcome models, baseline variables showing residual confounding in the matched cohorts were adjusted on.

The adjusted odds ratio comparing DuoResp to Turbohaler in terms of the primary outcome - achieving risk domain control in the combined asthma and COPD groups - was 1.31 (95% confidence interval [CI], 0.99-1.73). The adjusted difference in achieving risk domain control was 6.6% (95% confidence interval [CI], -0.3-13.5) demonstrating non-inferiority of DuoResp compared to Turbohaler.

In the asthma group only, the DuoResp switch cohort had: a lower rate of exacerbations than the control cohort (adjusted rate ratio [RR], 0.76; 95% CI, 0.60-0.99); higher odds of achieving treatment stability (adjusted odds ratio [OR], 1.44; 95% CI, 1.02-2.04); lower odds of being in a high SABA dose category (adjusted OR, 0.71; 95% CI, 0.52-0.98), and; used less SABA inhalers than the control cohort (adjusted RR, 0.92; 95% CI, 0.86-0.99). No differences were found in the rate of respiratory-related hospitalisations, or in the likelihood of pneumonia incidence. In the COPD group, no significant differences were found in the secondary outcomes, between the DuoResp and Turbohaler treatment arms.

Adjusted mean healthcare cost was £492 (95% CI: £461, £523) for DuoResp users and £597 (95% CI: £575, £620) for Turbohaler users, for a difference of -£105 (95% CI: -£132, -£78) after adjusting for all baseline costs. This was estimated in the combined asthma/COPD group. The difference in cost over the difference in effectiveness resulted in a dominant incremental cost-effectiveness ratio (ICER) [*i.e.*, less costly, more effective].

1.5 Conclusion

Phase 3 - Switching from Turbohaler to DuoResp was not associated with poorer outcomes in the year following the switch compared to the baseline period.

Phase 4 - When comparing patients who switched to DuoResp to similar patients who remained on Turbohaler, DuoResp was found to be non-inferior to Turbohaler in terms of risk domain control of asthma/COPD. In patients with asthma, switching to DuoResp was associated with better outcomes, including: less exacerbations, treatment stability and lower SABA usage. Differences were not found in the COPD group. Finally, patients with asthma and/or COPD who switched to DuoResp incurred less respiratory-related healthcare costs per patient per year, compared to those who remained on Turbohaler, showing DuoResp to be cost-saving.

2.0 Background

Asthma and chronic obstructive pulmonary disease (COPD) are major non-communicable diseases associated with high morbidity, mortality and socio-economic costs.[1,2] For those affected, the symptoms experienced can have a considerable impact on day-to-day quality of life and can lead to increased healthcare use. Symptoms of COPD include cough, sputum production and shortness of breath: acute worsening of symptoms is known as an "exacerbation", which needs immediate medical care. As a result, patients with COPD can have poor health-related quality of life, which increases with the severity of airflow obstruction.[3] Patients with asthma have similar respiratory symptoms to COPD. Poor control of these symptoms (which may also result in an exacerbation) can reduce quality of life, restrict their daily activities and cause night time wakening.[4-6]

Asthma and COPD affect 300 and 65 million people worldwide, respectively.[7,8] As well as the impact on patient health, both diseases place a substantial burden on healthcare systems around the world. In 2015, disease management of asthma and COPD was estimated at 560-813 million Euro across Spain, Sweden and the UK.[9] The UK is among the highest in terms of asthma and COPD prevalence, globally, with research estimating a 13% COPD prevalence in those aged over 35,[10] and an asthma prevalence of approximately 16%.[7] It is clear that effective management of asthma and COPD is an important task in clinical and primary care in the UK.

Delivery of drugs by inhalation is a fundamental element of the modern management of asthma and COPD. It allows rapid delivery of drugs to the lungs in comparatively small doses. Inhaler device types include pressurised metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs), which are newer and intended to be more convenient to use than pMDIs.[11] DPIs do not require coordination of inhaler actuation and inhalation, which can be problematic to users of MDIs. They have dose counters, allowing users to know the amount of medication remaining in the device, whereas MDIs often do not have an external indication of when the device is empty. Functionality also varies between types of DPI, for example in the type of dose-loading mechanism or in the level of resistance to airflow within the device.

Despite efforts to improve usability, there is growing evidence in the literature that many patients do not use their inhalers correctly,[12-18] resulting in sub-optimal inhalation of medication, which may lead to poor control of symptoms.[19-23] A systematic review suggested that up to 94% of patients, depending on the DPI type and method of assessment, do not use their inhalers correctly.[24] Common errors include failure to exhale before inhalation[24,25] and not having a sufficient inhalation rate,[26] as inhalation must be rapid and forceful when using DPIs.[27]

DuoResp Spiromax® is a novel DPI device produced by Teva. It is a combination of budesonide and formoterol (BUD/FOR) for the management of asthma and COPD in adults (≥18 years old), where

use of an inhaled corticosteroid (ICS) /long-acting β2 agonist (LABA) is appropriate.[28] Teva received European Marketing Authorisation for this product in April 2014[29] and the product was launched in the UK in September 2014.[30]

DuoResp Spiromax® is indicated in the regular treatment of asthma in patients not adequately controlled with ICS and "as needed" inhaled short-acting β2 adrenoceptor agonists (SABA). It is also indicated in patients already adequately controlled on both ICS and LABA.[31] Further, DuoResp Spiromax® is recommended for treatment of patients with severe COPD (FEV_1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.[31]

DuoResp Spiromax® was developed to maximise user-friendliness, for improved treatment adherence and clinical outcomes.[32-34] The device provides patients with confirmation by taste (lactose) that a dose has been successfully administered, and a single-increment dose counter provides further means of monitoring therapy.[35]

With an increasing number of inhaler device options available, and high prevalence of incorrect inhalation technique among patients, choice of inhaler is becoming more and more important and so, there is a need to investigate comparative effectiveness. Pharmacokinetic equivalence of BUD/FOR DuoResp Spiromax® to BUD/FOR Turbohaler Turbohaler® was demonstrated in comparative studies.[36,37] However, the evidence of randomised controlled trials is limited.[38] Such trials often have strict inclusion and exclusion criteria which can exclude the most severe patients and patients who cannot use their devices correctly. Further, the monitoring of trials leads to a level of patient skill and compliance that is unlikely to be repeated in the real-life setting.[39] Evidence of the real-life effectiveness and cost-effectiveness[40] of DuoResp Spiromax® in comparison with other devices, is required, and is possible with the use of longitudinal electronic data from primary care databases.

The following report presents results of the last two phases of a 4-phase study which utilised clinical practice data from the two years following DuoResp Spiromax® launch. Phase 1 characterised patients with asthma and/or COPD who switched from other licensed fixed-dose combination (FDC) ICS/LABA inhalers, to DuoResp Spiromax®, and found that the majority had had poor disease control in the period before they switched*. Phase 2 investigated the persistence of the switch to DuoResp Spiromax® and found that in a six-month period, only 9.4% of patients switched again, from DuoResp Spiromax® to a different FDC ICS/LABA†.

The final phases aimed to assess the real-world effectiveness and the cost-effectiveness of

* Poster presented at ERS, London, September 2016
† Poster presented at ISPOR EU, Vienna, November 2016

DuoResp Spiromax® (further on only referred to as *DuoResp*) in patients that switched from Symbicort Turbohaler® (further on only referred to as *Turbohaler*) or Seretide Accuhaler® (further on only referred to as *Accuhaler*). Phase 3 aimed to compare outcomes in the year following the switch to those in the year up to the switch in DuoResp users only, while Phase 4 aimed to compare outcomes of patients prescribed DuoResp in the year following their switch to DuoResp from Turbohaler/Accuhaler, with patients who remained on Turbohaler/Accuhaler.

3.0 Study aims and objectives

3.1 Phase 3

3.1.1 Aims

To evaluate whether disease control, healthcare resource utilisation and costs are non-inferior or improve after a change to DuoResp within patients by comparing the patients' asthma and COPD outcomes and related costs before and after their change to DuoResp from other ICS/LABA FDCs. The study design was based on changes from either Turbohaler or Accuhaler. At the patient selection stage, however, it became apparent that including the Accuhaler patients was likely to weaken the analyses, given Accuhaler is not only a different inhaler device, but also contains different drug substances. The decision was made to focus on Turbohaler only, which is discussed in the results section. The objectives and methods in this report will refer to the study as originally planned and therefore will include Accuhaler, though the Accuhaler users were not analysed.

3.1.2 Objectives

1. To evaluate whether DuoResp is non-inferior to the patients' baseline therapy in terms of achieving Risk Domain Control. This was based on a non-inferiority limit of 10% (explained later) reduction in Risk Domain Control.
2. To analyse the change in moderate/severe exacerbations, and respiratory hospitalisations before and after the change from Turbohaler or Accuhaler to DuoResp.
3. To compare healthcare utilisation and related costs before and after change to DuoResp in terms of respiratory drug prescriptions, primary care consultations and respiratory related hospital costs.

3.2 Phase 4

3.2.1 Aims

To evaluate whether the level of disease control, healthcare resource utilisation and costs is non-inferior or superior in patients who have changed to DuoResp from other ICS/LABA FDCs compared with patients who continue this use.

3.2.2 Objectives

1. To analyse whether DuoResp is non-inferior or superior to other ICS/LABA FDCs in terms of achieving disease control in asthma and COPD during the outcome period, using the following treatment arms:
   A. Patients changing from Turbohaler or Accuhaler to DuoResp.
   B. Patients continuing treatment with Turbohaler or Accuhaler.
   Non-inferiority was based on a non-inferiority limit of 10% (explained later) reduction in risk domain control.
2. To compare moderate/severe exacerbations, hospitalisations, change in treatment stability and health-related costs in relation to asthma and COPD outcomes between the two arms described above.

4.0 Study design

4.1 Phase 3

This was a historic single-arm cohort study involving patients with COPD and/or asthma who changed their FDC therapy to DuoResp from another ICS/LABA FDC (either Turbohaler or

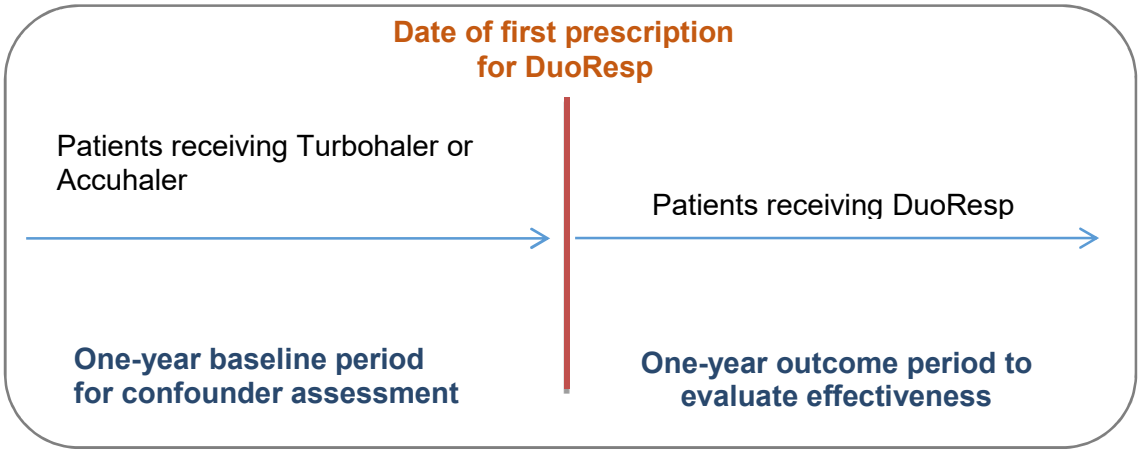


Figure 1: Study design - phase 3

Accuhaler). Patients with a minimum of one-year data prior to (baseline) and one-year data post (outcome) the date that they received their first DuoResp prescription (*index date*) were included in the study. The patients' baseline data was compared to their outcome data.

4.2 Phase 4

This was a matched, historic cohort study of patients with COPD and/or asthma, in which the following two treatment arms were compared:

- ***DuoResp switch arm*** → patients who changed to DuoResp after treatment with Turbohaler or Accuhaler
- ***Control arm*** → patients who continued to receive the same ICS/LABA FDC (Turbohaler or Accuhaler) in the outcome period

The date of the first prescription of DuoResp or the (matched) date of the repeat prescription of Turbohaler/Accuhaler in the control arm was the *index date*. The study consists of a one-year baseline period and a one-year outcome period.

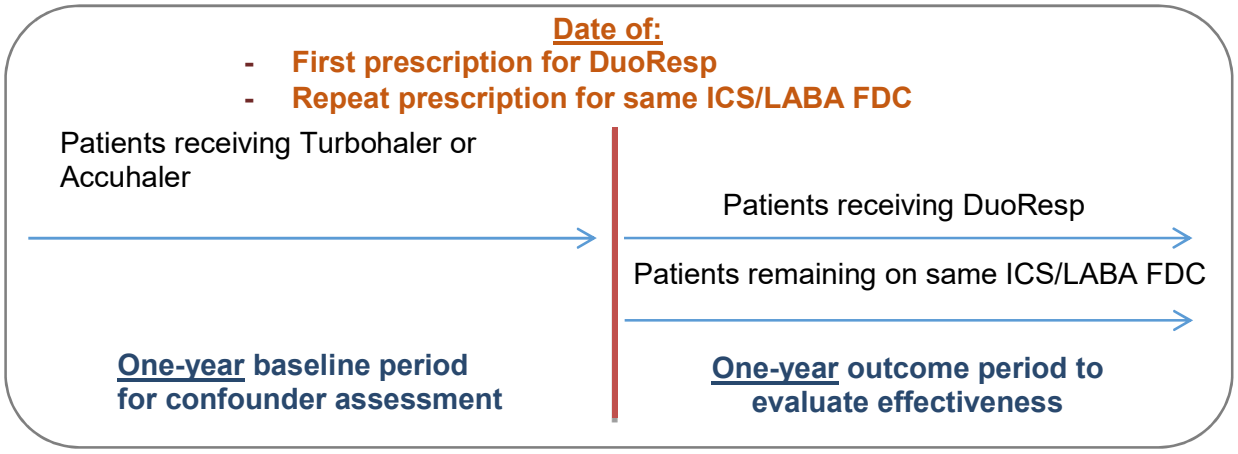


Figure 2: Study design - phase 4

5.0 Study population

5.1 Inclusion and exclusion criteria

Table 1. Inclusion and exclusion criteria – phases 3 and 4

Inclusion criteria
Asthma group: • Aged ≥18 years at first prescription for DuoResp • Evidence of asthma, defined as a diagnostic Read code and/or ≥2 prescriptions for asthma therapy * during the baseline year.
COPD group: • Aged ≥40 years at first prescription for DuoResp • A diagnostic Read code for COPD qualifying for the inclusion in the register of patients with COPD, which GP practices in the UK maintain for the Quality Outcomes Framework.[41] This requires a post-bronchodilator FEV_1/FVC <0.70
Asthma & COPD groups: • Evidence of at least 3 prescriptions for ICS/LABA FDC (Turbohaler or Accuhaler) therapy during the baseline period • Evidence of at least 1 prescription for DuoResp during the outcome period, excluding the first DuoResp prescription • Continuous medical record data during the study period, comprising of a minimum of 1-year baseline and 1-year outcome period • DuoResp patients must be registered at practices considered to have a policy of DuoResp adoption or wholesale change. Such practices will be identified as those at which ≥5 patients change to DuoResp within a three-month period • *Phase 4 only*: ICS/LABA FDC continuation arm: evidence of at least 1 prescription for ICS/LABA FDC during outcome period (same therapy as that prescribed in baseline)
Exclusion criteria
Asthma group: • Diagnosis for any chronic respiratory disease diagnosis, except asthma, at any time. This includes sarcoidosis, respiratory disease due to external agents, pneumoconiosis, interstitial lung disorders, chronic rhinosinusitis, hypersensitivity pneumonitis, lung cancer, lung fibrosis, chronic pleural diseases, pulmonary eosinophilia, cystic fibrosis and bronchiectasis

5.2 Data sources

The studies used patient data from both the Optimum Patient Care Research Database (OPCRD)[42] and the Clinical Practice Research Datalink (CPRD).[43] The study team worked with fully anonymised data, removed of any patient identifiable information.

* Includes prescriptions for bronchodilators including beta2-agonists, anticholinergics, theophylline, inhaled corticosteroids, combination inhaled corticosteroids and bronchodilator therapy

The OPCRD is developed, maintained, and owned by Optimum Patient Care (OPC), a social enterprise company that aims to improve patient outcomes through medical research and services. OPC provides evidence-based recommendations to UK general practices through bespoke software and practice reports.

The OPCRD currently comprises longitudinal medical records for over 2.2 million patients from over 550 primary care practices across the UK. The OPCRD contains two types of data: (1) routinely-recorded clinical data and (2) questionnaire responses from over 40,000 patients with respiratory conditions. The OPC questionnaires are a compilation of validated questions covering symptoms, disease control, triggers, side effects, quality of life, and unique adherence measures. The OPCRD is the only database in the UK that complements routinely-recorded disease coding and prescribing information with patient-reported outcomes. The OPCRD also links with nationwide practice prescribing data to enable targeted delivery of dataset needs.

The database has received a favourable opinion from the Health Research Authority for clinical research use (REC reference: 15/EM/0150). Governance is provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG)[44] to govern the standard of research conducted on internationally recognised databases. All research using OPCRD is registered on established study databases such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).[45]

The CPRD is a large computerised primary care database, containing de-identified, longitudinal data from 5 million active medical records from more than 600 subscribing practices throughout the UK. A practice-based quality marker, the "up-to-standard date", is generated by the CPRD for each subscribing practice and data subsequent to the practice up-to-standard date are considered to be acceptable, research-quality, prospectively-recorded data. The CPRD is well-validated and used frequently for medical and health research.

The OPCRD and CPRD datasets for this study were constructed separately and checked for overlap (previously quantified at 2-3%), before pooling for analyses, in order to exclude patients with duplicate data. Identification of patients who were present in both OPCRD and CPRD datasets was conducted by matching on a number of variables, such as the year of birth, gender and index date.

6.0 Study variables and study outcomes

6.1 Exposure

The exposure of interest in the two studies was *prescribed DuoResp* during the one-year outcome period. The reference exposure was *prescribed Accuhaler or Turbohaler*. In Phase 3, the single-arm study, the reference exposure came from the baseline period, while in Phase 4, the two-arm study, the reference exposure came from control patients who continued their baseline ICS/LABA FDC medication during the outcome period.

6.2 Primary outcome

The primary outcome was achieving Risk Domain Control*, which is defined as follows:

Successful – absence of all of the following:

- Asthma/COPD-related hospital admission
- Asthma/COPD-related A&E attendance
- Prescriptions for acute courses of oral corticosteroids (see 6.3.1 for definition)
- Antibiotics prescribed with lower respiratory consultation

Unsuccessful - presence of one or more of the above

6.3 Secondary outcomes

6.3.1 Moderate/severe exacerbations

A moderate/severe exacerbation (COPD) or severe exacerbation (asthma) is defined following the ATS/ERS Task Force Position Statement,[46] as having one of the following conditions:

Hospital admission / A&E attendance	Consists of either a definite lower respiratory Hospital Admission or a definite lower respiratory Emergency Attendance; OR a generic hospitalisation Read code which has been recorded on the same day as a Lower Respiratory Consultation (excluding where the only lower respiratory code recorded on that day was for a lung function test); OR A&E attendance.

* The study's protocol erroneously included *unscheduled out-patient department attendance* to the definition of risk domain control

An acute course of oral corticosteroids	All courses that are definitely not maintenance therapy, and/or; all courses where dosing instructions suggest exacerbation treatment (*e.g.* 6,5,4,3,2,1 reducing, or 30mg as directed), and/or all courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions; "Maintenance therapy" is defined as: daily dosing instructions of ≤10mg Prednisolone or prescriptions for 1mg or 2.5mg Prednisolone tablets where daily dosing instructions are not available.
Antibiotics prescribed with lower respiratory consultation (COPD only)	Identified by Read codes for any of the following: (a) lower respiratory diagnosis (including asthma, COPD and lower respiratory tract infection codes); (b) asthma/COPD review codes excluding any monitoring letter codes; (c) lung function and/or asthma monitoring codes; and (d) any additional respiratory examinations, referrals, chest x-rays, or events.

Where the text, tables of figures in this report mention *Exacerbation*, it is short for severe/moderate exacerbation in COPD, and severe exacerbation in asthma.

6.3.2 Treatment stability

Treatment stability was defined as:

- Achieving Risk Domain Control AND
- No increased dose of AND/OR use of additional therapy defined as long-acting bronchodilator (LABA), theophylline (or leukotriene receptor antagonists [LTRAs] in asthma)
- No increase in dose, change in delivery device, change in type of ICS AND/OR use of additional therapy as defined by LABAs, theophylline, long-acting muscarinic antagonists (LAMAs) (or LTRAs in asthma)

Since treatment stability can only be assessed relative to a prior period, this secondary outcome is not used in the phase 3 study, where the follow-up year is compared to the baseline year.

6.3.3 SABA usage

SABA usage was expressed as average daily SABA dosage during the outcome year. It is calculated from prescriptions as follows:

([*Count of inhalers* x *doses in pack* x *µg strength*] / 365)

6.3.4 Lower respiratory hospitalisations

A lower respiratory hospitalisation was defined as:

- *Definite*: Hospitalisations coded with a lower respiratory code, including asthma and LRTI

codes; OR a generic hospitalisation Read code that has been recorded on the same day as a Lower Respiratory Consultation

- *Definite* + *Probable*: Hospitalisations occurring within a 7-day window (either side of the hospitalisation date) of a lower respiratory Read code

6.3.5 Pneumonia

A pneumonia event was defined as having a Read coded diagnosis (probable pneumonia), or a Read coded diagnosis with a hospital admission or chest x-ray within 1 month (definite).

6.3.6 Lower respiratory related costs

Each of the following categories individually and in total:

- Costs of respiratory drug prescriptions, including; ICS, SAMA, SABA, LABA, LAMA, LTRA, theophylline, acute oral corticosteroids and antibiotics for LRTIs and their combinations
- Costs of primary care consultations
- Respiratory-related hospital costs, including A&E visits

6.4 Demographic and baseline variables

6.4.1 Demographics

Age and gender	At index date
Body Mass Index	Closest to the index date. Defined as the ratio of weight (kg) to squared height (m^2), and categorised as *underweight* (< 18.5 kg/m^2), *normal weight* (≥ 18.5 kg/m^2 and < 25 kg/m^2), *overweight* (≥ 25 kg/m^2 and < 30 kg/m^2) and *obese* (≥ 30 kg/m^2)
Smoking status	Closest to the index date; categorised as *non-smoker*, *current smoker* and *ex-smoker*.

6.4.2 Comorbidities

The following comorbidities were based on a diagnostic code recorded at any time prior to or at the index date:

Asthma for COPD cohort	*i.e.* ACOS; unresolved asthma Read code in patients with COPD
Ischaemic heart disease	
Heart failure	
Diabetes	Non-specific

Pneumonia	*Probable*: Read code *Definite*: Read code with hospital admission or chest x-ray within 1 month
Other chronic lung diseases	Includes: Sarcoidosis, respiratory disease due to external agents, pneumoconiosis, interstitial lung disorders, chronic rhinosinusitis, hypersensitivity pneumonitis, lung cancer, lung fibrosis, chronic pleural diseases, pulmonary eosinophilia, cystic fibrosis, bronchiectasis
Charlson comorbidity index score (CCI)	A weighted index that takes into account the number and seriousness of comorbid diseases to estimate the risk of death from comorbid diseases[47]

The following comorbidities were based on a diagnostic code recorded AND treatment at any time prior to the index date:

Gastro-oesophageal reflux disease (GERD)

Allergic and non-allergic rhinitis

6.4.3 Lung function

Lung function was measured by the following, recorded closest to the index date:

FEV_1	Forced Expiratory Volume in one second (L), and the % of the predicted normal value for age, gender and height
PEF	Peak Expiratory Flow. The maximum flow at the outset of forced expiration
FEV_1 / FVC ratio	FEV_1 / Forced Vital Capacity ratio. The proportion of a person's vital capacity that they are able to expire in the first second of forced expiration

6.4.4 Disease severity and control

The following were recorded for patients in both the COPD and asthma groups, closest to the index date:

Moderate/severe exacerbations	Defined as the occurrence of any of the following (Where > 1 occurred within 2 weeks of each other, they will be considered to be the result of the same exacerbation, and only counted once):	
	Acute course of oral corticosteroids	Defined as any of the following: (a) courses that are definitely not maintenance therapy (defined as prescriptions for Prednisolone with daily dosing instructions of ≤ 10 mg, and for 1 mg or 2.5 mg Prednisolone tablets where daily dosing instructions are not

		available); (b) courses where dosing instructions suggest exacerbation treatment (e.g. 6-1 reducing, or 30 mg as directed); and (c) courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions.
	Antibiotics prescribed with a lower respiratory consultation (COPD only)	Identified by Read codes for any of the following: (a) lower respiratory diagnosis (including asthma, COPD and lower respiratory tract infection codes); (b) asthma/COPD review codes excluding any monitoring letter codes; (c) lung function and/or asthma monitoring codes; and (d) any additional respiratory examinations, referrals, chest x-rays, or events.
	COPD/Asthma-related, unscheduled hospital admission / emergency department attendance	Identified by Read codes for any of the following: (a) definite asthma or COPD emergency attendance or definite asthma or COPD hospital admission; (b) generic hospitalisation code which has been recorded on the same day as a lower respiratory consultation (see above, refers to (a) - (c) only and excluding those where the lower respiratory code was for a lung function test only).

Where the text, tables of figures in this report mention *Exacerbation*, it is short for *severe/moderate* exacerbation in COPD, and *severe* exacerbation in asthma.

Risk domain control — As defined in section 6.2

The following were recorded for patients in the COPD group, closest to the index date:

mMRC score — Refers to the *modified British Medical Research Council* questionnaire for assessing the severity of breathlessness, graded from 0, lowest score of breathlessness, to 4, highest score of breathlessness.[48] Both routine medical practice recorded and patient questionnaire mMRC scores will be used, with the most recent score taking precedence.

GOLD group — Classification based on the 2014 GOLD guidelines:[49]

A = low risk, less symptoms	mMRC of ≤ 1; and FEV_1 ≥ 50% and/or ≤ 1 exacerbation per year (with no hospitalisations for exacerbations).

B = low risk, more symptoms	mMRC of ≥ 2; and FEV_1 ≥ 50% and/or ≤ 1 exacerbation per year (with no hospitalisations for exacerbations).
C = high risk, less symptoms	mMRC of ≤ 1; and FEV_1 < 50% and/or ≥ 2 exacerbations per year (or ≥ 1 hospitalisation for exacerbation).
D = high risk, more symptoms	mMRC of ≥ 2; and FEV_1 < 50% and/or ≥ 2 exacerbations per year (or ≥ 1 hospitalisation for exacerbation).

CAT score Based on COPD Assessment Test (where available).

The following were recorded for patients in the asthma group, closest to the index date:

GINA steps of treatment Steps of treatment 1-5, based on GINA guidelines 2014.

GINA control Based on GINA guidelines 2014.[50]

Step 1	Symptoms < once weekly; brief acute respiratory events; nocturnal symptoms ≤ twice monthly; PEF or FEV_1 variability < 20%
Step 2	Symptoms > once weekly but < once daily; acute respiratory events may affect activity and sleep; nocturnal symptoms > twice monthly; PEF or FEV_1 variability 20-30%
Step 3	Symptoms daily; acute respiratory events may affect activity and sleep; nocturnal symptoms > once weekly; PEF or FEV_1 variability > 30%
Step 4	Symptoms daily; frequent acute respiratory events; frequent nocturnal asthma symptoms; limitations of physical activities; PEF or FEV_1 variability > 30%

6.4.5 Medication

Number of prescriptions in the year prior to the index date was recorded for the following medications:

SABA	Short-acting β_2 agonist
LABA	Long-acting β_2 agonist, single or combination
SAMA	Short-acting muscarinic antagonist
LAMA	Long-acting muscarinic antagonist
ICS	Inhaled corticosteroids, single or combination
LTRA	Leukotriene receptor antagonist
Antibiotics	Antibiotics prescribed with lower respiratory consultation
OCS	Oral corticosteroids

Average daily dose in the year prior to the index date was derived from prescription information as follows: [count of inhalers x doses in pack x µg strength] / 365
for:

SABA	µg/day salbutamol equivalent
ICS	µg/day beclomethasone equivalent

7.0 Statistical analysis

7.1 Software used

All statistical analyses have been conducted using Stata MP6 version 12 and Stata SE version 14 (StataCorp, College Station, TX).

A statistically significant result is defined as a $p < 0.05$.

7.2 Power calculation

The sample size was computed to achieve 90% power and a 0.050 one-sided significance level to reject the null hypothesis that the proportions in the primary outcome are not equivalent, *i.e.* the difference in proportions, DuoResp - Control, is 0.10 or further from zero in the same direction. For the calculation, an expected difference in proportions of zero was used, assuming that the proportion of discordant pairs is 0.458. This assumption was based on previous studies showing that a weighted average of 71.6% of asthma and COPD patients prescribed FDC therapy have no exacerbations over a one-year period.[51,52]

For Phase 3 the required sample size was 393, while for Phase 4 each exposure arm needed 349 patients (assuming 1:1 ratio of patients in the exposure arms).

7.3 Quality control and assurance

Most of the presented output was generated as presented by specific scripts or programs. This approach minimises errors due to coding mistakes and errors introduced by manually transferring results from statistical software output to the report.
A second researcher or statistician has verified data processing and analyses scripts and specific programs. Code was checked for errors visually, and OPRI-written programs have been validated by comparing results with those obtained from analyses done by an independent statistician on the same data. OPRI-written programs were used for matching, balance statistics, bias potential and baseline- and outcome descriptive statistics stratified by study arms.

7.4 Baseline characterisation

Descriptive statistics of all baseline demographic characteristics, co-morbidities, medication use, indicators of disease severity and other patient characteristics were computed for a) Phase 3: the patients before switching to DuoResp; b) Phase 4: separately for the patients in the DuoResp and Turbohaler/Accuhaler arm, using the following conventions.

The characterisation was done separately for patients in the asthma and COPD groups. In case

multiple observations existed for a patient, a random observation was selected. Continuous variables were summarised using the number of non-missing observations, percentage of non-missings, mean, standard deviation, median and inter-quartile range (difference between the 25th and 75th percentile). A P-value for the Kruskal-Wallis equality-of-populations rank test was computed and the distribution of the variable will be shown in a chart combining a histogram and a boxplot.

Binary and categorical variables were summarised using the percentage of non-missings, the frequency and percentages (based on the non-missing sample size) of observed levels, and a P-value for the Pearson's chi-square test of independent categories. The distribution of the variable will be shown in a bar chart.

7.5 Matching

This section only applies to Phase 4, where patients who switched to DuoResp were matched to patients who remained on their initial ICS/LABA FDC. Matching was done using the most relevant confounders of the association between the treatment (DuoResp vs. Turbohaler/Accuhaler) and the primary outcome (achieving risk domain control). This section describes the approach used to handle confounding. Potential confounders were identified based on a combination of baseline imbalance, bias potential in relation to the primary outcome, as well as expert judgement. Through this, the most relevant confounders have been used for direct matching. Direct matching can only use a limited number of variables to match on without restricting the patient population. It is therefore necessary to exclude variables that do not relevantly affect the association of interest.

After matching, this approach was repeated in the matched sample to identify any residual confounding, selecting confounders for direct adjustment in the outcome analyses.

A different matching process was used for the primary outcome and the secondary cost-effectiveness outcomes, due to the large difference in the nature of the outcomes.

7.6 Confounder identification

7.6.1 Baseline balance

For a confounder to have an impact on the association between the treatment arms and the outcome, it must be unequally distributed in the arms. If a confounder is perfectly balanced between treatment arms it will not be able to directly bias the association of interest.

Together with the baseline characterisation (0), the differences between the arms were quantified using the Standardised Difference (SDD).[53,54] This measure is not affected by the number of observations in a sample, and thus is a better way to judge imbalance than a P-value of a

hypothesis test of difference. The SDD was calculated as described below. An SDD ≤ 0.1[55] was taken as sufficient balance between the arms.

Table 2. Formulas for Standardised Difference

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

7.6.2 Bias potential

Bias potential assesses the degree to which the observed association between the exposure of interest and the outcome is affected by conditioning on another variable. It is also called change-in-estimate.[56,57] In the case of the primary outcome, a binary indicator for achieving risk domain control, the definition of bias potential was:

$$Bias\ potential = abs(1 - e^{(\beta_{crude} - \beta_{adjusted})})$$

where β_{crude} = ln(OR) (=natural log of the Odds Ratio) of exposure from the model without the covariate and β_{crude} = ln(OR) of exposure after adding the covariate to the model. It is called *bias potential* since the bias was estimated without other covariates in the model. To what extent a variable introduces bias into a model will depend on the total model.

A bias potential of ≥2% was considered to indicate a relevant change in the association between the outcome and exposure. Often a cut-off of 5% or even 10% is used to select confounders during model building,[58] but a more sensitive cut-off was applied for this study.

The baseline variables with the highest bias potential, that were also insufficiently balanced (SDD > 0.1), were presented to a panel of clinical experts for the final selection of variables to use for matching.

7.6.3 Matching process

Exact matching for categorical variables and matching within a maximum calliper (maximum distance allowed between a case and a control) for continuous variables was used to match patients, using nearest neighbour variable mixed matching with a match maximum of 3:1 without replacement. Patients in the asthma and COPD groups were matched separately with disease-specific matching criteria.

Mixed matching is a process that utilises more of the data by matching varying numbers of control arm patients to a treatment arm patient. In other words, there will be a cohort of unique patients matched 1:1, another cohort of unique patients matched 2:1, and a third cohort of unique patients matched 3:1. The analyses were conducted using all the matched patients even though some patients had 1 matched control while other patients had 3 matched controls. This imbalance in number of controls matched to cases could introduce residual confounding. Therefore, we verified our assumption that this will not affect the study outcomes through a sensitivity analysis, in which the outcome analyses were also done in the subpopulation of patients in the DuoResp arm with exactly 3 matched patients in the Turbohaler arm.

Although the patients in the Turbohaler arm could have multiple records per patient to optimise the matching process, only one record per patient contributed to the matching.

Matching was repeated 20 times with a different random patient sequence to select the run that resulted in the highest number of matched patients.

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

7.6.4 Post-matching evaluation

The quality of the matching was evaluated using the same methods used to identify the confounders: standardised difference in combination with bias potential.

To minimise the number of covariates used to adjust the outcome model, a forward assessment of bias potential was used. The identified confounders were entered one-by-one, and the relative change in the effect size of exposure was assessed against the effect size before introducing the variable. If the relative change in effect size was ≥0.02, the variables remained in the model, and the next one was evaluated.

7.7 Analysis of study outcomes

7.7.1 Primary outcome

Phase 3

Conditional logistic regression of the within-patient difference in the primary outcome from baseline to outcome was performed to provide a 95% confidence interval (CI) with which to assess non-inferiority. The analyses were done for the patients in the asthma and COPD groups combined. The model was adjusted for the total ICS dose.

Phase 4

Conditional logistic regression in the matched sample of the between-patient difference in the primary outcome was performed to provide a 95% CI with which to assess non-inferiority. The analyses were done for the patients in the asthma and COPD groups combined as well as by disease group. The model was adjusted for baseline variables that remained with bias potential after matching.

Non-inferiority will be claimed if the lower bound of the 95% confidence interval is above -10%. If non-inferiority is achieved, superiority will be tested. A difference of >10% is widely regarded as clinically important for outcomes in respiratory studies,[59,60] and has been used before in similar studies.[61,62]

7.7.2 Secondary outcomes

The secondary outcomes were analysed separately for the asthma and COPD groups.

In Phase 3, the models were adjusted for total ICS dose. In Phase 4 the analyses were done in the matched sample, and adjusted for baseline variables that remained with bias potential after matching.

Exacerbations and *hospitalisations* were analysed in the matched sample using conditional Poisson regression to obtain estimates of relative rates. The models were adjusted for baseline variables that remained with bias potential after matching. The adjusted conditional Rate Ratios were reported along with their 95% CIs.

Treatment Stability was analysed in the matched sample using conditional logistic regression. The adjusted conditional Odds Ratio (adjusted for baseline variables that remained with bias potential after matching) were compared between the matched treatment groups and reported along with their 95% CI.

SABA usage was analysed in the matched sample using conditional ordinal logistic regression, after the SABA average daily dose was categorised. The adjusted conditional Odds Ratio (adjusted for baseline variables that remained with bias potential after matching) were compared between the matched treatment groups and reported along with their 95% CI.

7.7.3 Secondary cost-effectiveness outcomes

As in the primary outcome analysis, patients in the asthma and COPD groups were analysed together.

Phase 3

Adjusted relative differences (with their 95% CI) of COPD/asthma-related healthcare costs between outcome and baseline periods were estimated using generalised linear models with a Gamma distribution and log link.

Phase 4

Mean COPD/asthma-related healthcare costs per patient per year were compared in the 3:1 matched sample, adjusting for confounding factors.

To test whether unadjusted mean cost differences were statistically different between each arm, measures of variability (standard errors, P-values and confidence intervals) were estimated/developed using two methods: (1) a parametric t-test with unequal standard deviations; and (2) non-parametric bootstrapping with 1000 samples taken with replacement from the dataset.

Adjusted COPD/asthma-related healthcare costs during the outcome period were estimated using generalised linear models with a Gamma distribution and log link, controlling for potential confounders at baseline to be determined from matched baseline characterisation. Differences in adjusted mean costs are reported with 95% CIs developed from non-parametric bootstrapping methods with 1000 random samples taken with replacement from the dataset.

The adjusted two-way differences (relative to comparators) in costs and the difference in percentage of patients achieving risk domain control for the 1000 random samples will be displayed graphically on a cost-effectiveness plane. The four quadrants of the cost-effectiveness plane (see Figure 3) are:

- Quadrant I (North-East): more costly and more effective (a trade-off);
- Quadrant II (North-West): more costly and less effective (reference exposure is dominant);
- Quadrant III (South-West): less costly and less effective (a trade-off); and
- Quadrant IV (South-East): less costly and more effective (exposure of interest is dominant).

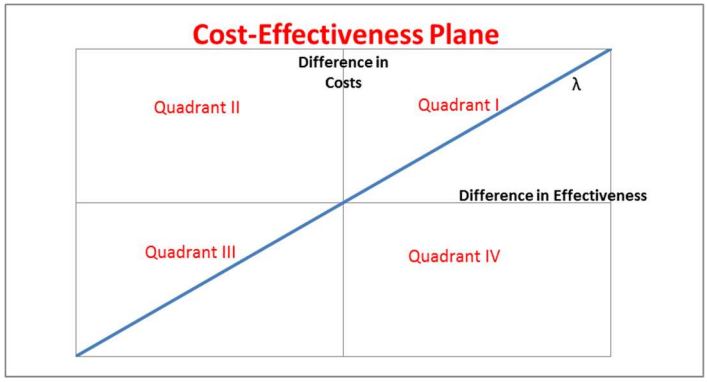


Figure 3. The cost-effectiveness plane

When point estimates result in a trade-off (*i.e.*quadrants I and III) between comparators, an incremental cost-effectiveness ratio (ICER) is calculated as the ratio of the mean difference in total COPD/asthma-related healthcare costs per patient (incremental costs) in the outcome year to the difference in proportions of patients achieving risk domain control in the outcome year (incremental effectiveness). If all replicated data are in one quadrant of the cost-effectiveness plane, the ICER is reported with a 95% CI developed from bootstrapping methods.

8.0 Results

8.1 Patient selection

The selection of patients was based on identifying individual prescriptions for the three ICS/LABA FDC inhalers (DuoResp, Accuhaler or Turbohaler) that met the inclusion and exclusion criteria. Therefore, a patient can contribute with a number of prescription dates. This results in a pool of control patient prescription records to match patients that switched to DuoResp on.

The number of eligible patients (Table 3) that switched to DuoResp was 385 in the OPCRD and 35 in the CPRD database. A total of 40,540 patients remained on Accuhaler and 50,351 remained on Turbohaler, with an average number of prescriptions per patient of 10.6 for Accuhaler and 11.7 for Turbohaler.

Table 3. Patient selection

	OPCRD			CPRD		
	DuoResp	Accuhaler	Turbohaler	DuoResp	Accuhaler	Turbohaler
ICS/LABA FDC prescription	8,275	1,366,020	1,854,661	12,256	1,477,757	1,609,536
Minimum time in practice	1,703	1,017,906	1,374,603	437	1,137,898	1,221,224
Excluded	*6,572*	*348,114*	*480,058*	*11,819*	*339,859*	*388,312*
≥3 Rx for Accuhaler/Turbohaler in baseline. No DuoResp in baseline.	466	847,345	1,122,965	94	984,882	1,019,795
Excluded	*1,237*	*170,561*	*251,638*	*343*	*153,016*	*201,429*
≥1 Rx during follow-up	433	831,513	1,106,595	84	969,136	1,004,111
Excluded	*33*	*15,832*	*16,370*	*10*	*15,746*	*15,684*
Single FDC device at index date	432	828,640	1,098,304	81	965,325	1,001,964
Excluded	*1*	*2,873*	*8,291*	*3*	*3,811*	*2,147*
Unresolved asthma diagnosis and age ≥18; COPD diagnosis and age ≥40	406	756,214	1,020,656	81	907,124	943,029
Excluded	*26*	*72,426*	*77,648*	*0*	*58,201*	*58,935*
No other chronic resp. disease prior to index	391	738,783	998,208	79	881,861	920,072
Excluded	*15*	*17,431*	*22,448*	*2*	*25,263*	*22,957*
≥5 DuoResp changes within 3 months in the practice	391	738,783	998,208	35	881,861	920,072
Excluded	*0*	*0*	*0*	*44*	*0*	*0*
Index date ≥2010	391	326,048	518,190	35	529,697	591,505
Excluded	*0*	*412,735*	*480,018*	*0*	*352,164*	*328,567*

	OPCRD			CPRD		
	DuoResp	Accuhaler	Turbohaler	DuoResp	Accuhaler	Turbohaler
Remove patients already in OPCRD dataset				35	107,849	78,964
Excluded				*0*	*421,848*	*512,541*
ACOS and age ≥40	391	325,455	516,406	35	107,587	78,811
Excluded	*0*	*593*	*153*	*0*	*262*	*153*
Exclude asthma resolved	385	322,276	509,457	35	106,379	77,702
Excluded	*6*	*3,179*	*6,949*	*0*	*1,208*	*1,109*
Number of patients	385	21,182	31,845	35	19,358	18,506
Combined	**420**	**40,540**	**50,351**			

Rx = prescription

The remaining 420 patients who switched from an ICS/LABA FDC to DuoResp after the inclusion/exclusion criteria have been applied are the basis for the analyses in phases 3 and 4.
To identify patients with only an asthma diagnosis, we refer to the *asthma group*, while to identify patients with a COPD diagnosis (with or without an asthma diagnosis) we refer to as the *COPD group*.

8.2 Phase 3

Of the 420 patients that switched from an ICS/LABA FDC inhaler to DuoResp, only 10 used Accuhaler before (Table 4). It was decided by the steering committee to restrict the further analyses to only those patients who switched to DuoResp from Turbohaler. The considerable gain in homogeneity of the patient population was considered to outweigh the limited reduction in number of patients.

Table 4. Baseline fixed dose combination device of DuoResp switchers

Group	Accuhaler	Turbohaler	Total
Asthma	3	262	265
COPD	7	148	155
Total	10	410	420

After excluding patients who switched from Accuhaler, a total of 410 patients were eligible for this study - 262 in the asthma group and 148 in the COPD group.

Of the 410 patients, 63 (15%) switched back to Turbohaler during the outcome period, and 2 switched to Accuhaler.

The switch from Turbohaler to DuoResp resulted in a significant increase in the average daily dose

of inhaled corticosteroids in the COPD group (p=0.0010, Figure 4 and Table 6), but not in the asthma group (p=0.1203).

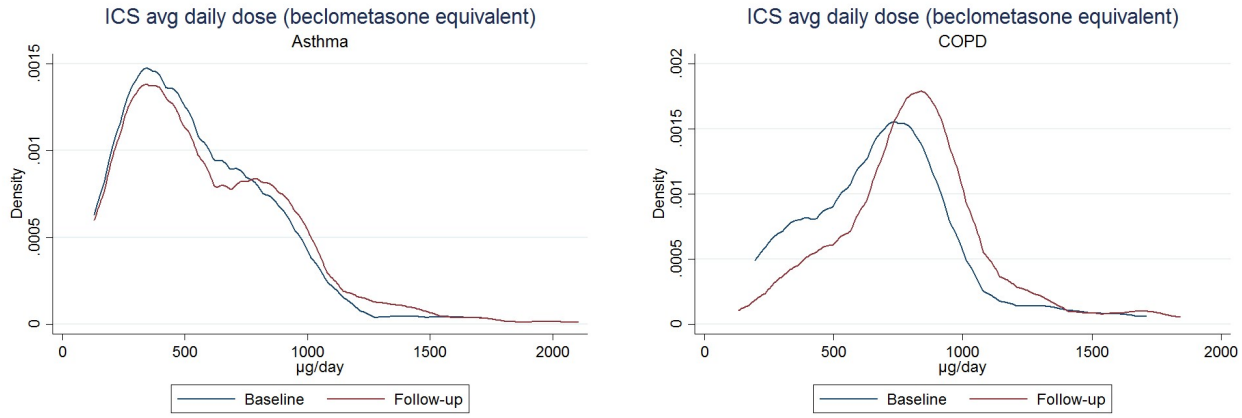


Figure 4. Distribution of ICS average daily dose (µg/day beclometasone equivalent) in the two periods for the two disease groups

Costs for ICS declined significantly after the switch in the asthma group (£-53, CI -37--69, p<0.001), but not significantly in the COPD group (£9, CI -35-16).

In the asthma group, there was a significant decrease in total respiratory medication costs (£-52, CI -71 - -33), but not in the COPD group (Figure 5).

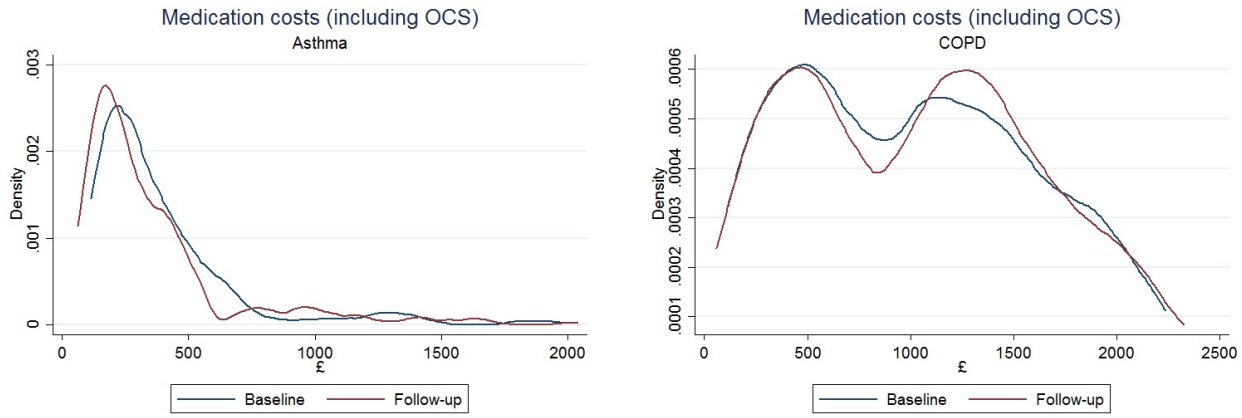


Figure 5. Distribution of medication costs, including OCS, in the two periods for the two disease groups

In both the asthma and COPD groups the average primary care consultation costs increased significantly, but this difference was only significant in the asthma group (0.030, £67 (5-128)) (***Figure 6***).

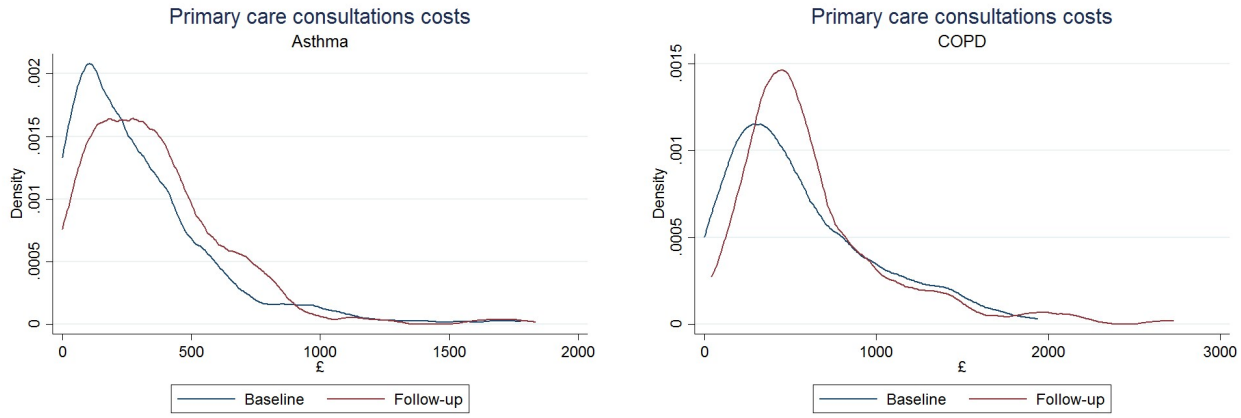


Figure 6. Distribution of primary care consultation costs, in the two periods for the two disease groups

Similar graphical presentation of the distribution of other characteristics are shown in the Appendix 14.4 on page 104.

Table 5. Overview of outcomes in the two periods – Asthma

Variable		Baseline	Follow-up	P-value
Risk domain control	N (% non-missing)	262 (100.0)	262 (100.0)	0.7740
	Controlled, n (%)	183 (69.8)	186 (71.0)	
ICS avg daily dose (µg/day), total	N (% non-missing)	262 (100.0)	262 (100.0)	0.1203
	≤400, n (%)	113 (43.1)	110 (42.0)	
	>400 - ≤800, n (%)	102 (38.9)	84 (32.1)	
	>800 - ≤1600, n (%)	44 (16.8)	65 (24.8)	
	>1600, n (%)	3 (1.1)	3 (1.1)	
ICS avg daily dose (µg/day), FDC only	N (% non-missing)	262 (100.0)	262 (100.0)	0.0058
	≤400, n (%)	113 (43.1)	149 (56.9)	
	>400 - ≤800, n (%)	103 (39.3)	88 (33.6)	
	>800 - ≤1600, n (%)	43 (16.4)	24 (9.2)	
	>1600, n (%)	3 (1.1)	1 (0.4)	
Medication regimen	N (% non-missing)	262 (100.0)	262 (100.0)	0.0008
	ICS + LABA +/- SAMA +/- SABA, n (%)	223 (85.1)	207 (79.0)	
	ICS + LABA + LAMA +/- SAMA +/- SABA, n (%)	11 (4.2)	13 (5.0)	
	ICS + LABA + LAMA + LTRA +/- SAMA +/- SABA, n (%)	4 (1.5)	8 (3.1)	
	ICS + LABA + LTRA +/- SAMA +/- SABA, n (%)	24 (9.2)	18 (6.9)	
	Other, n (%)	0 (0.0)	16 (6.1)	
SABA inhalers	N (% non-missing)	262 (100.0)	262 (100.0)	0.5912
	0, n (%)	65 (24.8)	75 (28.6)	
	1, n (%)	25 (9.5)	22 (8.4)	
	≥2, n (%)	172 (65.6)	165 (63.0)	
SABA avg daily dose (µg/day)	N (% non-missing)	262 (100.0)	262 (100.0)	0.8019
	0, n (%)	65 (24.8)	75 (28.6)	
	>0 - ≤200, n (%)	72 (27.5)	65 (24.8)	
	>200 - ≤400, n (%)	57 (21.8)	59 (22.5)	
	>400 - ≤600, n (%)	26 (9.9)	21 (8.0)	
	>600, n (%)	42 (16.0)	42 (16.0)	
LAMA ≥1 prescriptions	N (% non-missing)	262 (100.0)	262 (100.0)	0.3001
	Yes, n (%)	15 (5.7)	21 (8.0)	
Acute OCS courses	N (% non-missing)	262 (100.0)	262 (100.0)	0.7524
	0, n (%)	202 (77.1)	207 (79.0)	
	1, n (%)	43 (16.4)	38 (14.5)	
	2, n (%)	12 (4.6)	9 (3.4)	
	3, n (%)	4 (1.5)	5 (1.9)	
	≥4, n (%)	1 (0.4)	3 (1.1)	
Acute OCS prescriptions	N (% non-missing)	262 (100.0)	262 (100.0)	0.8072
	0, n (%)	202 (77.1)	207 (79.0)	
	1, n (%)	42 (16.0)	37 (14.1)	
	2, n (%)	11 (4.2)	8 (3.1)	
	3, n (%)	5 (1.9)	6 (2.3)	
	≥4, n (%)	2 (0.8)	4 (1.5)	
Exacerbations	N (% non-missing)	262 (100.0)	262 (100.0)	0.7253
	0, n (%)	200 (76.3)	206 (78.6)	
	1, n (%)	45 (17.2)	39 (14.9)	
	2, n (%)	12 (4.6)	9 (3.4)	
	3, n (%)	4 (1.5)	5 (1.9)	
	≥4, n (%)	1 (0.4)	3 (1.1)	

Variable		Baseline	Follow-up	P-value
Acute respiratory events	N (% non-missing)	262 (100.0)	262 (100.0)	0.6505
	0, n (%)	183 (69.8)	186 (71.0)	
	1, n (%)	52 (19.8)	53 (20.2)	
	2, n (%)	17 (6.5)	12 (4.6)	
	3, n (%)	8 (3.1)	6 (2.3)	
	≥4, n (%)	2 (0.8)	5 (1.9)	
Antibiotics	N (% non-missing)	262 (100.0)	262 (100.0)	0.4678
	0, n (%)	214 (81.7)	213 (81.3)	
	1, n (%)	35 (13.4)	39 (14.9)	
	2, n (%)	9 (3.4)	4 (1.5)	
	≥3, n (%)	4 (1.5)	6 (2.3)	
Pneumonia (definite)	N (% non-missing)	262 (100.0)	262 (100.0)	
	Yes, n (%)	0 (0.0)	0 (0.0)	
Pneumonia (probable)	N (% non-missing)	262 (100.0)	262 (100.0)	0.3168
	Yes, n (%)	1 (0.4)	0 (0.0)	
In- and outpatient hospitalisations, vague	N (% non-missing)	262 (100.0)	262 (100.0)	0.3207
	0, n (%)	255 (97.3)	253 (96.6)	
	1, n (%)	3 (1.1)	7 (2.7)	
	≥2, n (%)	4 (1.5)	2 (0.8)	
In- and outpatient hospitalisations, strict	N (% non-missing)	262 (100.0)	262 (100.0)	0.6477
	0, n (%)	256 (97.7)	257 (98.1)	
	1, n (%)	2 (0.8)	3 (1.1)	
	≥2, n (%)	4 (1.5)	2 (0.8)	
Hospitalisation costs	N (% non-missing)	262 (100.0)	262 (100.0)	1.0000
	>0, n (%)	7 (2.7)	7 (2.7)	
GP based consultation costs	N (% non-missing)	262 (100.0)	262 (100.0)	0.0011
	≤60, n (%)	50 (19.1)	25 (9.5)	
	61-180, n (%)	64 (24.4)	51 (19.5)	
	181-350, n (%)	65 (24.8)	66 (25.2)	
	351-570, n (%)	47 (17.9)	69 (26.3)	
	571-880, n (%)	23 (8.8)	42 (16.0)	
	>880, n (%)	13 (5.0)	9 (3.4)	
Resp. medication costs, excluding OCS	N (% non-missing)	261 (99.6)	262 (100.0)	0.1046
	≤250, n (%)	106 (40.6)	135 (51.5)	
	251-460, n (%)	93 (35.6)	72 (27.5)	
	461-940, n (%)	46 (17.6)	36 (13.7)	
	941-1500, n (%)	13 (5.0)	15 (5.7)	
	>1500, n (%)	3 (1.1)	4 (1.5)	
Resp. medication costs, including OCS	N (% non-missing)	261 (99.6)	262 (100.0)	0.1267
	≤250, n (%)	106 (40.6)	134 (51.1)	
	251-460, n (%)	92 (35.2)	72 (27.5)	
	461-940, n (%)	47 (18.0)	37 (14.1)	
	941-1500, n (%)	13 (5.0)	15 (5.7)	
	>1500, n (%)	3 (1.1)	4 (1.5)	
ICS/LABA FDC costs	N (% non-missing)	262 (100.0)	262 (100.0)	0.0006
	Mean (SD)	318.6 (170.3)	273.8 (160.5)	
	Median (IQR)	266.0 (228.0)	225.8 (239.8)	
SAMA costs	N (% non-missing)	262 (100.0)	262 (100.0)	0.9651
	Mean (SD)	0.2 (3.5)	0.2 (2.7)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	
SABA costs	N (% non-missing)	262 (100.0)	262 (100.0)	0.5683
	Mean (SD)	13.9 (26.9)	13.7 (27.1)	
	Median (IQR)	6.0 (13.5)	6.0 (15.0)	
LAMA costs	N (% non-missing)	262 (100.0)	262 (100.0)	0.2438
	Mean (SD)	45.1 (192.2)	59.1 (219.5)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	

Variable		Baseline	Follow-up	P-value
OCS costs	N (% non-missing)	262 (100.0)	262 (100.0)	0.5423
	Mean (SD)	1.3 (5.5)	1.5 (6.3)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	
LTRA costs	N (% non-missing)	262 (100.0)	262 (100.0)	0.9780
	Mean (SD)	2.9 (16.6)	2.9 (16.7)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	

Table 6. Overview of outcomes in the two periods – COPD

Variable		Baseline	Follow-up	P-value
Risk domain control	N (% non-missing)	148 (100.0)	148 (100.0)	0.8123
	Controlled, n (%)	58 (39.2)	60 (40.5)	
ICS avg daily dose (µg/day), total	N (% non-missing)	148 (100.0)	148 (100.0)	0.0010
	≤400, n (%)	31 (20.9)	14 (9.5)	
	>400 - ≤800, n (%)	75 (50.7)	61 (41.2)	
	>800 - ≤1600, n (%)	40 (27.0)	69 (46.6)	
	>1600, n (%)	2 (1.4)	4 (2.7)	
ICS avg daily dose (µg/day), FDC only	N (% non-missing)	148 (100.0)	148 (100.0)	0.2760
	≤400, n (%)	32 (21.6)	36 (24.3)	
	>400 - ≤800, n (%)	76 (51.4)	86 (58.1)	
	>800 - ≤1600, n (%)	38 (25.7)	25 (16.9)	
	>1600, n (%)	2 (1.4)	1 (0.7)	
Medication regimen	N (% non-missing)	148 (100.0)	148 (100.0)	0.0155
	ICS + LABA +/- SAMA +/- SABA, n (%)	37 (25.0)	29 (19.6)	
	ICS + LABA + LAMA +/- SAMA +/- SABA, n (%)	102 (68.9)	101 (68.2)	
	ICS + LABA + LAMA + LTRA +/- SAMA +/- SABA, n (%)	8 (5.4)	6 (4.1)	
	ICS + LABA + LTRA +/- SAMA +/- SABA, n (%)	1 (0.7)	1 (0.7)	
	Other, n (%)	0 (0.0)	11 (7.4)	
SABA inhalers	N (% non-missing)	148 (100.0)	148 (100.0)	0.9880
	0, n (%)	25 (16.9)	26 (17.6)	
	1, n (%)	11 (7.4)	11 (7.4)	
	≥2, n (%)	112 (75.7)	111 (75.0)	
SABA avg daily dose (µg/day)	N (% non-missing)	148 (100.0)	148 (100.0)	0.3458
	0, n (%)	25 (16.9)	26 (17.6)	
	>0 - ≤200, n (%)	23 (15.5)	27 (18.2)	
	>200 - ≤400, n (%)	36 (24.3)	23 (15.5)	
	>400 - ≤600, n (%)	8 (5.4)	13 (8.8)	
	>600, n (%)	56 (37.8)	59 (39.9)	
LAMA ≥1 prescriptions	N (% non-missing)	148 (100.0)	148 (100.0)	0.6934
	Yes, n (%)	110 (74.3)	107 (72.3)	
Acute OCS courses	N (% non-missing)	148 (100.0)	148 (100.0)	0.7754
	0, n (%)	89 (60.1)	82 (55.4)	
	1, n (%)	28 (18.9)	29 (19.6)	
	2, n (%)	10 (6.8)	16 (10.8)	
	3, n (%)	11 (7.4)	10 (6.8)	
	≥4, n (%)	10 (6.8)	11 (7.4)	
Acute OCS prescriptions	N (% non-missing)	148 (100.0)	148 (100.0)	0.7594
	0, n (%)	89 (60.1)	82 (55.4)	
	1, n (%)	24 (16.2)	28 (18.9)	
	2, n (%)	11 (7.4)	13 (8.8)	
	3, n (%)	8 (5.4)	12 (8.1)	
	≥4, n (%)	16 (10.8)	13 (8.8)	
Exacerbations	N (% non-missing)	148 (100.0)	148 (100.0)	0.0620
	0, n (%)	58 (39.2)	60 (40.5)	
	1, n (%)	44 (29.7)	31 (20.9)	
	2, n (%)	15 (10.1)	29 (19.6)	
	3, n (%)	18 (12.2)	11 (7.4)	
	≥4, n (%)	13 (8.8)	17 (11.5)	
Antibiotics	N (% non-missing)	148 (100.0)	148 (100.0)	0.1794
	0, n (%)	81 (54.7)	90 (60.8)	
	1, n (%)	45 (30.4)	33 (22.3)	
	2, n (%)	11 (7.4)	18 (12.2)	
	≥3, n (%)	11 (7.4)	7 (4.7)	

Variable		Baseline	Follow-up	P-value
Pneumonia (definite)	N (% non-missing)	148 (100.0)	148 (100.0)	0.4094
	Yes, n (%)	2 (1.4)	4 (2.7)	
Pneumonia (probable)	N (% non-missing)	148 (100.0)	148 (100.0)	0.2512
	Yes, n (%)	2 (1.4)	5 (3.4)	
In- and outpatient hospitalisations, probable	N (% non-missing)	148 (100.0)	148 (100.0)	0.3933
	0, n (%)	124 (83.8)	132 (89.2)	
	1, n (%)	14 (9.5)	9 (6.1)	
	≥2, n (%)	10 (6.8)	7 (4.7)	
In- and outpatient hospitalisations, definite	N (% non-missing)	148 (100.0)	148 (100.0)	0.1531
	0, n (%)	126 (85.1)	136 (91.9)	
	1, n (%)	12 (8.1)	8 (5.4)	
	≥2, n (%)	10 (6.8)	4 (2.7)	
Hospitalisation costs	N (% non-missing)	148 (100.0)	148 (100.0)	0.1548
	>0, n (%)	22 (14.9)	14 (9.5)	
GP based consultation costs	N (% non-missing)	148 (100.0)	148 (100.0)	0.0055
	≤60, n (%)	9 (6.1)	1 (0.7)	
	61-180, n (%)	17 (11.5)	9 (6.1)	
	181-350, n (%)	31 (20.9)	22 (14.9)	
	351-570, n (%)	33 (22.3)	56 (37.8)	
	571-880, n (%)	28 (18.9)	31 (20.9)	
	>880, n (%)	30 (20.3)	29 (19.6)	
Resp. medication costs, excluding OCS	N (% non-missing)	148 (100.0)	147 (99.3)	0.1006
	≤250, n (%)	12 (8.1)	7 (4.8)	
	251-460, n (%)	21 (14.2)	33 (22.4)	
	461-940, n (%)	38 (25.7)	25 (17.0)	
	941-1500, n (%)	43 (29.1)	52 (35.4)	
	>1500, n (%)	34 (23.0)	30 (20.4)	
Resp. medication costs, including OCS	N (% non-missing)	148 (100.0)	147 (99.3)	0.1093
	≤250, n (%)	12 (8.1)	7 (4.8)	
	251-460, n (%)	21 (14.2)	33 (22.4)	
	461-940, n (%)	37 (25.0)	24 (16.3)	
	941-1500, n (%)	44 (29.7)	52 (35.4)	
	>1500, n (%)	34 (23.0)	31 (21.1)	
ICS/LABA FDC costs	N (% non-missing)	148 (100.0)	148 (100.0)	0.3041
	Mean (SD)	391.4 (167.7)	375.3 (138.8)	
	Median (IQR)	418.0 (228.0)	359.6 (111.8)	
SAMA costs	N (% non-missing)	148 (100.0)	148 (100.0)	0.8197
	Mean (SD)	4.4 (18.4)	5.5 (23.2)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	
SABA costs	N (% non-missing)	148 (100.0)	148 (100.0)	0.7571
	Mean (SD)	20.6 (26.3)	22.5 (28.7)	
	Median (IQR)	12.0 (22.5)	13.5 (28.5)	
LAMA costs	N (% non-missing)	147 (99.3)	147 (99.3)	0.3285
	Mean (SD)	586.4 (495.6)	625.0 (519.6)	
	Median (IQR)	603.0 (804.0)	737.0 (873.7)	
OCS costs	N (% non-missing)	148 (100.0)	148 (100.0)	0.7618
	Mean (SD)	5.7 (14.7)	6.3 (18.8)	
	Median (IQR)	0.0 (5.5)	0.0 (4.8)	
LTRA costs	N (% non-missing)	148 (100.0)	148 (100.0)	0.6448
	Mean (SD)	1.1 (4.8)	1.2 (5.6)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	
THEO costs	N (% non-missing)	148 (100.0)	148 (100.0)	0.8098
	Mean (SD)	1.2 (5.8)	1.0 (5.4)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	

Table 7. Overview of outcomes in the two periods – All patients

Variable		Baseline	Follow-up	P-value
Risk domain control	N (% non-missing)	410 (100.0)	410 (100.0)	0.7222
	Controlled, n (%)	241 (58.8)	246 (60.0)	
ICS avg daily dose (µg/day), total	N (% non-missing)	410 (100.0)	410 (100.0)	0.0009
	≤400, n (%)	144 (35.1)	124 (30.2)	
	>400 - ≤800, n (%)	177 (43.2)	145 (35.4)	
	>800 - ≤1600, n (%)	84 (20.5)	134 (32.7)	
	>1600, n (%)	5 (1.2)	7 (1.7)	
ICS avg daily dose (µg/day), FDC only	N (% non-missing)	410 (100.0)	410 (100.0)	0.0028
	≤400, n (%)	145 (35.4)	185 (45.1)	
	>400 - ≤800, n (%)	179 (43.7)	174 (42.4)	
	>800 - ≤1600, n (%)	81 (19.8)	49 (12.0)	
	>1600, n (%)	5 (1.2)	2 (0.5)	
Medication regimen	N (% non-missing)	410 (100.0)	410 (100.0)	<0.0001
	ICS + LABA +/- SAMA +/- SABA, n (%)	260 (63.4)	236 (57.6)	
	ICS + LABA + LAMA +/- SAMA +/- SABA, n (%)	113 (27.6)	114 (27.8)	
	ICS + LABA + LAMA + LTRA +/- SAMA +/- SABA, n (%)	12 (2.9)	14 (3.4)	
	ICS + LABA + LTRA +/- SAMA +/- SABA, n (%)	25 (6.1)	19 (4.6)	
	Other, n (%)	0 (0.0)	27 (6.6)	
SABA inhalers	N (% non-missing)	410 (100.0)	410 (100.0)	0.6446
	0, n (%)	90 (22.0)	101 (24.6)	
	1, n (%)	36 (8.8)	33 (8.0)	
	≥2, n (%)	284 (69.3)	276 (67.3)	
SABA avg daily dose (µg/day)	N (% non-missing)	410 (100.0)	410 (100.0)	0.8410
	0, n (%)	90 (22.0)	101 (24.6)	
	>0 - ≤200, n (%)	95 (23.2)	92 (22.4)	
	>200 - ≤400, n (%)	93 (22.7)	82 (20.0)	
	>400 - ≤600, n (%)	34 (8.3)	34 (8.3)	
	>600, n (%)	98 (23.9)	101 (24.6)	
LAMA ≥1 prescriptions	N (% non-missing)	410 (100.0)	410 (100.0)	0.8206
	Yes, n (%)	125 (30.5)	128 (31.2)	
Acute OCS courses	N (% non-missing)	410 (100.0)	410 (100.0)	0.9545
	0, n (%)	291 (71.0)	289 (70.5)	
	1, n (%)	71 (17.3)	67 (16.3)	
	2, n (%)	22 (5.4)	25 (6.1)	
	3, n (%)	15 (3.7)	15 (3.7)	
	≥4, n (%)	11 (2.7)	14 (3.4)	
Acute OCS prescriptions	N (% non-missing)	410 (100.0)	410 (100.0)	0.9284
	0, n (%)	291 (71.0)	289 (70.5)	
	1, n (%)	66 (16.1)	65 (15.9)	
	2, n (%)	22 (5.4)	21 (5.1)	
	3, n (%)	13 (3.2)	18 (4.4)	
	≥4, n (%)	18 (4.4)	17 (4.1)	
Exacerbations	N (% non-missing)	410 (100.0)	410 (100.0)	0.1805
	0, n (%)	258 (62.9)	266 (64.9)	
	1, n (%)	89 (21.7)	70 (17.1)	
	2, n (%)	27 (6.6)	38 (9.3)	
	3, n (%)	22 (5.4)	16 (3.9)	
	≥4, n (%)	14 (3.4)	20 (4.9)	

Variable		Baseline	Follow-up	P-value
Antibiotics	N (% non-missing)	410 (100.0)	410 (100.0)	0.8575
	0, n (%)	295 (72.0)	303 (73.9)	
	1, n (%)	80 (19.5)	72 (17.6)	
	2, n (%)	20 (4.9)	22 (5.4)	
	≥3, n (%)	15 (3.7)	13 (3.2)	
Pneumonia (definite)	N (% non-missing)	410 (100.0)	410 (100.0)	0.4125
	Yes, n (%)	2 (0.5)	4 (1.0)	
Pneumonia (probable)	N (% non-missing)	410 (100.0)	410 (100.0)	0.4773
	Yes, n (%)	3 (0.7)	5 (1.2)	
In- and outpatient hospitalisations, vague	N (% non-missing)	410 (100.0)	410 (100.0)	0.5587
	0, n (%)	379 (92.4)	385 (93.9)	
	1, n (%)	17 (4.1)	16 (3.9)	
	≥2, n (%)	14 (3.4)	9 (2.2)	
In- and outpatient hospitalisations, strict	N (% non-missing)	410 (100.0)	410 (100.0)	0.1560
	0, n (%)	382 (93.2)	393 (95.9)	
	1, n (%)	14 (3.4)	11 (2.7)	
	≥2, n (%)	14 (3.4)	6 (1.5)	
Hospitalisation costs	N (% non-missing)	410 (100.0)	410 (100.0)	0.2430
	>0, n (%)	29 (7.1)	21 (5.1)	
GP based consultation costs	N (% non-missing)	410 (100.0)	410 (100.0)	<0.0001
	≤60, n (%)	59 (14.4)	26 (6.3)	
	61-180, n (%)	81 (19.8)	60 (14.6)	
	181-350, n (%)	96 (23.4)	88 (21.5)	
	351-570, n (%)	80 (19.5)	125 (30.5)	
	571-880, n (%)	51 (12.4)	73 (17.8)	
	>880, n (%)	43 (10.5)	38 (9.3)	
Resp. medication costs, excluding OCS	N (% non-missing)	409 (99.8)	409 (99.8)	0.1188
	≤250, n (%)	118 (28.9)	142 (34.7)	
	251-460, n (%)	114 (27.9)	105 (25.7)	
	461-940, n (%)	84 (20.5)	61 (14.9)	
	941-1500, n (%)	56 (13.7)	67 (16.4)	
	>1500, n (%)	37 (9.0)	34 (8.3)	
Resp. medication costs, including OCS	N (% non-missing)	409 (99.8)	409 (99.8)	0.1442
	≤250, n (%)	118 (28.9)	141 (34.5)	
	251-460, n (%)	113 (27.6)	105 (25.7)	
	461-940, n (%)	84 (20.5)	61 (14.9)	
	941-1500, n (%)	57 (13.9)	67 (16.4)	
	>1500, n (%)	37 (9.0)	35 (8.6)	
ICS/LABA FDC costs	N (% non-missing)	410 (100.0)	410 (100.0)	0.0037
	Mean (SD)	344.8 (172.8)	310.4 (160.5)	
	Median (IQR)	342.0 (266.0)	324.9 (209.8)	
SAMA costs	N (% non-missing)	410 (100.0)	410 (100.0)	0.8398
	Mean (SD)	1.7 (11.5)	2.1 (14.3)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	
SABA costs	N (% non-missing)	410 (100.0)	410 (100.0)	0.7424
	Mean (SD)	16.3 (26.9)	16.9 (27.9)	
	Median (IQR)	7.5 (18.0)	7.5 (19.5)	
LAMA costs	N (% non-missing)	409 (99.8)	409 (99.8)	0.4162
	Mean (SD)	239.6 (423.3)	262.5 (448.7)	
	Median (IQR)	0.0 (402.0)	0.0 (436.9)	
OCS costs	N (% non-missing)	410 (100.0)	410 (100.0)	0.8735
	Mean (SD)	2.9 (10.1)	3.3 (12.6)	
	Median (IQR)	0.0 (1.4)	0.0 (2.0)	
LTRA costs	N (% non-missing)	410 (100.0)	410 (100.0)	0.8513
	Mean (SD)	2.3 (13.6)	2.3 (13.8)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	

Variable		Baseline	Follow-up	P-value
THEO costs	N (% non-missing)	410 (100.0)	410 (100.0)	0.8457
	Mean (SD)	0.7 (4.8)	0.7 (4.7)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	

8.2.1 Outcome models

8.2.1.1 Primary outcome

There was not a significant difference in achieving risk domain control between the baseline and follow-up periods for the combined disease groups as well as the individual groups (Table 8). However, the lower bound of the 95% CI of the difference was higher than -10% in the combined groups and the Asthma group, indicating that outcomes did not worsen following the switch from Turbohaler to DuoResp.

Table 8. Adjusted Odds Ratio and difference for Risk domain control between follow-up and baseline periods, plus 95% CI

Statistic	Value (95% CI)	P
All patients		
Odds ratio	1.14 (0.78 – 1.67)	0.498
Difference (%)	3.1 (-5.9 - 12.1)	
Asthma group		
Odds ratio	1.14 (0.71 – 1.84)	0.581
Difference (%)	3.2 (-8.0 – 14.5)	
COPD group		
Odds ratio	1.17 (0.61 – 2.21)	0.639
Difference (%)	3.6 (-11.3 – 18.4)	

Adjusted for average daily ICS dose

8.2.1.2 Secondary outcomes

In the asthma group the average daily dose of SABA decreased significantly from baseline to follow-up, and the costs for all respiratory drugs increased significantly (Table 9), on average £115.
In the COPD group (Table 10) the respiratory medication costs increased significantly as well (average £ 133).

Table 9. Adjusted effect sizes and differences for secondary outcomes between follow-up and baseline periods, plus 95% CI – Asthma group

Outcome	Statistic	OR (95% CI)	P
Risk domain control*	Odds ratio	1.14 (0.71 – 1.84)	0.581
	Difference (%)	3.2 (-8.1 – 14.5)	
Exacerbation rate*	IR ratio	1.03 (0.75 – 1.41)	0.861
	Difference (I)	0.03 (-0.29 - 0.34)	
SABA avg. daily dose*	Odds ratio	0.57 (0.38 – 0.86)	0.008
Hospitalisation*	IR ratio	0.95 (0.24 – 3.70)	0.939
	Difference (I)	-0.05 (-1.41 – 1.31)	
Respiratory drugs including all OCS, costs	Relative difference	1.30 (1.23 – 1.38)	0.000
	Difference (£)	115.2 (87.9 – 142.5)	
Primary care consultations costs*	Relative difference	1.16 (0.94 – 1.43)	0.162
	Difference (£)	NC	
Respiratory-related hospital costs*	Relative difference	0.99 (0.85 – 1.15)	0.919
	Difference (£)	-0.00 (-0.01 – 0.01)	

*Adjusted for average daily ICS dose; NC = model did not converge

Table 10. Adjusted effect sizes and differences for secondary outcomes between follow-up and baseline periods, plus 95% CI – COPD group

Outcome	Statistic	OR (95% CI)	P
Risk domain control*	Odds ratio	1.17 (0.61 – 2.21)	0.639
	Difference (%)	3.5 (-11.2 – 18.4)	
Exacerbation rate*	IR ratio	1.07 (0.87 – 1.32)	0.513
	Difference (I)	0.07 (-0.14 - 0.28)	
SABA avg. daily dose*	Odds ratio	NC	
Hospitalisation*	IR ratio	0.60 (0.34 – 1.04)	0.069
	Difference (I)	-0.52 (-1.07 – 0.04)	
Respiratory drugs including all OCS, costs	Relative difference	1.13 (1.05 – 1.22)	0.002
	Difference (£)	132.6 (47.3 – 218.0)	
Primary care consultations costs*	Relative difference	1.10 (0.89 – 1.36)	0.398
	Difference (£)	NC	
Respiratory-related hospital costs*	Relative difference	NC	
	Difference (£)	NC	

*Adjusted for average daily ICS dose; NC = model did not converge

8.3 Phase 4

8.3.1 Unmatched baseline characterisation

The following sections describe the baseline characterisation of the study population.

Of the 410 patients, 63 (15%) switched back to Turbohaler during the outcome period, and 2 switched to Accuhaler.

8.3.1.1 Demographics

Patients in the asthma group who switched to DuoResp were on average older than those who remained on Accuhaler or Turbohaler (Table 11). The patients in the asthma group that remained on Accuhaler were more likely to be male than those that remained on Turbohaler or switched to DuoResp. In the COPD group, the differences in age and gender between the treatment arms were less pronounced. The other demographic characteristics (BMI, smoking status) showed little difference between the treatment arms in both disease groups.

8.3.1.2 Comorbidity

In both disease groups the patients that remained on Accuhaler were more often diagnosed with ischaemic heart disease and heart failure compared to patients in the Turbohaler or DuoResp arms (Table 12), and the Charlson comorbidity index was lower in the DuoResp switchers, *i.e.* those who switched to DuoResp. In the COPD group, rhinitis was more prevalent in the DuoResp switch arm than in the control arm.

8.3.1.3 Medication

In comparison to the other treatment arms, the patients in the asthma group that switched to DuoResp had a slightly less complex medication regimen at baseline (Table 13), but in the COPD group this was reversed.

Patients in both disease groups that switched to DuoResp were on a higher average daily dose of SABA, especially compared to patients that remained on Turbohaler.

Patients in both disease groups that switched to DuoResp were on a lower ICS average daily dose compared to patients who remained on Accuhaler, but a higher ICS average dose compared to patients who remained on Turbohaler.

Patients who switched to DuoResp had used less antibiotic and acute oral corticosteroid courses during the baseline year compared to the other treatment arms, in both disease groups.

8.3.1.4 Disease control

In patients in the asthma group, about 27% of the DuoResp switch arm were controlled according to GINA standards[50] (Table 14), while in the other treatment arms this was 13% in patients on Accuhaler and 18% in patients on Turbohaler. This also reflects in the percentage of patients that had no exacerbation during the baseline period. This was 77% in patients that switched to DuoResp, and 70% and 72% in patients remaining on Accuhaler and Turbohaler, respectively. The percentages of patients achieving risk domain control in the baseline year was 69% for patients switching to DuoResp, and 55% and 60% in patients remaining on Accuhaler and Turbohaler.

In patients in the COPD group who switched to DuoResp, 34% were in GOLD A group compared to 55% in the Accuhaler arm and 60% in the Turbohaler arm, and the mMRC score for DuoResp switchers was lower compared to the other arms. The percentage of patients achieving risk domain control during the baseline year did not differ much.

8.3.1.5 Spirometry

The availability of spirometry results was too low to be used for matching. Less than 40% of the patients in the asthma group had an FEV_1 result (Table 15), while this was between 71% and 89% in the COPD group. In the COPD group, the lung function was slightly better in patients switching to DuoResp compared to the other arms.

8.3.2 Matching

The matching process is described in detail in Appendix 14.1, page 79.

Table 11. Demographics by inhaler group and disease

Variable		DuoResp (n=420)	Accuhaler (n=39,353)	Turbohaler (n=49,386)	P-value	SDD_1	SDD_2
Asthma							
Age (years)	N (% non-missing)	265 (100.0)	17,393 (100.0)	32,071 (100.0)	<0.0001	0.227	0.121
	Mean (SD)	56.3 (15.5)	52.5 (17.8)	50.4 (17.4)			
	Median (IQR)	56.0 (22.0)	52.0 (26.0)	49.0 (26.0)			
Gender	N (% non-missing)	265 (100.0)	17,393 (100.0)	32,071 (100.0)	<0.0001	0.126	0.055
	Male, n (%)	121 (45.7)	6,863 (39.5)	13,520 (42.2)			
BMI (kg/m2)	N (% non-missing)	250 (94.3)	16,753 (96.3)	30,938 (96.5)	<0.0001	0.066	0.052
	<18.5, n (%)	4 (1.6)	255 (1.5)	395 (1.3)			
	≥18.5-<25, n (%)	68 (27.2)	4,398 (26.3)	8,604 (27.8)			
	≥25-<30, n (%)	89 (35.6)	5,611 (33.5)	10,614 (34.3)			
	≥30, n (%)	89 (35.6)	6,489 (38.7)	11,325 (36.6)			
Smoking status	N (% non-missing)	260 (98.1)	17,323 (99.6)	31,884 (99.4)	0.1366	0.086	0.020
	Non-smoker, n (%)	129 (49.6)	9,225 (53.3)	17,291 (54.2)			
	Current smoker, n (%)	47 (18.1)	3,166 (18.3)	5,736 (18.0)			
	Ex-smoker, n (%)	84 (32.3)	4,932 (28.5)	8,857 (27.8)			
COPD							
Age (years)	N (% non-missing)	155 (100.0)	21,960 (100.0)	17,315 (100.0)	0.0109	0.015	0.035
	Mean (SD)	70.2 (9.1)	70.3 (10.9)	69.9 (11.0)			
	Median (IQR)	70.0 (14.0)	71.0 (16.0)	71.0 (15.0)			
Gender	N (% non-missing)	155 (100.0)	21,960 (100.0)	17,315 (100.0)	0.5883	0.062	0.006
	Male, n (%)	77 (49.7)	11,595 (52.8)	9,198 (53.1)			
BMI (kg/m2)	N (% non-missing)	151 (97.4)	21,660 (98.6)	17,129 (98.9)	0.0001	0.045	0.053
	<18.5, n (%)	7 (4.6)	1,074 (5.0)	725 (4.2)			
	18.5-<25, n (%)	48 (31.8)	7,263 (33.5)	5,480 (32.0)			
	25-<30, n (%)	50 (33.1)	6,833 (31.5)	5,685 (33.2)			
	≥30, n (%)	46 (30.5)	6,490 (30.0)	5,239 (30.6)			
Smoking status	N (% non-missing)	155 (100.0)	21,900 (99.7)	17,266 (99.7)	<0.0001	0.096	0.107
	Non-smoker, n (%)	18 (11.6)	2,460 (11.2)	2,518 (14.6)			
	Current smoker, n (%)	42 (27.1)	6,883 (31.4)	4,948 (28.7)			
	Ex-smoker, n (%)	95 (61.3)	12,557 (57.3)	9,800 (56.8)			

P-value = p-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD_1 = Standardised difference for DuoResp vs. Accuhaler; SDD_2 = Standardised difference for DuoResp vs. Turbohaler; Values in red are indicative of imbalance (>0.1)

Table 12. Comorbidities by inhaler group and disease

Variable		DuoResp (n=420)	Accuhaler (n=39,353)	Turbohaler (n=49,386)	P-value	SDD_1	SDD_2
Asthma							
Ischaemic heart disease	N (% non-missing) Yes, n (%)	265 (100.0) 15 (5.7)	17,393 (100.0) 1,437 (8.3)	32,071 (100.0) 1,945 (6.1)	<0.0001	0.102	0.085
Heart failure	N (% non-missing) Yes, n (%)	265 (100.0) 1 (0.4)	17,393 (100.0) 300 (1.7)	32,071 (100.0) 338 (1.1)	<0.0001	0.132	0.057
Diabetes	N (% non-missing) Yes, n (%)	265 (100.0) 21 (7.9)	17,393 (100.0) 1,654 (9.5)	32,071 (100.0) 2,297 (7.2)	<0.0001	0.056	0.085
Pneumonia, probable	N (% non-missing) Yes, n (%)	265 (100.0) 1 (0.4)	17,393 (100.0) 84 (0.5)	32,071 (100.0) 136 (0.4)	0.6341	0.016	0.009
GERD	N (% non-missing) Yes, n (%)	265 (100.0) 41 (15.5)	17,393 (100.0) 2,334 (13.4)	32,071 (100.0) 3,896 (12.1)	0.0001	0.058	0.038
Rhinitis	N (% non-missing) Yes, n (%)	265 (100.0) 63 (23.8)	17,393 (100.0) 3,494 (20.1)	32,071 (100.0) 6,341 (19.8)	0.2007	0.089	0.008
Charlson CI	N (% non-missing) 0, n (%) 1-4, n (%) ≥5, n (%)	265 (100.0) 74 (27.9) 164 (61.9) 27 (10.2)	17,393 (100.0) 5,974 (34.3) 10,106 (58.1) 1,313 (7.5)	32,071 (100.0) 10,394 (32.4) 19,749 (61.6) 1,928 (6.0)	<0.0001	0.154	0.081
COPD							
Ischaemic heart disease	N (% non-missing) Yes, n (%)	155 (100.0) 29 (18.7)	21,960 (100.0) 5,092 (23.2)	17,315 (100.0) 3,771 (21.8)	0.0021	0.110	0.034
Heart failure	N (% non-missing) Yes, n (%)	155 (100.0) 5 (3.2)	21,960 (100.0) 1,533 (7.0)	17,315 (100.0) 1,115 (6.4)	0.0228	0.171	0.022
Diabetes	N (% non-missing) Yes, n (%)	155 (100.0) 20 (12.9)	21,960 (100.0) 3,418 (15.6)	17,315 (100.0) 2,533 (14.6)	0.0273	0.076	0.026
Pneumonia, probable	N (% non-missing) Yes, n (%)	155 (100.0) 2 (1.3)	21,960 (100.0) 485 (2.2)	17,315 (100.0) 298 (1.7)	0.0023	0.070	0.035
GERD	N (% non-missing) Yes, n (%)	155 (100.0) 25 (16.1)	21,960 (100.0) 3,717 (16.9)	17,315 (100.0) 2,709 (15.6)	0.0030	0.021	0.035
Rhinitis	N (% non-missing) Yes, n (%)	155 (100.0) 17 (11.0)	21,960 (100.0) 1,532 (7.0)	17,315 (100.0) 1,544 (8.9)	<0.0001	0.140	0.072

Variable		DuoResp (n=420)	Accuhaler (n=39,353)	Turbohaler (n=49,386)	P-value	SDD_1	SDD_2
Charlson CI	N (% non-missing)	155 (100.0)	21,960 (100.0)	17,315 (100.0)	0.0002	0.160	0.043
	0, n (%)	102 (65.8)	12,764 (58.1)	10,018 (57.9)			
	1-4, n (%)	37 (23.9)	6,300 (28.7)	5,220 (30.1)			
	≥5, n (%)	16 (10.3)	2,896 (13.2)	2,077 (12.0)			

P-value = p-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD_1 = Standardised difference for DuoResp vs. Accuhaler; SDD_2 = Standardised difference for DuoResp vs. Turbohaler; Values in red are indicative of imbalance (>0.1)

Table 13. Medication by inhaler group and disease

Variable		DuoResp (n=420)	Accuhaler (n=39,353)	Turbohaler (n=49,386)	P-value	SDD_1	SDD_2
		Asthma					
Drug therapy	N (% non-missing)	265 (100.0)	17,393 (100.0)	32,071 (100.0)	<0.0001	0.157	0.130
	ICS+LABA, n (%)	225 (84.9)	13,974 (80.3)	26,879 (83.8)			
	ICS+LABA+LAMA, n (%)	11 (4.2)	664 (3.8)	615 (1.9)			
	ICS+LABA+LAMA+LTRA, n (%)	4 (1.5)	237 (1.4)	298 (0.9)			
	ICS+LABA+LTRA, n (%)	25 (9.4)	2,516 (14.5)	4,278 (13.3)			
	Other, n (%)	0 (0.0)	2 (0.0)	1 (0.0)			
SABA average daily dose (salbutamol equivalence)	N (% non-missing)	239 (90.2)	15,558 (89.4)	29,068 (90.6)	<0.0001	0.116	0.138
	0, n (%)	65 (27.2)	4,495 (28.9)	9,929 (34.2)			
	>0 - ≤200, n (%)	74 (31.0)	4,354 (28.0)	8,268 (28.4)			
	>200 - ≤400, n (%)	57 (23.8)	3,823 (24.6)	6,576 (22.6)			
	>400 - ≤600, n (%)	27 (11.3)	1,494 (9.6)	2,237 (7.7)			
	>600, n (%)	16 (6.7)	1,392 (8.9)	2,058 (7.1)			
ICS average daily dose (Beclometasone equivalence)	N (% non-missing)	265 (100.0)	17,393 (100.0)	32,071 (100.0)	<0.0001	0.634	0.779
	≤400, n (%)	113 (42.6)	5,217 (30.0)	17,184 (53.6)			
	>400 - ≤800, n (%)	103 (38.9)	4,536 (26.1)	10,701 (33.4)			
	>800 - ≤1600, n (%)	44 (16.6)	5,031 (28.9)	3,772 (11.8)			
	>1600, n (%)	5 (1.9)	2,609 (15.0)	414 (1.3)			
No. antibiotic courses	N (% non-missing)	265 (100.0)	17,393 (100.0)	32,071 (100.0)	<0.0001	0.395	0.105
	0, n (%)	215 (81.1)	11,368 (65.4)	22,392 (69.8)			
	1, n (%)	35 (13.2)	3,470 (20.0)	5,929 (18.5)			
	2, n (%)	11 (4.2)	1,415 (8.1)	2,147 (6.7)			
	≥3, n (%)	4 (1.5)	1,140 (6.6)	1,603 (5.0)			
No. acute oral corticosteroid courses§	N (% non-missing)	265 (100.0)	17,393 (100.0)	32,071 (100.0)	<0.0001	0.216	0.059
	0, n (%)	205 (77.4)	12,324 (70.9)	23,336 (72.8)			
	1, n (%)	43 (16.2)	2,990 (17.2)	5,374 (16.8)			
	2, n (%)	12 (4.5)	1,168 (6.7)	2,041 (6.4)			
	≥3, n (%)	5 (1.9)	911 (5.2)	1,320 (4.1)			

Variable		DuoResp (n=420)	Accuhaler (n=39,353)	Turbohaler (n=49,386)	P-value	SDD_1	SDD_2
		COPD					
Drug therapy	N (% non-missing)	155 (100.0)	21,960 (100.0)	17,315 (100.0)	<0.0001	0.192	0.217
	ICS+LABA, n (%)	38 (24.5)	6,845 (31.2)	6,987 (40.4)			
	ICS+LABA+LAMA, n (%)	108 (69.7)	13,986 (63.7)	9,244 (53.4)			
	ICS+LABA+LAMA+LTRA, n (%)	8 (5.2)	767 (3.5)	625 (3.6)			
	ICS+LABA+LTRA, n (%)	1 (0.6)	361 (1.6)	459 (2.7)			
	Other, n (%)	0 (0.0)	1 (0.0)	0 (0.0)			
SABA average daily dose (salbutamol equivalence)	N (% non-missing)	147 (94.8)	19,240 (87.6)	15,262 (88.1)	0.0003	0.259	0.048
	0, n (%)	27 (18.4)	5,217 (27.1)	3,927 (25.7)			
	>0 - ≤200, n (%)	23 (15.6)	3,625 (18.8)	3,109 (20.4)			
	>200 - ≤400, n (%)	37 (25.2)	4,300 (22.3)	3,487 (22.8)			
	>400 - ≤600, n (%)	32 (21.8)	3,189 (16.6)	2,524 (16.5)			
	>600, n (%)	28 (19.0)	2,909 (15.1)	2,215 (14.5)			
ICS average daily dose (beclometasone equivalence)	N (% non-missing)	155 (100.0)	21,960 (100.0)	17,315 (100.0)	<0.0001	1.387	1.501
	≤400, n (%)	33 (21.3)	1,209 (5.5)	5,886 (34.0)			
	>400 - ≤800, n (%)	77 (49.7)	3,409 (15.5)	7,369 (42.6)			
	>800 - ≤1600, n (%)	41 (26.5)	7,762 (35.3)	3,497 (20.2)			
	>1600, n (%)	4 (2.6)	9,580 (43.6)	563 (3.3)			
No. antibiotic courses	N (% non-missing)	155 (100.0)	21,960 (100.0)	17,315 (100.0)	<0.0001	0.319	0.084
	0, n (%)	82 (52.9)	10,219 (46.5)	8,638 (49.9)			
	1, n (%)	49 (31.6)	5,512 (25.1)	4,320 (24.9)			
	2, n (%)	11 (7.1)	2,750 (12.5)	2,051 (11.8)			
	≥3, n (%)	13 (8.4)	3,479 (15.8)	2,306 (13.3)			
No. acute oral corticosteroid courses§	N (% non-missing)	155 (100.0)	21,960 (100.0)	17,315 (100.0)	<0.0001	0.220	0.077
	0, n (%)	91 (58.7)	11,407 (51.9)	9,608 (55.5)			
	1, n (%)	29 (18.7)	4,794 (21.8)	3,650 (21.1)			
	2, n (%)	11 (7.1)	2,799 (12.7)	2,019 (11.7)			
	≥3, n (%)	24 (15.5)	2,960 (13.5)	2,038 (11.8)			

P-value = p-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD_1 = Standardised difference for DuoResp vs. Accuhaler; SDD_2 = Standardised difference for DuoResp vs. Turbohaler; Values in red are indicative of imbalance (>0.1)
§ Acute oral CS: a) Dosing instructions are for tapered or short course OR b) Daily dosage is greater than 10mg OR c) Strength of drug is greater than 10mg if daily dosage is unavailable OR d) Lower respiratory tract infection on same day e) not maintenance and <5 prescriptions in 12 months

Table 14. Disease control by inhaler group and disease

Variable		DuoResp (n=420)	Accuhaler (n=39,353)	Turbohaler (n=49,386)	P-value	SDD_1	SDD_2
Asthma							
GINA control	N (% non-missing)	236 (89.1)	13,359 (76.8)	25,298 (78.9)	<0.0001	0.367	0.144
	Controlled, n (%)	63 (26.7)	1,776 (13.3)	4,654 (18.4)			
	Partly controlled, n (%)	148 (62.7)	9,246 (69.2)	16,778 (66.3)			
	Uncontrolled, n (%)	25 (10.6)	2,337 (17.5)	3,866 (15.3)			
No. exacerbations	N (% non-missing)	265 (100.0)	17,393 (100.0)	32,071 (100.0)	<0.0001	0.230	0.164
	0, n (%)	203 (76.6)	12,090 (69.5)	23,095 (72.0)			
	1, n (%)	45 (17.0)	3,154 (18.1)	5,503 (17.2)			
	2, n (%)	12 (4.5)	1,199 (6.9)	2,108 (6.6)			
	3, n (%)	4 (1.5)	558 (3.2)	850 (2.7)			
	4+, n (%)	1 (0.4)	392 (2.3)	515 (1.6)			
No. acute respiratory events	N (% non-missing)	265 (100.0)	17,393 (100.0)	32,071 (100.0)	<0.0001	0.348	0.103
	0, n (%)	184 (69.4)	9,605 (55.2)	19,082 (59.5)			
	1, n (%)	52 (19.6)	4,038 (23.2)	7,191 (22.4)			
	2, n (%)	19 (7.2)	1,951 (11.2)	3,219 (10.0)			
	≥3, n (%)	10 (3.8)	1,799 (10.3)	2,579 (8.0)			
Risk domain control	N (% non-missing)	265 (100.0)	17,393 (100.0)	32,071 (100.0)	<0.0001	0.296	0.087
	Controlled, n (%)	184 (69.4)	9,605 (55.2)	19,082 (59.5)			
COPD							
GOLD Risk	N (% non-missing)	152 (98.1)	21,411 (97.5)	16,731 (96.6)	<0.0001	0.279	0.121
	A, n (%)	51 (33.6)	4,589 (21.4)	4,350 (26.0)			
	B, n (%)	27 (17.8)	4,511 (21.1)	3,401 (20.3)			
	C, n (%)	30 (19.7)	4,550 (21.3)	3,630 (21.7)			
	D, n (%)	44 (28.9)	7,761 (36.2)	5,350 (32.0)			
Total CAT Score	N (% non-missing)	11 (7.1)	1,413 (6.4)	1,652 (9.5)	0.0014	0.408	0.122
	Mean (SD)	15.5 (8.0)	19.1 (9.3)	18.0 (8.8)			
	Median (IQR)	13.0 (9.0)	19.0 (13.0)	17.0 (13.0)			
mMRC score	N (% non-missing)	152 (98.1)	21,411 (97.5)	16,731 (96.6)	<0.0001	0.213	0.101
	0-1, n (%)	81 (53.3)	9,139 (42.7)	7,980 (47.7)			
	≥2, n (%)	71 (46.7)	12,272 (57.3)	8,751 (52.3)			
No. exacerbations	N (% non-missing)	155 (100.0)	21,960 (100.0)	17,315 (100.0)	<0.0001	0.222	0.099
	0, n (%)	59 (38.1)	7,412 (33.8)	6,477 (37.4)			
	1, n (%)	46 (29.7)	5,410 (24.6)	4,381 (25.3)			
	2, n (%)	16 (10.3)	3,673 (16.7)	2,772 (16.0)			
	≥3, n (%)	34 (21.9)	5,465 (24.9)	3,685 (21.3)			

Variable		DuoResp (n=420)	Accuhaler (n=39,353)	Turbohaler (n=49,386)	P-value	SDD_1	SDD_2
Risk domain control	N (% non-missing)	155 (100.0)	21,960 (100.0)	17,315 (100.0)	<0.0001	0.090	0.076
	Controlled, n (%)	59 (38.1)	7,412 (33.8)	6,477 (37.4)			

P-value = p-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD_1 = Standardised difference for DuoResp vs. Accuhaler; SDD_2 = Standardised difference for DuoResp vs. Turbohaler; Values in red are indicative of imbalance (>0.1)

Table 15. Spirometry by inhaler group and disease

Variable		DuoResp (n=420)	Accuhaler (n=39,353)	Turbohaler (n=49,386)
		Asthma		
FEV_1 % predicted	N (% non-missing)	104 (39.2)	5,781 (33.2)	10,504 (32.8)
	Mean (SD)	80.3 (19.9)	80.2 (23.7)	82.1 (21.7)
	Median (IQR)	81.8 (26.0)	82.0 (30.0)	83.3 (27.0)
FEV_1 % predicted	N (% non-missing)	104 (39.2)	5,781 (33.2)	10,504 (32.8)
	<30 (very severe), n (%)	0 (0.0)	137 (2.4)	169 (1.6)
	30-49 (severe), n (%)	6 (5.8)	473 (8.2)	637 (6.1)
	50-79 (moderate), n (%)	42 (40.4)	2,020 (34.9)	3,568 (34.0)
	≥80 (mild), n (%)	56 (53.8)	3,151 (54.5)	6,130 (58.4)
FEV_1	N (% non-missing)	103 (38.9)	5,388 (31.0)	9,845 (30.7)
	Mean (SD)	2.3 (0.8)	2.2 (0.8)	2.3 (0.8)
	Median (IQR)	2.3 (1.2)	2.1 (1.1)	2.3 (1.2)
PEF % predicted	N (% non-missing)	16 (6.0)	7,833 (45.0)	11,240 (35.0)
	Mean (SD)	72.1 (16.4)	75.7 (19.4)	78.1 (18.9)
	Median (IQR)	74.8 (29.8)	76.6 (26.6)	78.8 (25.4)
PEF % predicted	N (% non-missing)	16 (6.0)	7,833 (45.0)	11,240 (35.0)
	Green, n (%)	6 (37.5)	3,399 (43.4)	5,332 (47.4)
	Red, n (%)	2 (12.5)	812 (10.4)	840 (7.5)
	Yellow, n (%)	8 (50.0)	3,622 (46.2)	5,068 (45.1)
FEV_1/FVC ratio	N (% non-missing)	91 (34.3)	3,994 (23.0)	7,759 (24.2)
	Mean (SD)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)
	Median (IQR)	0.7 (0.2)	0.7 (0.2)	0.8 (0.2)
		COPD		
FEV_1 % predicted	N (% non-missing)	138 (89.0)	15,561 (70.9)	13,282 (76.7)
	Mean (SD)	59.9 (20.8)	56.5 (21.1)	58.3 (20.8)
	Median (IQR)	58.9 (28.0)	55.0 (29.0)	57.0 (29.0)
FEV_1 % predicted	N (% non-missing)	138 (89.0)	15,561 (70.9)	13,282 (76.7)
	<30 (very severe), n (%)	9 (6.5)	1,353 (8.7)	1,035 (7.8)
	30-49 (severe), n (%)	34 (24.6)	4,834 (31.1)	3,674 (27.7)
	50-79 (moderate), n (%)	69 (50.0)	7,291 (46.9)	6,566 (49.4)
	≥80 (mild), n (%)	26 (18.8)	2,083 (13.4)	2,007 (15.1)
FEV_1	N (% non-missing)	139 (89.7)	15,010 (68.4)	12,924 (74.6)
	Mean (SD)	1.5 (0.6)	1.4 (0.6)	1.4 (0.6)
	Median (IQR)	1.4 (0.9)	1.3 (0.8)	1.3 (0.8)
PEF % predicted	N (% non-missing)	9 (5.8)	3,956 (18.0)	2,786 (16.1)

Variable		DuoResp (n=420)	Accuhaler (n=39,353)	Turbohaler (n=49,386)
	Mean (SD)	55.2 (14.6)	53.1 (18.1)	54.8 (18.3)
	Median (IQR)	53.5 (23.9)	51.6 (25.9)	53.0 (26.0)
PEF % predicted	N (% non-missing)	9 (5.8)	3,956 (18.0)	2,786 (16.1)
	Green, n (%)	1 (11.1)	323 (8.2)	264 (9.5)
	Red, n (%)	4 (44.4)	1,876 (47.4)	1,210 (43.4)
	Yellow, n (%)	4 (44.4)	1,757 (44.4)	1,312 (47.1)
FEV_1/FVC ratio	N (% non-missing)	130 (83.9)	12,902 (58.8)	11,196 (64.7)
	Mean (SD)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)
	Median (IQR)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)

8.3.3 Outcomes

Descriptive statistics of the main disease outcome characteristics over the study arms are presented in Table 16 and Table 17.

Table 16. Overview of disease outcomes in the matched patients – Asthma group

	DuoResp (N=253)				Turbohaler (N=743)			
	Mean	SD	Median	IQR	Mean	SD	Median	IQR
Risk domain control (%)	73.1				68.0			
Exacerbations	0.3	0.7	0.0	0.0	0.4	0.7	0.0	0.0
Treatment stability (%)	72.7				66.9			
SABA average daily dose	1.4	1.9	0.8	1.9	1.5	2.9	0.6	2.2
SABA inhalers	5.1	6.8	3.0	7.0	5.5	10.7	2.0	8.0
Antibiotics prescriptions	0.2	0.7	0.0	0.0	0.4	0.8	0.0	0.0
Acute OCS courses	0.3	0.7	0.0	0.0	0.3	0.7	0.0	0.0
FDC average daily dose	382.1	351.3	328.8	394.5	505.3	585.0	526.0	494.0
FDC inhalers	14.0	8.9	12.0	11.0	10.8	5.6	11.0	6.0
Respiratory A&E attendances	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.0
Respiratory inpatient hospitalisations, probable	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.0
Respiratory inpatient hospitalisations, definite	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.0
Pneumonia, probable (%)	0.0				0.0	0.4		
Pneumonia, definite (%)	0.0				0.0	0.3		

Table 17. Overview of disease outcomes in the matched patients – COPD group

	DuoResp (N=132)				Turbohaler (N=348)			
	Mean	SD	Median	IQR	Mean	SD	Median	IQR
Risk domain control (%)	40.2				37.1			
Exacerbations	1.1	1.7	0.0	2.0	1.0	1.4	0.0	1.0
Treatment stability (%)	39.4				37.1			
SABA average daily dose	2.6	2.9	1.9	3.6	2.4	2.3	1.9	3.0
SABA inhalers	9.5	11.0	7.0	13.0	8.7	8.5	7.0	11.0
Antibiotics prescriptions	0.7	1.1	0.0	1.0	0.8	1.1	0.0	1.0
Acute OCS courses	1.0	1.7	0.0	1.5	0.9	1.3	0.0	1.0
FDC average daily dose	555.3	427.1	631.2	297.5	561.8	646.1	723.3	524.1
FDC inhalers	15.0	6.7	13.0	8.0	11.9	5.4	12.0	5.0
Respiratory A&E attendances	0.0	0.2	0.0	0.0	0.1	0.4	0.0	0.0
Respiratory inpatient hospitalisations, probable	0.1	0.4	0.0	0.0	0.1	0.5	0.0	0.0
Respiratory inpatient hospitalisations, definite	0.0	0.3	0.0	0.0	0.1	0.4	0.0	0.0
Pneumonia, probable (%)	3.0				2.3			
Pneumonia, definite (%)	2.3				0.6			

8.3.3.1 Primary outcome

Patients who switched to DuoResp more often achieved risk domain control than patients who remained on Turbohaler (60.0 vs. 55.6%) in the unmatched population (Table 18). This difference was largest in the asthma group. The difference remained in the matched sample (Table 19), but was smaller.

Table 18. Frequency of achieving risk domain control, unmatched patients.

	DuoResp		Turbohaler	
Group	N (%)	Total	N (%)	Total
Asthma	186 (71.0)	262	20,965 (62.9)	33,352
COPD	60 (40.5)	148	7,003 (41.2)	16,977
Combined	246 (60.0)	410	27,968 (55.6)	50,329

Table 19. Frequency of achieving risk domain control, matched patients.

	DuoResp		Turbohaler	
Group	N (%)	Total	N (%)	Total
Asthma	185 (73.1)	253	505 (68.0)	743
COPD	53 (40.2)	132	129 (37.1)	348
Combined	238 (61.8)	385	634 (58.1)	1,091

The conditional logistic regression model, in all matched patients, showed an adjusted Odds Ratio of 1.31 for DuoResp vs. Turbohaler for achieving risk domain control, which did not achieve statistical significance at the 0.05 level (Table 20). In the sensitivity analysis, where only DuoResp switchers that had 3 matched control patients were used, the Odds Ratio was slightly higher (1.41) and was significant (p=0.022); the average effect size of switching to Duoresp was similar for the main analysis and its sensitivity analysis.

The regression models in the asthma group showed similar effect sizes, but they did not reach statistical significance at the 5% level. The models in the COPD group also showed similar results, with no significant effects. The results for the sensitivity analysis were somewhat different here (OR 1.49, compared to 1.24 in the principal analysis), which is indicative for more residual confounding in the 3:1 compared to the 1:1 matching.

Table 20. Adjusted Odds Ratios achieving risk domain control.

Cohort	OR (95% CI)	P	N
All patients			
All matched	1.31 (0.99-1.73)	0.0610	971
3:1 only	1.41 (1.05-1.90)	0.0220	928
Asthma group			
All matched	1.36 (0.94-1.92)	0.100	658
3:1 only	1.36 (0.95-1.96)	0.092	644
COPD group			
All matched	1.24 (0.77-1.99)	0.372	313
3:1 only	1.49 (0.90-2.50)	0.123	284

Adjusted for BMI and Ischaemic heart disease. All matched = at least 1 matched control per case; 3:1 only = 3 matched controls per case.

The lower bound of the 95% CI of the adjusted percentage difference in the combined population is at -0.3% (Table 21), and the non-inferiority bound was set at -10%. Therefore, we can claim non-inferiority of switching to DuoResp compared to remaining on Turbohaler.

Because the lower bound of the 95% CI of the absolute difference was below 0.0 (Table 21), we cannot claim superiority.

The adjusted differences in percentage of patients achieving risk domain control were similar to the combined group in the asthma group. In the COPD group the adjusted differences were of similar magnitude compare to the other and the combined groups in the main analysis. In this group the sensitivity analysis showed a dissimilar effect as well (average adjusted difference of almost 10%, but with a wide confidence interval from -2.4% to 22.2%).

Table 21. Adjusted percentage difference in achieving risk domain control.

Cohort	Adj. % (95% CI)	P
All patients		
All matched	6.6 (-0.3 – 13.5)	0.0600
3:1 only	8.3 (1.0 – 15.6)	0.0250
Asthma group		
All matched	6.2 (-2.8 – 15.2)	0.175
3:1 only	6.5 (-2.7 – 15.7)	0.168
COPD group		
All matched	5.0 (-5.8 – 15.8)	0.363
3:1 only	9.9 (-2.4 – 22.2)	0.114

8.3.3.2 Secondary outcomes

8.3.3.2.1 Exacerbations

The number of patients without exacerbations was higher in the DuoResp switchers than the control arm in the asthma unmatched group (Table 22 and Figure 7), while the COPD unmatched group showed the opposite. The difference remained after matching in the asthma group, but in the matched COPD group the distributions were similar.

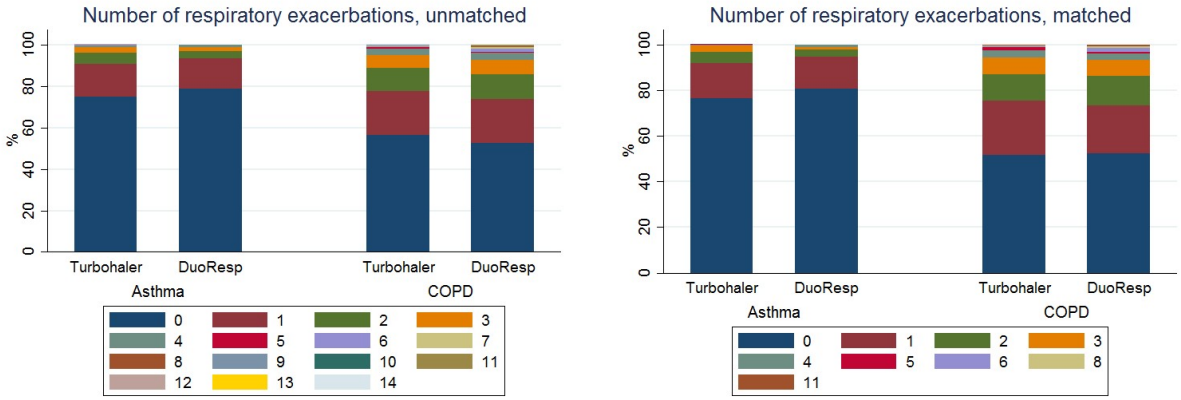


Figure 7. Number of exacerbations in the unmatched and matched patients, by disease group

8.3.3.2.2 Treatment stability

Treatment stability was higher in the DuoResp arm than the control arm in the unmatched asthma group, but not in the COPD group. After matching the difference became smaller in the asthma group, but increased in the COPD group in favour of DuoResp switchers (Table 22).

8.3.3.2.3 SABA usage

The distribution of the average daily doses of Short-Acting β-Agonists (SABA) was similar in the unmatched patients in the asthma group between the treatments (Table 22 and Figure 8), and remained so after matching.

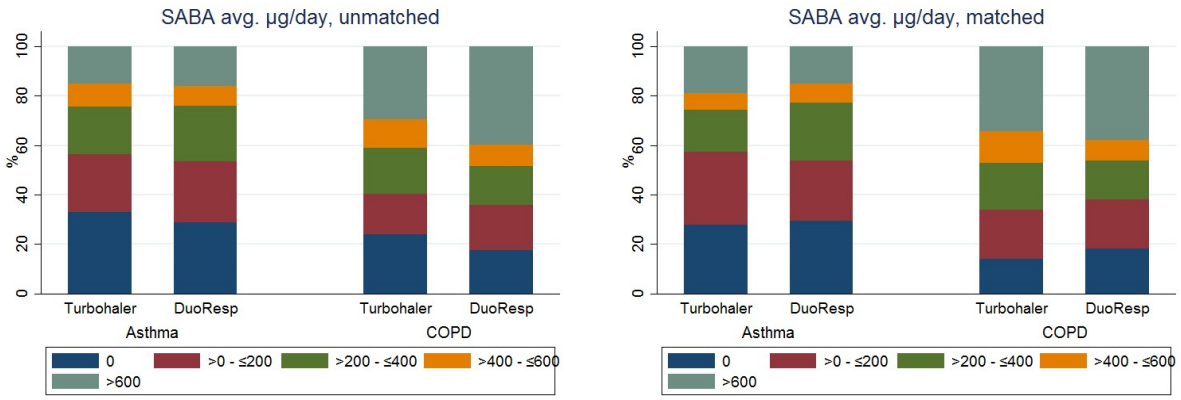


Figure 8. SABA average daily dose in the unmatched and matched patients, by disease group

In the COPD group, the DuoResp treatment group received higher reliever medication doses than the control arm in the unmatched, but this reversed in the matched patients. This is also visible in the number of SABA inhalers (Figure 9).

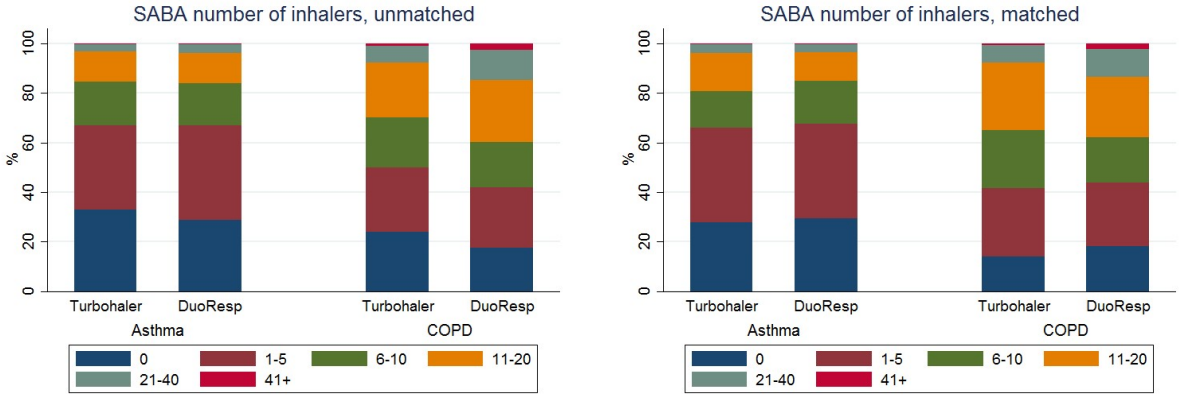


Figure 9. Number of SABA inhalers in the unmatched and matched, by disease group

8.3.3.2.4 Lower respiratory hospitalisations

In both the asthma and COPD groups there were only very small differences in number of respiratory hospitalisations, before and after matching (Figure 10).

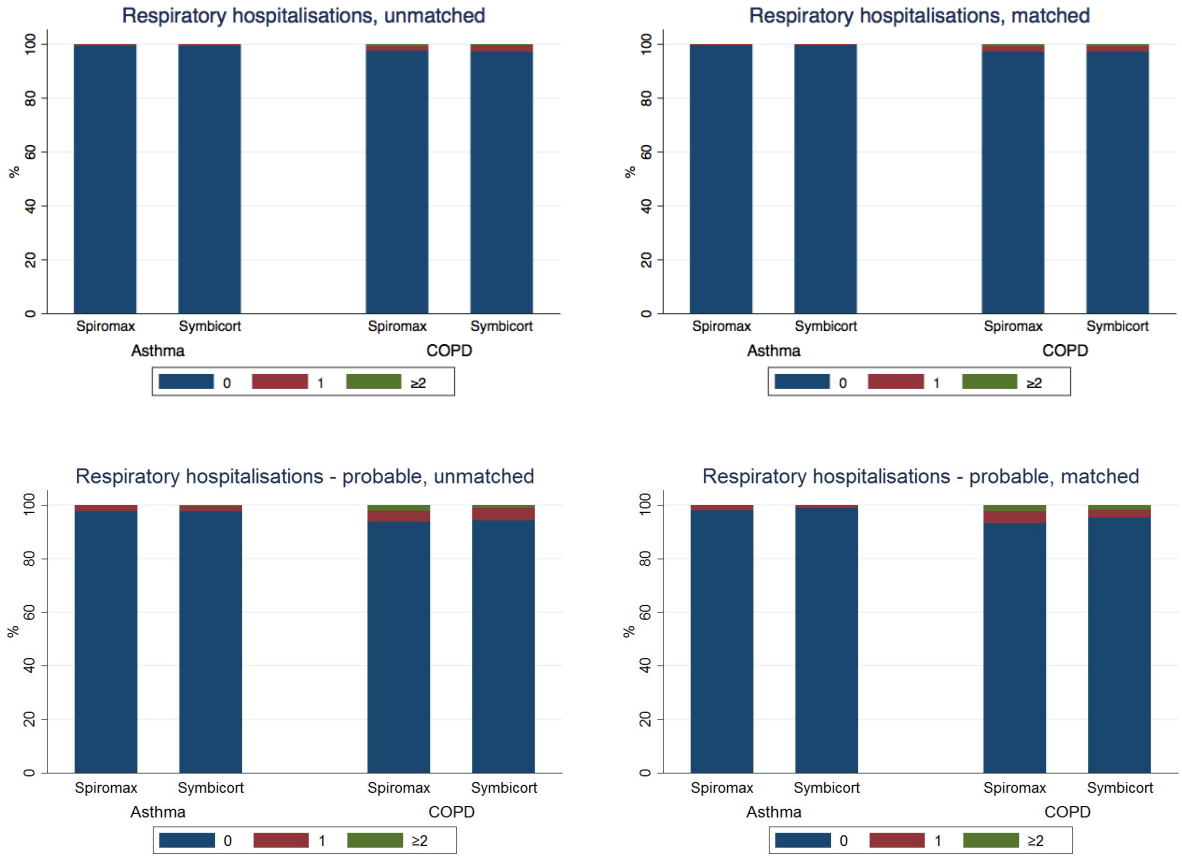


Figure 10. Number of definite and probable respiratory inpatient hospitalisations in the unmatched and matched, by disease group.

Table 22. Frequency of secondary outcomes, in unmatched and matched patients.

		Unmatched					Matched			
		DuoResp		Turbohaler			DuoResp		Turbohaler	
Group	Category	N (%)	Total	N (%)	Total		N (%)	Total	N (%)	Total
Achieving Risk Domain Control										
Asthma		186 (71.0)	262	20,965 (62.9)	33,352		185 (73.1)	253	505 (68.0)	743
COPD		60 (40.5)	148	7,003 (41.2)	16,977		53 (40.2)	132	129 (37.1)	348
Combined		246 (60.0)	410	27,968 (55.6)	50,329		238 (61.8)	385	634 (58.1)	1,091
Exacerbations										
Asthma	0	206 (78.6)	262	24,966 (74.9)	33,352		204 (80.6)	253	568 (76.4)	743
	1	39 (14.9)		5,269 (15.8)			36 (14.2)		114 (15.3)	
	≥2	17 (6.5)		3,117 (9.3)			13 (5.1)		61 (8.2)	
COPD	0	60 (40.5)	148	7,003 (41.2)	16,977		53 (40.2)	132	129 (37.1)	348
	1	31 (21.0)		4,192 (24.7)			28 (21.2)		104 (30.0)	
	≥2	57 (38.5)		5,782 (34.1)			51 (38.6)		115 (33.0)	
Treatment stability										
Asthma		185 (70.6)	262	20,511 (61.5)	33,352		184 (72.7)	253	497 (66.9)	743
COPD		59 (39.9)	148	6,911 (40.7)	16,977		52 (39.4)	132	129 (37.1)	348
Lower respiratory hospitalisations - definite										
Asthma	0	260 (99.2)	262	33,030 (99.0)	33,352		251 (99.2)	253	739 (99.5)	743
	1	2 (0.8)		291 (0.9)			2 (0.8)		4 (0.5)	
	≥2	0 (0.0)		31 (0.1)			0 (0.0)		0 (0.0)	
COPD	0	143 (96.6)	148	16,585 (97.7)	16,977		127 (96.2)	132	335 (96.3)	348
	1	4 (2.7)		340 (2.0)			4 (3.0)		11 (3.2)	
	≥2	1 (0.7)		52 (0.3)			1 (0.8)		2 (0.6)	
Lower respiratory hospitalisations - probable										
Asthma	0	260 (99.2)	262	33,049 (99.1)	33,352		252 (99.6)	253	740 (99.6)	743
	1	2 (0.8)	262	271 (0.8)			1 (0.4)	253	3 (0.4)	
	≥2	0 (0.0)	262	32 (0.1)			0 (0.0)	253	0 (0.0)	
COPD	0	144 (97.3)	148	16,501 (97.2)	16,977		128 (97.0)	132	338 (97.1)	348
	1	3 (2.0)	148	415 (2.4)			3 (2.3)	132	7 (2.0)	
	≥2	1 (0.7)	148	61 (0.4)			1 (0.8)	132	3 (0.9)	

		Unmatched					Matched			
		DuoResp		Turbohaler			DuoResp		Turbohaler	
Group	Category	N (%)	Total	N (%)	Total		N (%)	Total	N (%)	Total
SABA avg daily dose										
Asthma	0	75 (28.6)	262	10,984 (32.9)	33,352		74 (29.2)	253	207 (27.9)	743
	≤200	65 (24.8)		7,788 (23.4)			62 (24.5)		219 (29.5)	
	>200 ≤400	59 (22.5)		6,425 (19.3)			59 (23.3)		127 (17.1)	
	>400 ≤600	21 (8.0)		3,096 (9.3)			20 (7.9)		49 (6.6)	
	>600	42 (16.0)		5,059 (15.2)			38 (15.0)		141 (19.0)	
COPD	0	26 (17.6)	148	4,082 (24.0)	16,977		24 (18.2)	132	49 (14.1)	348
	≤200	27 (18.2)		2,751 (16.2)			26 (19.7)		69 (19.8)	
	>200 ≤400	23 (15.5)		3,189 (18.8)			21 (15.9)		66 (19.0)	
	>400 ≤600	13 (8.8)		1,922 (11.3)			11 (8.3)		44 (12.6)	
	>600	59 (39.9)		5,033 (29.6)			50 (37.9)		120 (34.5)	
SABA number of inhalers										
Asthma	0	75 (28.6)	262	10,984 (32.9)	33,352		74 (29.2)	253	207 (27.9)	743
	1-5	100 (38.2)		11,366 (34.1)			97 (38.3)		284 (38.2)	
	6-10	45 (17.2)		5,893 (17.7)			44 (17.4)		109 (14.7)	
	11-20	32 (12.2)		4,014 (12.0)			29 (11.5)		113 (15.2)	
	21-40	9 (3.4)		996 (3.0)			8 (3.2)		28 (3.8)	
	≥41	1 (0.4)		99 (0.3)			1 (0.4)		2 (0.3)	
COPD	0	26 (17.6)	148	4,082 (24.0)	16,977		24 (18.2)	132	49 (14.1)	348
	1-5	36 (24.3)		4,371 (25.7)			34 (25.8)		96 (27.6)	
	6-10	27 (18.2)		3,464 (20.4)			24 (18.2)		81 (23.3)	
	11-20	37 (25.0)		3,763 (22.2)			32 (24.2)		95 (27.3)	
	21-40	18 (12.2)		1,126 (6.6)			15 (11.4)		25 (7.2)	
	≥41	4 (2.7)		171 (1.0)			3 (2.3)		2 (0.6)	

		Unmatched					Matched			
		DuoResp		Turbohaler			DuoResp		Turbohaler	
Group	Category	N (%)	Total	N (%)	Total		N (%)	Total	N (%)	Total
Number of resp. hospitalisations - definite										
Asthma	0	260 (99.2)	262	33,049 (99.1)	33,352		252 (99.6)	253	740 (99.6)	743
	1	2 (0.8)		271 (0.8)			1 (0.4)		3 (0.4)	
	≥2	0 (0.0)		32 (0.1)			0 (0.0)		0 (0.0)	
COPD	0	144 (97.3)	148	16,501 (97.2)	16,977		128 (97.0)	132	338 (97.1)	348
	1	3 (2.0)		415 (2.4)			3 (2.3)		7 (2.0)	
	≥2	1 (0.7)		61 (0.4)			1 (0.8)		3 (0.9)	
Pneumonia, probable										
Asthma		0 (0.0)	262	117 (0.4)	33,352		0 (0.0)	253	3 (0.4)	743
COPD		5 (3.4)	148	260 (1.5)	16,977		4 (3.0)	132	8 (2.3)	348
Pneumonia, definite										
Asthma		0 (0.0)	262	53 (0.2)	33,352		0 (0.0)	253	2 (0.3)	743
COPD		4 (2.7)	148	125 (0.7)	16,977		3 (2.3)	132	2 (0.6)	348

Table 23. Model results of secondary outcomes, in all matched and 3:1 matched patients, by disease group.

Exacerbations			Respiratory hospitalisations - definite		
Cohort	RR (95% CI)	P	Cohort	RR (95% CI)	P
	Asthma			**Asthma**	
All matched	0.76 (0.60-0.99)	0.0440	All matched	0.90 (0.09-8.68)	0.9250
3:1 only	0.70 (0.51-0.94)	0.0200	3:1 only	NC	
	COPD			**COPD**	
All matched	1.03 (0.87-1.23)	0.7120	All matched	0.87 (0.34-2.18)	0.7620
3:1 only	0.98 (0.62-1.56)	0.9380	3:1 only	1.13 (0.44-2.87)	0.8060

Treatment stability			Respiratory hospitalisations - probable		
Cohort	OR (95% CI)	P	Cohort	OR (95% CI)	P
	Asthma			**Asthma**	
All matched	1.44 (1.02-2.04)	0.0370	All matched	1.66 (0.54-5.15)	0.378
3:1 only	1.47 (1.03-2.09)	0.0320	3:1 only	1.13 (0.30-4.24)	0.862
	COPD			**COPD**	
All matched	1.31 (0.79-2.16)	0.2960	All matched	1.17 (0.60-2.27)	0.643
3:1 only	1.43 (0.84-2.44)	0.1830	3:1 only	1.25 (0.60-2.61)	0.553

SABA avg daily dose			Pneumonia, probable		
Cohort	OR (95% CI)	P	Cohort	OR (95% CI)	P
	Asthma			**Asthma**	
All matched	0.71 (0.52-0.98)	0.0340	All matched	NC	
3:1 only	0.69 (0.50-0.95)	0.0230	3:1 only	NC	
	COPD			**COPD**	
All matched	0.67 (0.44-1.03)	0.0690	All matched	1.18 (0.35-4.03)	0.7890
3:1 only	0.57 (0.36-0.92)	0.0220	3:1 only	0.86 (0.18-4.13)	0.8480

SABA inhalers			Pneumonia, definite		
Cohort	RR (95% CI)	P	Cohort	OR (95% CI)	P
	Asthma			**Asthma**	
All matched	0.92 (0.86-0.99)	0.0190	All matched	NC	
3:1 only	0.92 (0.85-0.98)	0.0160	3:1 only	NC	
	COPD			**COPD**	
All matched	0.97 (0.90-1.04)	0.3630	All matched	3.41 (0.55-21.13)	0.1870
3:1 only	0.86 (0.79-0.94)	0.0010	3:1 only	1.5 (0.14-16.54)	0.7410

All matched = at least 1 matched control per case; 3:1 only = 3 matched control per case; NC = Model did not converge.
Covariates for adjustment are specified in Table 37.

8.3.3.2.5 Health-related costs

Patients who switched to DuoResp had a lower baseline total cost as compared to Turbohaler patients. This difference was largely driven by the difference in medication costs (Table 24). During the outcome year, lower medication costs persisted for DuoResp patients (£579 vs. £659; p<0.001) (Table 25).

Table 24. Baseline mean (SD) medication and service costs for matched cohorts – Combined (2014 £)

Variable[a]	Turbohaler (n=1165)	DuoResp (n=397)	P-value[a]
Baseline asthma/COPD medication costs			
ICS inhalers	362 (167)	340 (166)	<0.001
Short-acting beta-2 agonist inhalers	19 (30)	16 (26)	0.017
Long-acting beta-2 agonist inhalers	1 (12)	0 (0)	0.007
Short-acting muscarinic antagonist inhaler costs	2 (26)	2 (12)	0.519
Long-acting muscarinic antagonist inhaler costs	202 (429)	225 (418)	0.163
Leukotriene receptor antagonist prescriptions	2 (11)	2 (14)	0.735
Theophylline costs	2 (10)	1 (4)	0.009
Antibiotic prescriptions	1 (2)	1 (2)	0.898
Oral steroid prescriptions	2 (7)	2 (7)	0.771
Total medication costs	593 (520)	587 (508)	0.107
Total medication costs excluding ICS	230 (441)	247 (426)	0.519
Baseline primary and secondary care costs			
Respiratory-related primary care consultation costs	50 (83)	36 (51)	<0.001
Respiratory-related hospitalisations	22 (110)	25 (118)	0.643
Respiratory-related inpatient	9 (74)	9 (92)	0.970
Respiratory-related outpatient	11 (62)	16 (73)	0.391
Respiratory-related emergency department visits	2 (24)	1 (13)	0.200
Total respiratory-related costs excluding ICS costs	302 (503)	309 (472)	0.712
Total respiratory-related costs including ICS costs	664 (583)	648 (552)	0.036

[a] P-values using bootstrapped-t percentile method using 1000 samples taken with replacement from the dataset

Table 25. Respiratory-related mean (SD) medication and service-level costs during the outcome period – Combined (2014 £)

Variable[a]	Turbohaler (n=1,165)	DuoResp (n=397)	P-value[a]
Outcome period asthma/COPD medication costs			
ICS inhalers	409 (199)	306 (156)	<0.001
Short-acting beta-2 agonist inhalers	20 (31)	16 (26)	0.005
Long-acting beta-2 agonist inhalers	0.5 (8)	0.06 (1)	0.197
Short-acting muscarinic antagonist inhaler costs	2 (33)	2 (14)	0.686
Long-acting muscarinic antagonist inhaler costs	220 (433)	250 (444)	0.095
Leukotriene receptor antagonist prescriptions	3 (12)	2 (14)	0.488
Theophylline costs	2 (11)	1 (4)	0.002
Antibiotic prescriptions	1 (7)	1 (2)	0.234
Oral steroid prescriptions	2 (6)	2 (10)	0.746
Total medication costs	659 (553)	579 (534)	<0.001
Total medication costs excluding ICS	250 (448)	273 (452)	0.403
Outcome primary and secondary care costs			
Respiratory-related primary care consultation costs	47 (81)	34 (48)	<0.001
Respiratory-related hospitalizations	21 (121)	22 (148)	0.977
Respiratory-related inpatient	11 (95)	12 (109)	0.887
Respiratory-related outpatient	8 (56)	7 (42)	0.523
Respiratory-related emergency department visits	3 (21)	4 (28)	0.600
Total outcome respiratory-related costs excluding ICS costs	318 (519)	329 (507)	0.895
Total outcome respiratory-related costs including ICS costs	727 (620)	635 (591)	<0.001

[a] P-values using bootstrapped-t percentile method using 1000 samples taken with replacement from the dataset

The adjusted proportion of patients achieving control, as defined by risk-domain asthma control, was 0.58 (95% CI: 0.52, 0.64) for DuoResp users and 0.54 (95% CI: 0.50, 0.58) for Turbohaler users, for a difference of 0.04 (95% CI: -0.01, 0.10) after adjusting for rhinitis (Table 26). Adjusted mean cost was £492 (95% CI: £461, £523) for DuoResp users and £597 (95% CI: £575, £620) for Turbohaler users, for a difference of -£105 (95% CI: -£132, -£78) after adjusting for all baseline costs. The difference in cost over the difference in effectiveness results in a dominant incremental cost-effectiveness ratio (ICER) [*i.e.*, less costly, more effective]. This suggests we can be 95% confident that DuoResp is good value for money compared to Turbohaler for willingness-to-pay (WTP) values up to approximately £7,014. For WTP values above £7,014 we cannot be 95% confident that DuoResp and Turbohaler differ in value.

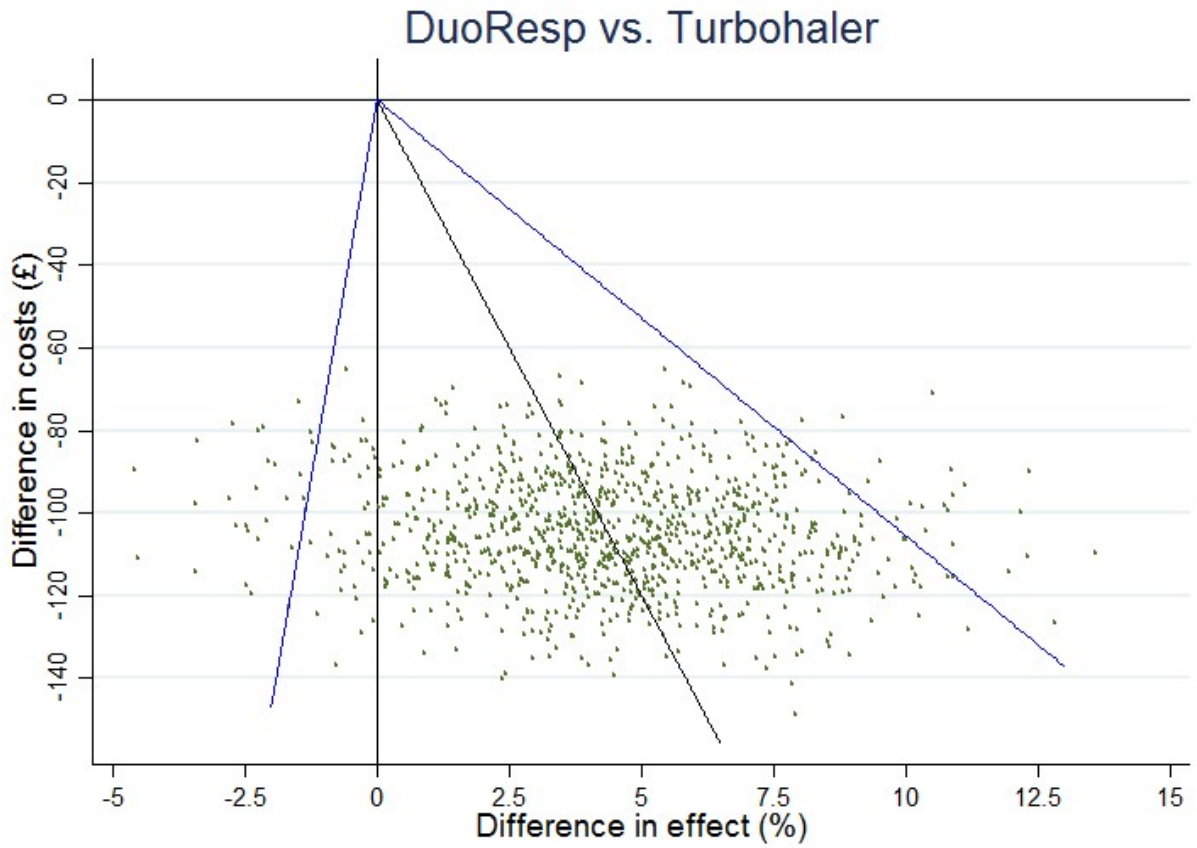
The results of the resampling are shown on the cost-effectiveness plane in Figure 11. Of the 1,000

bootstrapped estimates 937 resided in the SE quadrant (less costly, more ***effective***).

Table 26. Incremental cost-effectiveness results: DuoResp vs. Turbohaler (2014 £)

Variable/difference	Turbohaler (N=1,165)	DuoResp (N=397)	Incremental Difference (DuoResp vs. Turbohaler)
Risk-domain control, adjusted proportion (95% CI)[a]	0.54 (0.50 - 0.58)	0.58 (0.52 - 0.64)	0.04 (-0.01 - 0.10)
Adjusted mean respiratory-related healthcare costs per patient per year (95% CI)[a]	£597 (£575 - £620)	£492 (£461 - £523)	-£105 (-£132 - -£78)
Incremental cost-effectiveness ratio (95% CI)[a] [DuoResp vs. Turbohaler]		**Dominant** per additionally controlled patient [Less costly, more effective]	

[a] Bootstrapped acceptability 95% confidence intervals



Blue lines indicate 95% CI

Figure 11. Cost-effectiveness plane showing spread of difference in costs and effects between DuoResp and Turbohaler (reference) based on 1000 replicated samples.

9.0 Discussion and overall conclusions

This report presented results from the final two phases of a 4-phase study to investigate patients with asthma and/or COPD who switched treatment to ICS/LABA FDC delivered by DuoResp. These phases were historical cohort analyses utilising real-life databases, to compare patient health and economic outcomes following a switch to DuoResp.

The strength of the study is that it is based on real-life data that were obtained from high-quality databases containing information on patients as registered during regular care, and therefore of a non-selective patient population. The size and scope of these databases allowed for the collection of important clinical variables and a sufficient follow-up period for observing relevant outcomes. Notably, the study's time horizon of one year has minimized the impact of potential seasonal differences in disease activity.[63] As such, it was well-powered to investigate the primary outcome – risk domain control of disease.

The study found that, in terms of risk domain control, DuoResp was non-inferior to Turbohaler. In a sensitivity analysis, which included only DuoResp users that could be matched to three controls rather than one, two or three, DuoResp was found to be superior to Turbohaler in the combined disease groups: patients who switched to DuoResp had 40% higher odds of achieve risk domain control compared to patients who remained on Turbohaler. Since the effect size in the principal and sensitivity analyses were similar in the combined and the asthma group, the study results are robust for the use 3:1 matching approach.

DuoResp was found to be more effective than Turbohaler in several of the secondary outcomes including rate of exacerbations, treatment stability and SABA usage. In the main analyses these associations were only observed in the asthma group and not in the COPD group. However, in the sensitivity analyses, there was evidence of DuoResp users requiring less SABA use than Turbohaler users among the COPD group.

In terms of cost-effectiveness, DuoResp was found to be less costly and more effective, with an incremental difference of -£105, for respiratory-related healthcare costs per patient per year. Results were robust in sensitivity analyses.

The results observed here are consistent with previous evidence gained from randomised controlled trials (RCTs) where DuoResp was found to have similar effectiveness as Turbohaler.[38] The current study demonstrated superiority of DuoResp in secondary outcomes: the fact that this result has not been seen in the previous RCTs is perhaps a reflection of extra information gained from real-life studies in terms of everyday inhaler use. For example, adherence to treatment in real-life observational studies is usually much lower than in RCTs.[39] It is also likely that inhaler training received by patients differs between RCTs and a real-life setting. Given that in clinical trials inhaler

technique is often artificially high because of patient selection, extensive training and close monitoring, hardly any differences in outcomes between devices have been observed.[64] In daily practice however, patients' differential ability to correctly use their specific inhaler may result in profoundly larger differences in health and economic outcomes. A previous study suggested that higher peak inspiratory flow rates were achieved with the DuoResp compared with the Turbuhaler.[65]

This is the first study that provides an indication of DuoResp' cost-effectiveness compared with usual care. The cost-effectiveness results are consistent with other literature that suggests potential savings for DuoResp use.[66] Of note, assessment of cost-effectiveness using real-life data is in line with one of the key recommendations of a recent systematic review on cost-effectiveness analyses in COPD.[40]

10.0 Limitations

The datasets represent information collected for clinical and routine use rather than specifically for research purposes. Although extensive quality control and validity checks are conducted on the practice level, the validity and completeness of individual patient records can be limited. Hospital admissions, A&E attendances and Outpatient visits are not systematically recorded in GP databases. The applied definition to identify asthma-related hospital admissions or A&E events may give false positive events. However, theoretically this limitation would affect both treatment groups in a similar extent.

A limitation of all observational studies is the possibility of confounding of the results, arising from systematic differences between the patients being compared. In this study, confounding was minimised where possible using matching techniques, to create cohorts that were comparable in terms of important demographic and clinical characteristics. At the analysis stage, multivariate models were adjusted by those variables that remained relevantly confounding the associations of interest. However, in the COPD group, due to a limited number of patients, only a limited set of variables could be used for matching and model adjustment with the used approach. Therefore it is unsure whether confounding of the association of interest was sufficiently addressed in this group.

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14.0 Appendix

14.1 Matching process details

14.1.1 Associations and bias potential

In for the asthma disease group and Table 28 for the COPD disease group, the associations of all relevant baseline variables with both the exposure (DuoResp vs. Accuhaler/Turbohaler) and the primary outcome (achieving risk domain control) is presented, expressed as the significance level of the variable's coefficient in a prediction model.

The tables also provide the bias estimate, which tells how much the association between exposure and the outcome changed when adjusting for the variable. For instance, in the asthma group this means the coefficient for age will change by 4.2%.

The variables that showed highest bias potential in both disease groups were exacerbations, acute oral corticosteroids use and antibiotic courses, which are components of risk domain control. In the COPD disease group the average dose of SABA and ICS also had high bias potential.

Table 27. Asthma cohort – association with outcome and exposure, and bias potential

	Outcome		Exposure		Bias	
Variable	N	P	N	P	RCC	Rank
Age (years)	49,729	<0.0001	49,729	<0.0001	4.2	7
Gender	49,729	<0.0001	49,729	0.1376	1.6	12
BMI (kg/m^2)	47,941	<0.0001	47,941	0.9229	2.0	9
Smoking status	49,467	<0.0001	49,467	0.2632	2.0	10
Ischaemic heart disease	49,729	<0.0001	49,729	0.4597	0.4	17
Heart failure	49,729	<0.0001	49,729	0.2204	0.5	16
Diabetes	49,729	<0.0001	49,729	0.9555	0.0	18
Pneumonia (probable)	49,729	<0.0001	49,729	0.8767	0.0	19
GERD	49,729	<0.0001	49,729	0.1551	1.5	14
Rhinitis	49,729	<0.0001	49,729	0.1179	1.3	15
Charlson CI	49,729	<0.0001	49,729	0.0200	2.6	8
GINA control	38,956	<0.0001	38,956	0.0001	5.9	6
No. exacerbations	49,729	<0.0001	49,729	0.1241	9.3	4
No. acute resp. events	49,729	<0.0001	49,729	<0.0001	21.7	1
Risk domain control	49,729	<0.0001	49,729	0.0002	14.5	3
Drug therapy	49,727	<0.0001	49,727	0.0906	0.0	20
SABA daily dose	44,821	<0.0001	44,821	0.2692	1.6	13
ICS daily dose	49,729	<0.0001	49,729	0.0062	1.7	11
No. antibiotic courses	49,729	<0.0001	49,729	0.0001	19.5	2
Acute oral steroid Rx	49,729	<0.0001	49,729	0.0930	8.0	5

Through logistic regression; RCC = relative coefficient change (%) of exposure on outcome after introducing the covariate to the model. Rank: Ranking of the RCC. Outcome = risk domain control; Exposure = DuoResp vs. Accuhaler/Turbohaler. All variables categorised as in balance tables, except age.

Table 28. COPD cohort – association with outcome and exposure, and bias potential

	Outcome		Exposure		Bias	
Variable	N	P	N	P	RCC	Rank
Age (years)	39,430	0.0001	39,430	0.9793	0.0	20
Gender	39,430	<0.0001	39,430	0.4171	0.8	14
BMI (kg/m^2)	38,932	<0.0001	38,932	0.9930	3.5	10
Smoking status	39,321	<0.0001	39,321	0.5607	0.4	16
Asthma diagnosis	39,430	<0.0001	39,430	0.6711	0.2	18
Ischaemic heart disease	39,430	0.0005	39,430	0.2477	0.3	17
Heart failure	39,430	0.5566	39,430	0.0894	0.1	21
Diabetes	39,430	0.1651	39,430	0.4358	0.1	19
Pneumonia (probable)	39,430	<0.0001	39,430	0.5023	0.4	15
GERD	39,430	<0.0001	39,430	0.9344	0.0	21
Rhinitis	39,430	<0.0001	39,430	0.1477	0.9	13
Charlson CI	39,430	<0.0001	39,430	0.1553	1.3	12
GOLD Risk	38,285	<0.0001	38,285	0.0274	15.8	1
Total CAT Score	3,075	<0.0001	3,075	0.2853	6.1	7
mMRC score	38,285	<0.0001	38,285	0.0386	6.9	6
No. exacerbations	39,430	<0.0001	39,430	0.1829	7.7	5
Risk domain control	39,430	<0.0001	39,430	0.4577	3.3	11
Drug therapy	39,429	<0.0001	39,429	0.0171	5.1	8
SABA daily dose	34,720	<0.0001	34,720	0.0517	10.7	3
ICS daily dose	39,430	<0.0001	39,430	0.0000	9.4	4
No. antibiotic courses	39,430	<0.0001	39,430	0.0108	13.3	2
Acute oral steroid Rx	39,430	<0.0001	39,430	0.1383	4.8	9

Through logistic regression; RCC = relative coefficient change (%) of exposure on outcome after introducing the covariate to the model. Rank: Ranking of the RCC. Outcome = risk domain control; Exposure = DuoResp vs. Accuhaler/Turbohaler. All variables categorised as in balance tables, except age.

14.1.2 Matching decision

Based on the standardised differences of the baseline variables comparing DuoResp with the Accuhaler and Turbohaler cohorts, combined with the bias potential information in the previous section, the following lists of baseline characteristics were presented to the Steering Committee as a data-driven recommendation for variable selection for direct matching within each disease group (Table 29).

The “All candidates” listing consists of variables having at least a SDD >0.1 for the comparison of DuoResp arm with the Accuhaler arm or the Turbohaler arm, and a bias potential >2%. The “Most influential” listing excluded the variables in the “All candidates” listing that only had an SDD >0.1 in one of the comparisons.

Table 29. Proposed matching variables

Variables	All candidates		Most influential	
	Asthma	COPD	Asthma	COPD
Baseline FDC device	x	x	x	x
Demographics				
Age	x	x	x	x
Gender	x	x	x	x
Smoking status		x		
Comorbidities				
Ischaemic heart disease	x	x		
Heart failure	x	x		
Rhinitis		x		
Charlson CI	x	x		
Medication				
Drug therapy	x	x		x
SABA daily dose	x	x		
ICS average daily dose	x	x		x
No. antibiotic courses	x	x	x	x
No. acute oral corticosteroid courses	x	x	x	
Disease control				
GINA control*	x		x	
Exacerbations	x	x	x	x
Risk domain control	x		x	
Total CAT Score**		x		
GOLD Risk		x		x
mMRC score		x		

* 22% missing ** 92% missing

The steering committee agreed on the “Most influential” variable listing.

14.1.3 Matching process

The variables used for direct matching are show in Table 30.

Table 30. Variables used for direct matching, per disease cohort.

Variables	Asthma	COPD
Age	x	x
Gender	x	x
Drug therapy categories		x
ICS average daily dose categories		x
Number of antibiotic courses categories	x	x
Number of acute oral corticosteroid courses categories	x	
GINA control categories	x	
Exacerbations	x	x
Risk domain control	x	
GOLD Risk categories		x

Matching was repeated 20 times with a different patient sequence. In 5 out of the 20 repetitions, 384 patients had at least one matched control, while in 15 there were 385. One of these 15 repetitions

was chosen at random as the matched dataset to be used in the outcome analyses.

In Table 31 the detailed results of the matching are presented.

For the patients in the DuoResp arm there was a considerable higher percentage of matches with 3 controls (96%) in the asthma group than in the COPD group (75%). Only for 25 DuoResp switchers (6.1%) no control could be found, while for 342 switchers (83.4%) three controls were found.

Table 31. Number of matches found, 3:1 matching

Number of matched controls	Asthma		COPD		All	
	DuoResp	Turbohaler	DuoResp	Turbohaler	DuoResp	Turbohaler
0	9	0	16	0	25	0
1	6	6	15	15	21	21
2	4	8	18	36	22	44
3	243	729	99	297	342	1,026
Total matched	*253*	*743*	*132*	*348*	*385*	*1,091*

14.1.4 Matched baseline data

The matched baseline data are presented in Table 32 for the asthma group, in Table 33 for the COPD group and in Table 34 for the entire matched population. The descriptive statistics for all patients who switched to DuoResp with at least one matching control in the Turbohaler arm are presented.

The baseline variables for the asthma patient group were well balanced between treatment arms, except for BMI and ischaemic heart disease (Table 32). The baseline characteristics for the COPD group (Table 33) showed imbalance in smoking status, several comorbidities (Ischaemic heart disease, heart failure, diabetes, pneumonia), number of exacerbations and number of acute oral corticosteroid courses. In the combined matched sample (Table 34) the baseline characteristics were well balanced, except for BMI, ischaemic heart disease and heart failure. In Table 35 an overview of the characteristics that showed imbalance is given.

Table 32. Baseline balance statistics after 3:1 matching- Asthma.

Variable		DuoResp	Turbohaler	P-value	SDD
Age (years)*	N (% non-missing)	253 (100.0)	743 (100.0)	0.9101	0.007
	Mean (SD)	55.9 (15.3)	55.8 (15.1)		
	Median (IQR)	56.0 (21.0)	56.0 (21.0)		
Gender*	N (% non-missing)	253 (100.0)	743 (100.0)	0.9382	0.006
	Male, n (%)	112 (44.3)	331 (44.5)		
BMI (kg/m^2)	N (% non-missing)	239 (94.5)	726 (97.7)	0.4038	0.121
	<18.5, n (%)	3 (1.3)	9 (1.2)		
	18.5-<25, n (%)	65 (27.2)	163 (22.5)		
	25-<30, n (%)	88 (36.8)	265 (36.5)		
	>30, n (%)	83 (34.7)	289 (39.8)		
Smoking status	N (% non-missing)	248 (98.0)	740 (99.6)	0.7393	0.052
	Non-smoker, n (%)	126 (50.8)	397 (53.6)		
	Current smoker, n (%)	44 (17.7)	123 (16.6)		
	Ex-smoker, n (%)	78 (31.5)	220 (29.7)		
Ischaemic heart disease	N (% non-missing)	253 (100.0)	743 (100.0)	0.0951	0.128
	Yes, n (%)	13 (5.1)	62 (8.3)		
Heart failure	N (% non-missing)	253 (100.0)	743 (100.0)	0.3225	0.080
	Yes, n (%)	1 (0.4)	8 (1.1)		
Diabetes	N (% non-missing)	253 (100.0)	743 (100.0)	0.8782	0.011
	Yes, n (%)	20 (7.9)	61 (8.2)		
Pneumonia, probable	N (% non-missing)	253 (100.0)	743 (100.0)	0.7519	0.022
	Yes, n (%)	1 (0.4)	2 (0.3)		
GERD	N (% non-missing)	253 (100.0)	743 (100.0)	0.1648	0.098
	Yes, n (%)	40 (15.8)	92 (12.4)		
Rhinitis	N (% non-missing)	253 (100.0)	743 (100.0)	0.5032	0.048
	Yes, n (%)	61 (24.1)	164 (22.1)		
CCI score	N (% non-missing)	253 (100.0)	743 (100.0)	0.5600	0.064
	0, n (%)	74 (29.2)	230 (31.0)		
	1-4, n (%)	154 (60.9)	455 (61.2)		
	≥5, n (%)	25 (9.9)	58 (7.8)		

Variable		DuoResp	Turbohaler	P-value	SDD
GINA control*	N (% non-missing)	226 (89.3)	664 (89.4)	0.9787	0.013
	Controlled, n (%)	63 (27.9)	187 (28.2)		
	Partly controlled, n (%)	144 (63.7)	424 (63.9)		
	Uncontrolled, n (%)	19 (8.4)	53 (8.0)		
Acute respiratory events	N (% non-missing)	253 (100.0)	743 (100.0)	0.9013	0.055
	0, n (%)	183 (72.3)	549 (73.9)		
	1, n (%)	49 (19.4)	143 (19.2)		
	2, n (%)	14 (5.5)	37 (5.0)		
	3, n (%)	6 (2.4)	11 (1.5)		
	4+, n (%)	1 (0.4)	3 (0.4)		
Exacerbations*	N (% non-missing)	253 (100.0)	743 (100.0)	0.9869	0.036
	0, n (%)	199 (78.7)	593 (79.8)		
	1, n (%)	42 (16.6)	120 (16.2)		
	2, n (%)	7 (2.8)	18 (2.4)		
	3, n (%)	4 (1.6)	9 (1.2)		
	4+, n (%)	1 (0.4)	3 (0.4)		
Number of inpatient respiratory hospital admissions	N (% non-missing)	253 (100.0)	743 (100.0)	1.0000	0.000
	0, n (%)	253 (100.0)	743 (100.0)		
	1, n (%)	0 (0.0)	0 (0.0)		
	≥2, n (%)	0 (0.0)	0 (0.0)		
Risk domain control*	N (% non-missing)	253 (100.0)	743 (100.0)	0.6278	0.035
	Uncontrolled, n (%)	70 (27.7)	194 (26.1)		
Drug therapy	N (% non-missing)	253 (100.0)	743 (100.0)	0.0230	0.066
	ICS+LABA, n (%)	218 (86.2)	640 (86.1)		
	ICS+LABA+LAMA, n (%)	10 (4.0)	10 (1.3)		
	ICS+LABA+LAMA+LTRA, n (%)	4 (1.6)	6 (0.8)		
	ICS+LABA+LTRA, n (%)	21 (8.3)	87 (11.7)		
	Other, n (%)	0 (0.0)	0 (0.0)		
SABA avg daily dose (µg per day)	N (% non-missing)	253 (100.0)	743 (100.0)	0.4055	0.049
	0, n (%)	64 (25.3)	224 (30.1)		
	>0 - ≤200, n (%)	70 (27.7)	196 (26.4)		
	>200 - ≤400, n (%)	56 (22.1)	139 (18.7)		
	>400 - ≤600, n (%)	25 (9.9)	59 (7.9)		
	>600, n (%)	38 (15.0)	125 (16.8)		

Variable		DuoResp	Turbohaler	P-value	SDD
ICS avg daily dose (µg per day)	N (% non-missing)	253 (100.0)	743 (100.0)	0.6285	0.087
	≤400, n (%)	112 (44.3)	300 (40.4)		
	>400 - ≤800, n (%)	99 (39.1)	305 (41.0)		
	>800 - ≤1600, n (%)	39 (15.4)	123 (16.6)		
	>1600, n (%)	3 (1.2)	15 (2.0)		
Number of antibiotic courses*	N (% non-missing)	253 (100.0)	743 (100.0)	0.8362	0.055
	0, n (%)	212 (83.8)	630 (84.8)		
	1, n (%)	34 (13.4)	99 (13.3)		
	2, n (%)	5 (2.0)	12 (1.6)		
	3, n (%)	1 (0.4)	1 (0.1)		
	≥4, n (%)	1 (0.4)	1 (0.1)		
Number of acute oral corticosteroid courses*	N (% non-missing)	253 (100.0)	743 (100.0)	0.9869	0.036
	0, n (%)	199 (78.7)	593 (79.8)		
	1, n (%)	42 (16.6)	120 (16.2)		
	2, n (%)	7 (2.8)	18 (2.4)		
	3, n (%)	4 (1.6)	9 (1.2)		
	≥4, n (%)	1 (0.4)	3 (0.4)		

* Matching variable; P-value = p-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference for DuoResp vs. Turbohaler; Values in red are indicative of imbalance (>0.1)

Table 33. Baseline balance statistics after 3:1 matching- COPD

Variable		DuoResp	Turbohaler	P-value	SDD
Age (years)*	N (% non-missing)	132 (100.0)	348 (100.0)	0.9512	0.002
	Mean (SD)	70.5 (8.8)	70.5 (8.5)		
	Median (IQR)	70.0 (14.0)	70.0 (13.5)		
Gender*	N (% non-missing)	132 (100.0)	348 (100.0)	0.5736	0.057
	Male, n (%)	66 (50.0)	184 (52.9)		
BMI (kg/m^2)	N (% non-missing)	129 (97.7)	346 (99.4)	0.6977	0.074
	<18.5, n (%)	6 (4.7)	11 (3.2)		
	18.5-<25, n (%)	46 (35.7)	112 (32.4)		
	25-<30, n (%)	39 (30.2)	120 (34.7)		
	>30, n (%)	38 (29.5)	103 (29.8)		
Smoking status	N (% non-missing)	132 (100.0)	346 (99.4)	0.5696	0.108
	Non-smoker, n (%)	14 (10.6)	48 (13.9)		
	Current smoker, n (%)	36 (27.3)	98 (28.3)		
	Ex-smoker, n (%)	82 (62.1)	200 (57.8)		
Asthma diagnosis	N (% non-missing)	132 (100.0)	348 (100.0)	0.5459	0.062
	Yes, n (%)	48 (36.4)	137 (39.4)		
Ischaemic heart disease	N (% non-missing)	132 (100.0)	348 (100.0)	0.1662	0.145
	Yes, n (%)	22 (16.7)	78 (22.4)		
Heart failure	N (% non-missing)	132 (100.0)	348 (100.0)	0.1286	0.167
	Yes, n (%)	4 (3.0)	23 (6.6)		
Diabetes	N (% non-missing)	132 (100.0)	348 (100.0)	0.0223	0.250
	Yes, n (%)	10 (7.6)	54 (15.5)		
Pneumonia, probable	N (% non-missing)	132 (100.0)	348 (100.0)	0.2663	0.126
	Yes, n (%)	1 (0.8)	8 (2.3)		
GERD	N (% non-missing)	132 (100.0)	348 (100.0)	0.7368	0.034
	Yes, n (%)	19 (14.4)	46 (13.2)		
Rhinitis	N (% non-missing)	132 (100.0)	348 (100.0)	0.6392	0.047
	Yes, n (%)	14 (10.6)	32 (9.2)		

Variable		DuoResp	Turbohaler	P-value	SDD
CCI score	N (% non-missing)	132 (100.0)	348 (100.0)	0.0962	0.227
	0, n (%)	94 (71.2)	217 (62.4)		
	1-4, n (%)	28 (21.2)	82 (23.6)		
	≥5, n (%)	10 (7.6)	49 (14.1)		
GOLD Risk*	N (% non-missing)	130 (98.5)	344 (98.9)	0.6894	0.095
	A, n (%)	46 (35.4)	134 (39.0)		
	B, n (%)	22 (16.9)	66 (19.2)		
	C, n (%)	25 (19.2)	54 (15.7)		
	D, n (%)	37 (28.5)	90 (26.2)		
mMRC score	N (% non-missing)	130 (98.5)	344 (98.9)	0.9944	0.001
	≥2, n (%)	59 (45.4)	156 (45.3)		
Drug therapy*	N (% non-missing)	132 (100.0)	348 (100.0)	0.7690	0.035
	ICS+LABA, n (%)	34 (25.8)	92 (26.4)		
	ICS+LABA+LAMA, n (%)	97 (73.5)	255 (73.3)		
	ICS+LABA+LAMA+LTRA, n (%)	0 (0.0)	0 (0.0)		
	ICS+LABA+LTRA, n (%)	1 (0.8)	1 (0.3)		
Number of exacerbations*	N (% non-missing)	132 (100.0)	348 (100.0)	0.7809	0.129
	0, n (%)	54 (40.9)	156 (44.8)		
	1, n (%)	38 (28.8)	106 (30.5)		
	2, n (%)	15 (11.4)	35 (10.1)		
	3, n (%)	13 (9.8)	28 (8.0)		
	≥4, n (%)	12 (9.1)	23 (6.6)		
Number of inpatient resp. hospital admissions	N (% non-missing)	132 (100.0)	348 (100.0)	0.1460	0.028
	0, n (%)	129 (97.7)	338 (97.1)		
	1, n (%)	1 (0.8)	9 (2.6)		
	≥2, n (%)	2 (1.5)	≥2, n (%)		
Risk domain control	N (% non-missing)	132 (100.0)	348 (100.0)	0.4397	0.079
	Uncontrolled, n (%)	78 (59.1)	192 (55.2)		
SABA avg daily dose (µg per day)	N (% non-missing)	132 (100.0)	348 (100.0)	0.3524	0.084
	0, n (%)	23 (17.4)	65 (18.7)		
	>0 - ≤200, n (%)	22 (16.7)	66 (19.0)		
	>200 - ≤400, n (%)	32 (24.2)	78 (22.4)		
	>400 - ≤600, n (%)	5 (3.8)	29 (8.3)		
	>600, n (%)	50 (37.9)	110 (31.6)		

Variable		DuoResp	Turbohaler	P-value	SDD
ICS avg daily dose (µg per day)*	N (% non-missing)	132 (100.0)	348 (100.0)	0.8992	0.006
	≤400, n (%)	27 (20.5)	65 (18.7)		
	>400 - ≤800, n (%)	72 (54.5)	203 (58.3)		
	>800 - ≤1600, n (%)	32 (24.2)	78 (22.4)		
	>1600, n (%)	1 (0.8)	2 (0.6)		
Number of antibiotic courses*	N (% non-missing)	132 (100.0)	348 (100.0)	0.9478	0.064
	0, n (%)	74 (56.1)	198 (56.9)		
	1, n (%)	37 (28.0)	104 (29.9)		
	2, n (%)	11 (8.3)	26 (7.5)		
	3, n (%)	4 (3.0)	8 (2.3)		
	≥4, n (%)	6 (4.5)	12 (3.4)		
Number of acute oral corticosteroid courses	N (% non-missing)	132 (100.0)	348 (100.0)	0.6813	0.144
	0, n (%)	79 (59.8)	225 (64.7)		
	1, n (%)	28 (21.2)	74 (21.3)		
	2, n (%)	9 (6.8)	20 (5.7)		
	3, n (%)	7 (5.3)	15 (4.3)		
	≥4, n (%)	9 (6.8)	14 (4.0)		

* Matching variable; P-value = p-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference for DuoResp vs. Turbohaler; Values in red are indicative of imbalance (>0.1)

Table 34. Baseline balance statistics after 3:1 matching- Combined

Variable		DuoResp	Turbohaler	P-value	SDD
Age (years)	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.6265	0.028
	Mean (SD)	60.9 (15.1)	60.5 (15.0)		
	Median (IQR)	63.0 (21.0)	63.0 (22.0)		
Gender	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.7428	0.019
	Male, n (%)	178 (46.2)	515 (47.2)		
BMI (kg/m^2)	N (% non-missing)	368 (95.6)	1,072 (98.3)	0.2917	0.111
	<18.5, n (%)	9 (2.4)	20 (1.9)		
	18.5-<25, n (%)	111 (30.2)	275 (25.7)		
	25-<30, n (%)	127 (34.5)	385 (35.9)		
	>30, n (%)	121 (32.9)	392 (36.6)		
Smoking status	N (% non-missing)	380 (98.7)	1,086 (99.5)	0.3480	0.085
	Non-smoker, n (%)	140 (36.8)	445 (41.0)		
	Current smoker, n (%)	80 (21.1)	221 (20.3)		
	Ex-smoker, n (%)	160 (42.1)	420 (38.7)		
Ischaemic heart disease	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.0509	0.120
	Yes, n (%)	35 (9.1)	140 (12.8)		
Heart failure	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.0916	0.108
	Yes, n (%)	5 (1.3)	31 (2.8)		
Diabetes	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.1193	0.095
	Yes, n (%)	30 (7.8)	115 (10.5)		
Pneumonia, probable	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.4557	0.047
	Yes, n (%)	2 (0.5)	10 (0.9)		
GERD	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.1844	0.077
	Yes, n (%)	59 (15.3)	138 (12.6)		
Rhinitis	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.5091	0.039
	Yes, n (%)	75 (19.5)	196 (18.0)		

Variable		DuoResp	Turbohaler	P-value	SDD
CCI score	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.6510	0.053
	0, n (%)	168 (43.6)	447 (41.0)		
	1-4, n (%)	182 (47.3)	537 (49.2)		
	≥5, n (%)	35 (9.1)	107 (9.8)		
Number of exacerbations	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.6176	0.091
	0, n (%)	253 (65.7)	749 (68.7)		
	1, n (%)	80 (20.8)	226 (20.7)		
	2, n (%)	22 (5.7)	53 (4.9)		
	3, n (%)	17 (4.4)	37 (3.4)		
	≥4, n (%)	13 (3.4)	26 (2.4)		
Number of inpatient resp. hospital admissions	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.1419	0.022
	0, n (%)	382 (99.2)	1,081 (99.1)		
	1, n (%)	1 (0.3)	9 (0.8)		
	≥2, n (%)	2 (0.5)	1 (0.1)		
Risk domain control	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.2825	0.063
	Uncontrolled, n (%)	148 (38.4)	386 (35.4)		
Drug therapy	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.2022	0.031
	ICS+LABA, n (%)	252 (65.5)	732 (67.1)		
	ICS+LABA+LAMA, n (%)	107 (27.8)	265 (24.3)		
	ICS+LABA+LAMA+LTRA, n (%)	4 (1.0)	6 (0.5)		
	ICS+LABA+LTRA, n (%)	22 (5.7)	88 (8.1)		
	Other, n (%)	0 (0.0)	0 (0.0)		
SABA avg daily dose (µg per day)	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.5316	0.070
	0, n (%)	87 (22.6)	289 (26.5)		
	>0 - ≤200, n (%)	92 (23.9)	262 (24.0)		
	>200 - ≤400, n (%)	88 (22.9)	217 (19.9)		
	>400 - ≤600, n (%)	30 (7.8)	88 (8.1)		
	>600, n (%)	88 (22.9)	235 (21.5)		

Variable		DuoResp	Turbohaler	P-value	SDD
ICS avg daily dose (µg per day)	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.7034	0.049
	≤400, n (%)	139 (36.1)	365 (33.5)		
	>400 - ≤800, n (%)	171 (44.4)	508 (46.6)		
	>800 - ≤1600, n (%)	71 (18.4)	201 (18.4)		
	>1600, n (%)	4 (1.0)	17 (1.6)		
Number of antibiotic courses	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.7446	0.069
	0, n (%)	286 (74.3)	828 (75.9)		
	1, n (%)	71 (18.4)	203 (18.6)		
	2, n (%)	16 (4.2)	38 (3.5)		
	3, n (%)	5 (1.3)	9 (0.8)		
	≥4, n (%)	7 (1.8)	13 (1.2)		
Number of acute oral corticosteroid courses	N (% non-missing)	385 (100.0)	1,091 (100.0)	0.5798	0.093
	0, n (%)	278 (72.2)	818 (75.0)		
	1, n (%)	70 (18.2)	194 (17.8)		
	2, n (%)	16 (4.2)	38 (3.5)		
	3, n (%)	11 (2.9)	24 (2.2)		
	≥4, n (%)	10 (2.6)	17 (1.6)		

P-value = p-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference for DuoResp vs. Turbohaler; Values in red are indicative of imbalance (>0.1)

Table 35. Overview of imbalanced baseline characteristics in the matched sample, per disease group

	Cohort		
Variable	Asthma	COPD	Combined
BMI	x		x
Smoking status		x	
Ischaemic heart disease	x	x	x
Heart failure		x	x
Diabetes		x	
Pneumonia, probable		x	
CCI score		x	
Number of exacerbations / acute resp. events		x	
Number of acute oral corticosteroid courses		x	

"X" indicates variable with imbalance between treatment arms

14.1.5 Bias potential in matched sample

The bias potential, the extent to which the estimate of an exposure effect changes when conditioning on a variable, for the association between switching to DuoResp or remaining on Turbohaler and risk domain control (the primary outcome) largely agreed with the findings of imbalance in the baseline variables. Of the three variables found unbalanced in the combined asthma/COPD cohorts (used for the primary outcome), both BMI and the diagnosis of Ischaemic heart disease had a sufficiently large bias potential (≥2%) to be considered relevant.

Since patients have been matched on variables of relevance for the association between DuoResp vs. Turbohaler and the primary outcome (risk domain control), it can be expected that for the secondary outcomes there are different variables confounding the association of interest.

Table 36 shows the bias potentials for the seven secondary outcomes. Since these outcomes were assessed stratified by disease group, the data are presented for the asthma and COPD groups separately.

The pneumonia diagnosis secondary outcomes resulted in instable regression models, probably due to the low number of patients presenting a diagnosis of pneumonia during the outcome year in the matched sample (7 for definite and 15 for probable diagnosis). Also, the models for the number of inpatient hospital admission did not converge and are not presented.

Table 36. Bias potential of baseline variables in matched cohort for the primary and secondary outcomes.

	RDC	# Exacerbations		Treatment stability		SABA avg daily dose		# SABA inhalers		Pneumonia		Pneumonia, definite	
Baseline variable	All	Asthma	COPD	Asthma	COPD	Asthma	COPD	Asthma	COPD	Asthma	COPD	Asthma	COPD
Age (years)	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.0	0.0	0.0	0.0	0.0	0.0
Gender	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0
BMI (kg/m2)	2.3	1.2	1.5	1.8	4.3	3.3	4.2	0.8	0.7	-	24.5	-	33.1
Smoking status	1.9	1.5	0.0	4.5	0.4	4.3	0.5	2.1	1.4	-	23.2	-	26.4
Asthma	0.0		0.4		0.4		0.8		0.0		46.3		118.4
Ischaemic HD	2.0	0.2	0.3	4.4	0.8	0.9	0.7	0.1	0.3	-	1.5	0.0	1.4
Heart failure	0.6	0.1	0.3	0.6	0.2	0.1	1.2	0.2	0.5	0.0	11.2	0.0	0.0
Diabetes	0.1	1.2	1.3	0.2	0.1	0.2	5.3	0.0	2.1	-	9.4	-	35.7
Pneumonia	0.0	0.0	0.2	0.5	2.7	0.1	0.2	0.2	0.1	0.0	22.5	0.0	47.5
GERD	1.0	2.3	0.0	1.1	0.2	1.4	0.0	0.0	0.4	-	36.6	-	100.0
Rhinitis	0.0	0.8	0.2	0.0	2.1	0.2	0.2	0.3	0.0	0.0	4.7	0.0	43.7
CCI score	0.1	0.0	1.0	1.4	0.7	0.2	4.0	0.7	3.3	-	3.6	-	43.0
GINA control	0.0	1.3		5.0		8.3		4.3		0.0		0.0	
GOLD risk	0.0		0.0		0.0		3.6		0.2		23.0		25.8
mMRC score	0.0		0.0		0.0		1.0		0.2		23.0		25.8
No. exacerbations	1.1	0.0	0.0	0.0	3.0	0.6	2.3	0.0	0.0	0.0	5.3	0.0	47.5
Risk domain control	0.0	0.0	0.3	0.0	0.0	0.4	0.9	0.0	0.0	0.0	0.0	0.0	0.0
Drug therapy	0.8	1.3	0.0	1.3	0.0	2.9	0.7	5.6	0.0	-	0.0	-	0.0
SABA avg daily dose	1.2	2.5	0.6	0.7	4.9	23.6	29.5	1.6	9.9	-	19.4	-	70.6
ICS avg daily dose	0.8	0.4	0.0	1.2	0.0	6.5	0.9	2.7	0.0	0.0	0.0	-	0.0
Antibiotic courses	0.0	0.0	0.0	0.0	0.0	0.3	0.6	0.0	0.0	0.0	0.0	0.0	0.0
Acute oral CS courses	0.8	0.0	0.6	0.0	1.9	0.3	2.5	0.0	0.7	0.0	14.8	0.0	39.1
# Relevant variables	2	1	0	3	5	5	7	4	3	0	15	0	14

RDC = Risk Domain Control; Red: relevant RCC (≥ 0.02); Models for number of inpatient hospital admission did not converge.

To minimise the number of covariates to adjust on in the outcome analyses, a forward assessment of bias potential was used. The variables were entered one-by-one, and the relative change in the effect size of exposure was assessed against the effect size before introducing the variable. If this RCC was ≥0.02 the variables remained in the model.

The resulting set of variables to adjust on in the final models, following a forward-selection procedure, is presented in Table 37. As the models for pneumonia and number of respiratory hospitalisations did not converge, no confounders were selected for adjustment.

Table 37. Variables selected for adjustment in the matched outcome analyses

		Exacerbations		Treatment stability		SABA avg dose		SABA inhalers	
Baseline variable	RDC	A	C	A	C	A	C	A	C
BMI (kg/m2)	x				x	x	x		
Smoking status				x				x	
Ischaemic heart disease	x			x					
Diabetes							x		x
Pneumonia					x				
GERD		x							
Rhinitis					x				
CCI score									
GINA control						x			
Drug therapy								x	
SABA avg daily dose		x			x	x	x	x	x
Acute oral corticosteroids					x				

RDC=Risk Domain Control; A = Asthma; C=COPD

14.1.6 Matching for cost-effectiveness outcome

Since the effect of DuoResp vs. Turbohaler on cost outcomes can be expected to be confounded by different factors than with clinical outcomes, a different set of baseline characteristics was chosen to match on. For this no formal evaluation of bias potential was used. The selection was based on known factors that drive healthcare costs in asthma and COPD. These were:

- Age
- Gender
- ICS average daily dose
- Number of antibiotics prescriptions
- SABA average daily dose
- LAMA number of inhalers
- SAMA number of inhalers

For only 13 patients no matching control patient could be found, while for 380 (93%) patients, three controls were matched (Table 38).

Table 38. Number of matches found, 3:1 matching attempt, cost-effectiveness analysis

Number of matched controls	DuoResp	Turbohaler	Total
0	13	0	13
1	9	9	18
2	8	16	24
3	380	1,140	1,520
Total	*410*	*1,165*	*1,575*

Baseline characteristics of the matched cohorts showed good balance between most cost (Table 39) and clinical characteristics (Table 40) of the patients, confirming the correctness of the used matching variables.

For the health-related costs only ICS was relevantly different between the DuoResp and Turbohaler arms. Rhinitis was the only clinical aspect that was relevantly different between the cohorts. Therefore, the cost outcome models were adjusted for baseline costs, and the clinical outcome model was adjusted for rhinitis diagnosis.

Table 39. Matched baseline overview of costs. Values are 2014 £.

Variable		Turbohaler	DuoResp	P-value	SDD
ICS	N (% non-missing)	1,165 (100)	397 (100)	0.0195	0.136
	Mean (SD)	362 (167)	340 (166)		
	Median (IQR)	342 (228)	330 (266)		
SABA	N (% non-missing)	1,165 (100)	397 (100)	0.2003	0.106
	Mean (SD)	19 (30)	16 (26)		
	Median (IQR)	9 (20)	8 (17)		
LABA	N (% non-missing)	1,165 (100)	397 (100)	0.0282	0.141
	Mean (SD)	1 (12)	0 (0)		
	Median (IQR)	0 (0)	0 (0)		
SAMA	N (% non-missing)	1,165 (100)	397 (100)	0.8889	0.025
	Mean (SD)	2 (26)	2 (12)		
	Median (IQR)	0 (0)	0 (0)		
LAMA	N (% non-missing)	1,164 (100)	396 (100)	0.5639	0.055
	Mean (SD)	202 (429)	225 (418)		
	Median (IQR)	0 (205)	0 (319)		
LTRA	N (% non-missing)	1,165 (100)	397 (100)	0.2544	0.021
	Mean (SD)	2 (11)	2 (14)		
	Median (IQR)	0 (0)	0 (0)		
THEO	N (% non-missing)	1,165 (100)	397 (100)	0.1723	0.146
	Mean (SD)	2 (9)	1 (4)		
	Median (IQR)	0 (0)	0 (0)		
Antibiotic	N (% non-missing)	1,165 (100)	397 (100)	0.4434	0.005
	Mean (SD)	1 (2)	1 (2)		
	Median (IQR)	0 (0)	0 (0)		
Oral steroids	N (% non-missing)	1,165 (100)	397 (100)	0.3604	0.019
	Mean (SD)	3 (11)	3 (10)		
	Median (IQR)	0 (2)	0 (1)		
All medication	N (% non-missing)	1,164 (100)	396 (100)	0.1524	0.012
	Mean (SD)	594 (521)	588 (509)		
	Median (IQR)	418 (494)	392 (518)		
All medication, excluding ICS	N (% non-missing)	1,164 (100)	396 (100)	0.4046	0.040
	Mean (SD)	232 (442)	249 (427)		
	Median (IQR)	20 (270)	16 (326)		

Variable		Turbohaler	DuoResp	P-value	SDD
Respiratory consultations	N (% non-missing)	1,165 (100)	397 (100)	0.0630	0.182
	Mean (SD)	22 (55)	15 (24)		
	Median (IQR)	14 (29)	14 (14)		
Hospitalisations	N (% non-missing)	1,165 (100)	397 (100)	0.2655	0.049
	Mean (SD)	19 (99)	25 (116)		
	Median (IQR)	0 (0)	0 (0)		
Asthma inpatient consultations	N (% non-missing)	1,165 (100)	397 (100)	0.5798	0.004
	Mean (SD)	9 (74)	9 (92)		
	Median (IQR)	0 (0)	0 (0)		
Asthma outpatient consultations	N (% non-missing)	1,165 (100)	397 (100)	0.1517	0.074
	Mean (SD)	11 (62)	16 (73)		
	Median (IQR)	0 (0)	0 (0)		
Asthma A&E	N (% non-missing)	1,165 (100)	397 (100)	0.3343	0.073
	Mean (SD)	2 (24)	1 (13)		
	Median (IQR)	0 (0)	0 (0)		
Total respiratory-related costs excluding ICS	N (% non-missing)	1,164 (100)	396 (100)	0.2623	0.029
	Mean (SD)	276 (471)	289 (448)		
	Median (IQR)	53 (368)	44 (444)		
Total respiratory-related costs including ICS	N (% non-missing)	1,164 (100)	396 (100)	0.1446	0.018
	Mean (SD)	638 (552)	628 (530)		
	Median (IQR)	447 (523)	416 (581)		

P-value = p-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference for DuoResp vs. Turbohaler; Values in red are indicative of imbalance (>0.1)

Table 40. Matched baseline overview of clinical aspects – CE analysis

Variable		Turbohaler	DuoResp	P-value	SDD
Age (years)	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.8716	0.010
	Mean (SD)	61.0 (15.2)	61.1 (15.1)		
	Median (IQR)	63.0 (21.0)	63.0 (21.0)		
Gender	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.9822	0.001
	Male, n (%)	548 (47.0)	187 (47.1)		
BMI (kg/m^2)	N (% non-missing)	1,143 (98.1)	381 (96.0)	0.7342	0.064
	<18.5, n (%)	22 (1.9)	11 (2.9)		
	18.5-<25, n (%)	325 (28.4)	109 (28.6)		
	25-<30, n (%)	409 (35.8)	134 (35.2)		
	>30, n (%)	387 (33.9)	127 (33.3)		
Smoking status	N (% non-missing)	1,157 (99.3)	392 (98.7)	0.3825	0.081
	Non-smoker, n (%)	451 (39.0)	144 (36.7)		
	Current smoker, n (%)	250 (21.6)	78 (19.9)		
	Ex-smoker, n (%)	456 (39.4)	170 (43.4)		
Ischaemic heart disease	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.4950	0.040
	Yes, n (%)	138 (11.8)	42 (10.6)		
Heart failure	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.2555	0.070
	Yes, n (%)	29 (2.5)	6 (1.5)		
Diabetes diagnosis	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.3965	0.050
	Yes, n (%)	123 (10.6)	36 (9.1)		
Pneumonia	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.8871	0.008
	1, n (%)	8 (0.7)	3 (0.8)		
GERD	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.1180	0.089
	Yes, n (%)	138 (11.8)	59 (14.9)		
Rhinitis	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.0026	0.169
	Yes, n (%)	156 (13.4)	78 (19.6)		
Charlson CI	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.4255	0.076
	0, n (%)	531 (45.6)	166 (41.8)		
	1-4, n (%)	526 (45.2)	191 (48.1)		
	≥5, n (%)	108 (9.3)	40 (10.1)		

Variable		Turbohaler	DuoResp	P-value	SDD
Exacerbations	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.6233	0.097
	0, n (%)	679 (58.3)	237 (59.7)		
	1, n (%)	265 (22.7)	96 (24.2)		
	2, n (%)	103 (8.8)	29 (7.3)		
	3, n (%)	70 (6.0)	24 (6.0)		
	4+, n (%)	48 (4.1)	11 (2.8)		
Number of inpatient hospitalisations	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.1126	0.113
	0, n (%)	1,149 (98.6)	393 (99.0)		
	1, n (%)	15 (1.3)	2 (0.5)		
	≥2, n (%)	1 (0.1)	2 (0.5)		
Risk domain control	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.6211	0.029
	UNCONTROLLED, n (%)	486 (41.7)	160 (40.3)		
Drug therapy	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.6822	0.073
	ICS + LABA +/- SAMA +/- SABA, n (%)	752 (64.5)	258 (65.0)		
	ICS + LABA + LAMA +/- SAMA +/- SABA, n (%)	294 (25.2)	106 (26.7)		
	ICS + LABA + LAMA + LTRA +/- SAMA +/- SABA, n (%)	25 (2.1)	8 (2.0)		
	ICS + LABA + LTRA +/- SAMA +/- SABA, n (%)	94 (8.1)	25 (6.3)		
SABA avg daily dose	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.9998	0.012
	0, n (%)	255 (21.9)	86 (21.7)		
	>0 - ≤200, n (%)	276 (23.7)	93 (23.4)		
	>200 - ≤400, n (%)	272 (23.3)	93 (23.4)		
	>400 - ≤600, n (%)	100 (8.6)	34 (8.6)		
	>600, n (%)	262 (22.5)	91 (22.9)		
ICS avg daily dose	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.9981	0.011
	≤400, n (%)	420 (36.1)	142 (35.8)		
	>400 - ≤800, n (%)	517 (44.4)	176 (44.3)		
	>800 - ≤1600, n (%)	220 (18.9)	76 (19.1)		
	>1600, n (%)	8 (0.7)	3 (0.8)		
Antibiotic courses	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.9943	0.027
	0, n (%)	856 (73.5)	290 (73.0)		
	1, n (%)	229 (19.7)	77 (19.4)		
	2, n (%)	48 (4.1)	18 (4.5)		
	3, n (%)	19 (1.6)	7 (1.8)		
	4+, n (%)	13 (1.1)	5 (1.3)		

Variable		Turbohaler	DuoResp	P-value	SDD
Acute OCS prescriptions	N (% non-missing)	1,165 (100.0)	397 (100.0)	0.6716	0.092
	0, n (%)	808 (69.4)	285 (71.8)		
	1, n (%)	200 (17.2)	70 (17.6)		
	2, n (%)	74 (6.4)	21 (5.3)		
	3, n (%)	50 (4.3)	13 (3.3)		
	4+, n (%)	33 (2.8)	8 (2.0)		

P-value = p-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate; SDD = Standardised difference for DuoResp vs. Turbohaler; CE=cost-effectiveness. Values in red are indicative of imbalance (>0.1)

14.2 Phase 3 outcome listings – asthma

Variable	Category	Baseline	Follow-up	P
Actue OCS prescriptions	N (% non-missing)	262 (100.0)	262 (100.0)	0.5871
	0, n (%)	202 (77.1)	207 (79.0)	
	1, n (%)	42 (16.0)	37 (14.1)	
	2, n (%)	11 (4.2)	8 (3.1)	
	3, n (%)	5 (1.9)	6 (2.3)	
	4, n (%)	1 (0.4)	4 (1.5)	
	7, n (%)	1 (0.4)	0 (0.0)	
Acute OCS courses	N (% non-missing)	262 (100.0)	262 (100.0)	0.7524
	0, n (%)	202 (77.1)	207 (79.0)	
	1, n (%)	43 (16.4)	38 (14.5)	
	2, n (%)	12 (4.6)	9 (3.4)	
	3, n (%)	4 (1.5)	5 (1.9)	
	4, n (%)	1 (0.4)	3 (1.1)	
Antibiotic courses, resp.	N (% non-missing)	262 (100.0)	262 (100.0)	0.6575
	0, n (%)	214 (81.7)	213 (81.3)	
	1, n (%)	35 (13.4)	39 (14.9)	
	2, n (%)	9 (3.4)	4 (1.5)	
	3, n (%)	3 (1.1)	3 (1.1)	
	4, n (%)	1 (0.4)	1 (0.4)	
	5, n (%)	0 (0.0)	1 (0.4)	
	6, n (%)	0 (0.0)	1 (0.4)	
SABA prescriptions	N (% non-missing)	262 (100.0)	262 (100.0)	0.2667
	0, n (%)	65 (24.8)	75 (28.6)	
	1, n (%)	27 (10.3)	22 (8.4)	
	2, n (%)	28 (10.7)	30 (11.5)	
	3, n (%)	18 (6.9)	16 (6.1)	
	4, n (%)	12 (4.6)	15 (5.7)	
	5, n (%)	19 (7.3)	18 (6.9)	
	6, n (%)	12 (4.6)	13 (5.0)	
	7, n (%)	13 (5.0)	10 (3.8)	
	8, n (%)	11 (4.2)	11 (4.2)	
	9, n (%)	7 (2.7)	5 (1.9)	
	10, n (%)	8 (3.1)	5 (1.9)	
	11, n (%)	5 (1.9)	2 (0.8)	
	12, n (%)	3 (1.1)	4 (1.5)	
	13, n (%)	17 (6.5)	6 (2.3)	
	14, n (%)	3 (1.1)	10 (3.8)	
	15, n (%)	1 (0.4)	5 (1.9)	
	16, n (%)	5 (1.9)	2 (0.8)	
	17, n (%)	0 (0.0)	1 (0.4)	
	18, n (%)	1 (0.4)	0 (0.0)	
	19, n (%)	1 (0.4)	4 (1.5)	
	20, n (%)	2 (0.8)	0 (0.0)	
	21, n (%)	0 (0.0)	1 (0.4)	
	22, n (%)	0 (0.0)	2 (0.8)	
	25, n (%)	0 (0.0)	1 (0.4)	
	26, n (%)	1 (0.4)	0 (0.0)	
	27, n (%)	1 (0.4)	0 (0.0)	

Variable	Category	Baseline	Follow-up	P
	29, n (%)	0 (0.0)	1 (0.4)	
	32, n (%)	0 (0.0)	1 (0.4)	
	35, n (%)	0 (0.0)	1 (0.4)	
	36, n (%)	1 (0.4)	0 (0.0)	
	40, n (%)	1 (0.4)	0 (0.0)	
	52, n (%)	0 (0.0)	1 (0.4)	
Inpatient hospital admissions	N (% non-missing)	262 (100.0)	262 (100.0)	0.1565
	0, n (%)	262 (100.0)	260 (99.2)	
	1, n (%)	0 (0.0)	2 (0.8)	
Respiratory A&E attendance	N (% non-missing)	262 (100.0)	262 (100.0)	1.0000
	0, n (%)	260 (99.2)	260 (99.2)	
	1, n (%)	2 (0.8)	2 (0.8)	
Acute respiratory events	N (% non-missing)	262 (100.0)	262 (100.0)	0.7233
	0, n (%)	183 (69.8)	186 (71.0)	
	1, n (%)	52 (19.8)	53 (20.2)	
	2, n (%)	17 (6.5)	12 (4.6)	
	3, n (%)	8 (3.1)	6 (2.3)	
	4, n (%)	2 (0.8)	4 (1.5)	
	5, n (%)	0 (0.0)	1 (0.4)	
Exacerbations	N (% non-missing)	262 (100.0)	262 (100.0)	0.7253
	0, n (%)	200 (76.3)	206 (78.6)	
	1, n (%)	45 (17.2)	39 (14.9)	
	2, n (%)	12 (4.6)	9 (3.4)	
	3, n (%)	4 (1.5)	5 (1.9)	
	4, n (%)	1 (0.4)	3 (1.1)	

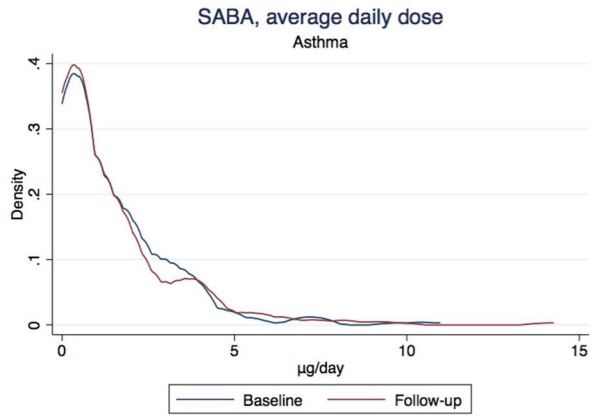
14.3 Phase 3 outcome listings – COPD

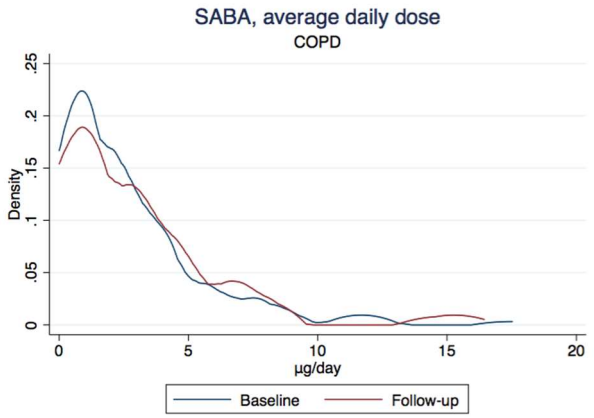
Variable	Category	Baseline	Follow-up	P
Actue OCS prescriptions	N (% non-missing)	148 (100.0)	148 (100.0)	0.5042
	0, n (%)	89 (60.1)	82 (55.4)	
	1, n (%)	24 (16.2)	28 (18.9)	
	2, n (%)	11 (7.4)	13 (8.8)	
	3, n (%)	8 (5.4)	12 (8.1)	
	4, n (%)	5 (3.4)	4 (2.7)	
	5, n (%)	5 (3.4)	2 (1.4)	
	6, n (%)	0 (0.0)	2 (1.4)	
	7, n (%)	0 (0.0)	1 (0.7)	
	8, n (%)	1 (0.7)	2 (1.4)	
	9, n (%)	0 (0.0)	1 (0.7)	
	10, n (%)	3 (2.0)	0 (0.0)	
	11, n (%)	1 (0.7)	0 (0.0)	
	15, n (%)	1 (0.7)	1 (0.7)	
Acute OCS courses	N (% non-missing)	148 (100.0)	148 (100.0)	0.4671
	0, n (%)	89 (60.1)	82 (55.4)	
	1, n (%)	28 (18.9)	29 (19.6)	
	2, n (%)	10 (6.8)	16 (10.8)	
	3, n (%)	11 (7.4)	10 (6.8)	
	4, n (%)	1 (0.7)	5 (3.4)	
	5, n (%)	3 (2.0)	1 (0.7)	
	6, n (%)	0 (0.0)	2 (1.4)	

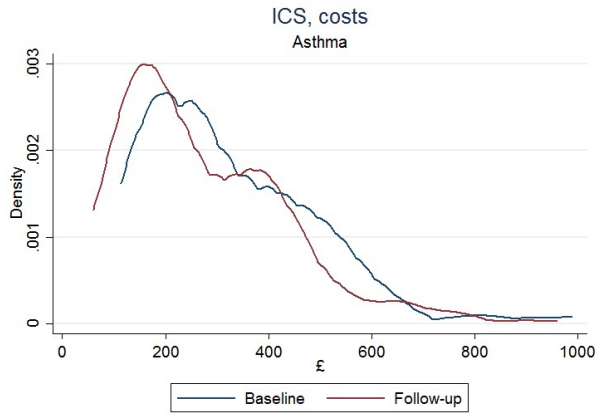
	7, n (%)	2 (1.4)	1 (0.7)	
	8, n (%)	1 (0.7)	1 (0.7)	
	9, n (%)	1 (0.7)	0 (0.0)	
	10, n (%)	1 (0.7)	0 (0.0)	
	11, n (%)	0 (0.0)	1 (0.7)	
	13, n (%)	1 (0.7)	0 (0.0)	
Antibiotic courses, resp.	N (% non-missing)	148 (100.0)	148 (100.0)	0.1552
	0, n (%)	81 (54.7)	90 (60.8)	
	1, n (%)	45 (30.4)	33 (22.3)	
	2, n (%)	11 (7.4)	18 (12.2)	
	3, n (%)	4 (2.7)	2 (1.4)	
	4, n (%)	5 (3.4)	1 (0.7)	
	5, n (%)	2 (1.4)	2 (1.4)	
	6, n (%)	0 (0.0)	2 (1.4)	
SABA prescriptions	N (% non-missing)	148 (100.0)	148 (100.0)	0.0323
	0, n (%)	25 (16.9)	26 (17.6)	
	1, n (%)	11 (7.4)	11 (7.4)	
	2, n (%)	1 (0.7)	12 (8.1)	
	3, n (%)	12 (8.1)	5 (3.4)	
	4, n (%)	10 (6.8)	3 (2.0)	
	5, n (%)	11 (7.4)	5 (3.4)	
	6, n (%)	9 (6.1)	7 (4.7)	
	7, n (%)	6 (4.1)	8 (5.4)	
	8, n (%)	5 (3.4)	9 (6.1)	
	9, n (%)	3 (2.0)	7 (4.7)	
	10, n (%)	1 (0.7)	3 (2.0)	
	11, n (%)	14 (9.5)	7 (4.7)	
	12, n (%)	11 (7.4)	7 (4.7)	
	13, n (%)	7 (4.7)	7 (4.7)	
	14, n (%)	9 (6.1)	16 (10.8)	
	15, n (%)	2 (1.4)	4 (2.7)	
	16, n (%)	3 (2.0)	4 (2.7)	
	17, n (%)	3 (2.0)	0 (0.0)	
	18, n (%)	1 (0.7)	2 (1.4)	
	19, n (%)	2 (1.4)	0 (0.0)	
	21, n (%)	0 (0.0)	1 (0.7)	
	22, n (%)	0 (0.0)	1 (0.7)	
	24, n (%)	0 (0.0)	1 (0.7)	
	26, n (%)	1 (0.7)	0 (0.0)	
	29, n (%)	0 (0.0)	1 (0.7)	
	44, n (%)	1 (0.7)	0 (0.0)	
	55, n (%)	0 (0.0)	1 (0.7)	
Inpatient hospital admissions	N (% non-missing)	148 (100.0)	148 (100.0)	0.3618
	0, n (%)	144 (97.3)	144 (97.3)	
	1, n (%)	2 (1.4)	3 (2.0)	
	2, n (%)	2 (1.4)	0 (0.0)	
	3, n (%)	0 (0.0)	1 (0.7)	
Respiratory A&E attendance	N (% non-missing)	148 (100.0)	148 (100.0)	0.0786
	0, n (%)	148 (100.0)	143 (96.6)	
	1, n (%)	0 (0.0)	4 (2.7)	
	2, n (%)	0 (0.0)	1 (0.7)	
Exacerbations	N (% non-missing)	148 (100.0)	148 (100.0)	0.1007

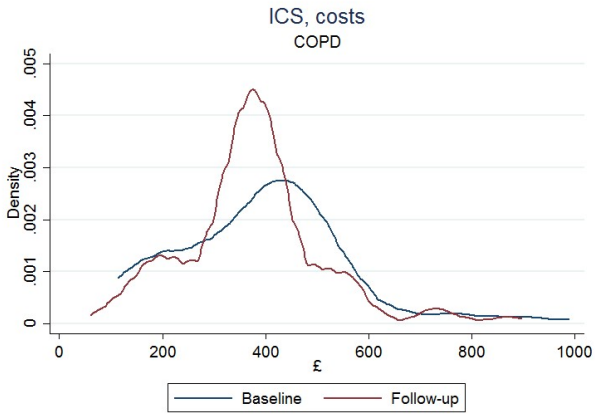
0, n (%)	58 (39.2)	60 (40.5)
1, n (%)	44 (29.7)	31 (20.9)
2, n (%)	15 (10.1)	29 (19.6)
3, n (%)	18 (12.2)	11 (7.4)
4, n (%)	4 (2.7)	7 (4.7)
5, n (%)	3 (2.0)	3 (2.0)
6, n (%)	0 (0.0)	4 (2.7)
7, n (%)	1 (0.7)	1 (0.7)
8, n (%)	3 (2.0)	1 (0.7)
10, n (%)	1 (0.7)	0 (0.0)
11, n (%)	0 (0.0)	1 (0.7)
13, n (%)	1 (0.7)	0 (0.0)

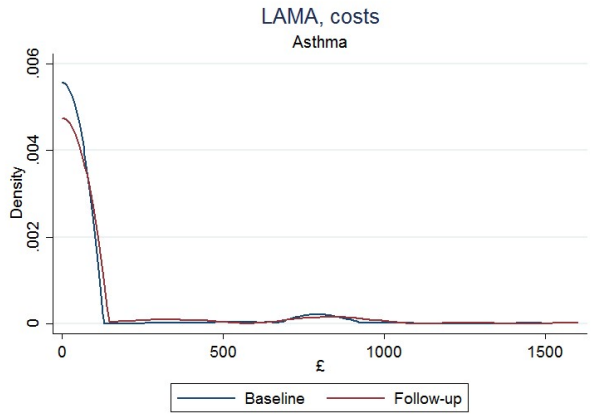
14.4 Phase 3 distributions

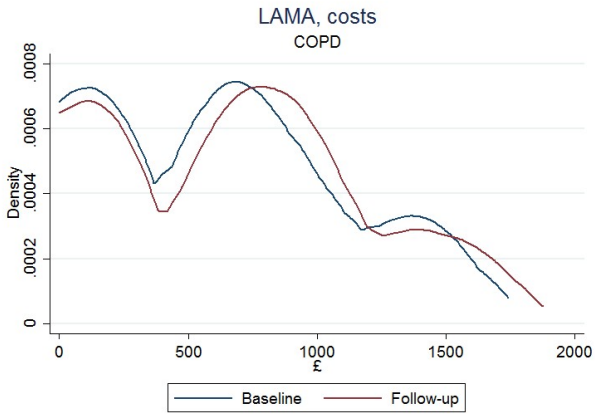









LAMA, costs
Asthma
Density
0
.002
.004
.006
0
500
1000
1500
£
Baseline
Follow-up


LAMA, costs
COPD
Density
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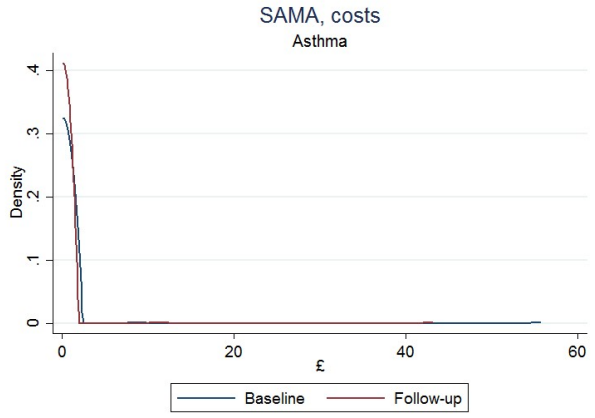
.0006
.0008
0
500
1000
1500
2000
£
Baseline
Follow-up


SAMA, costs
Asthma
Density
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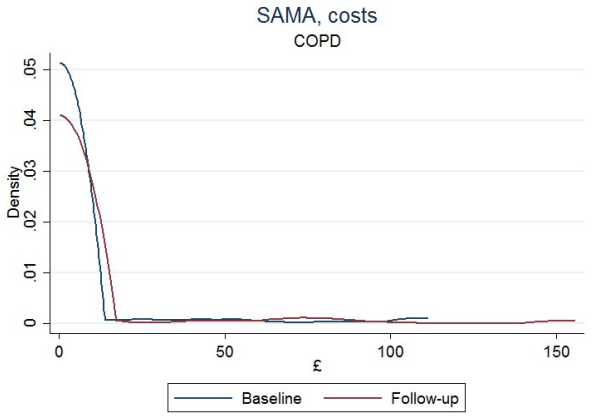
.1
.2
.3
.4
0
20
40
60
£
Baseline
Follow-up


SAMA, costs
COPD
Density
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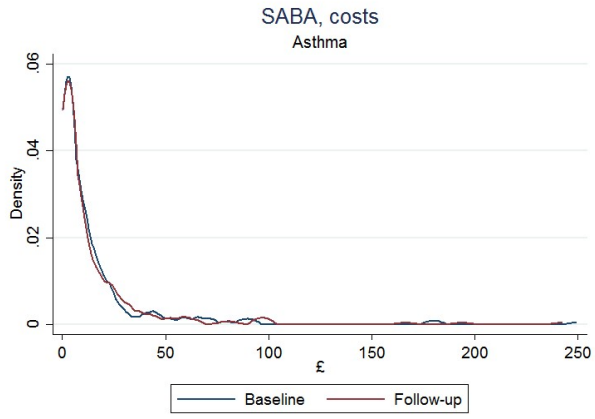
.01
.02
.03
.04
.05
0
50
100
150
£
Baseline
Follow-up


SABA, costs
Asthma
Density
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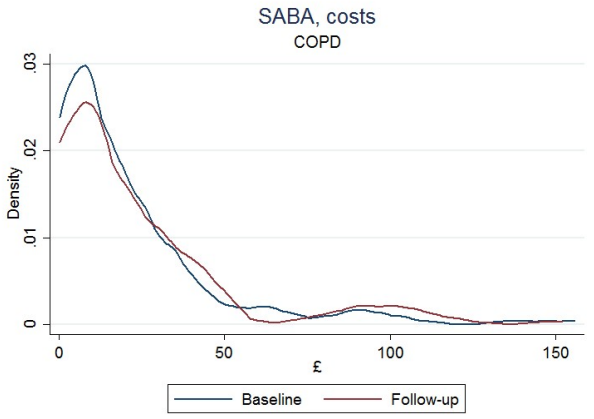
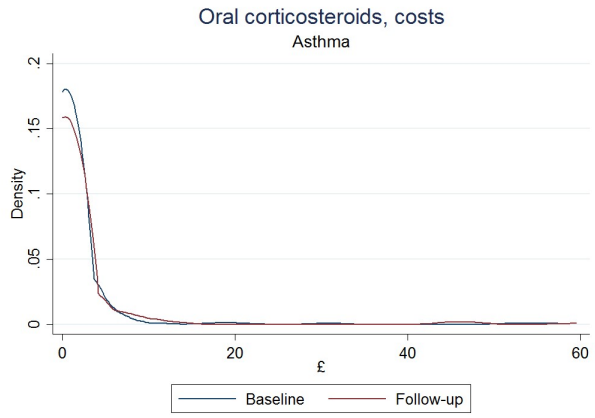
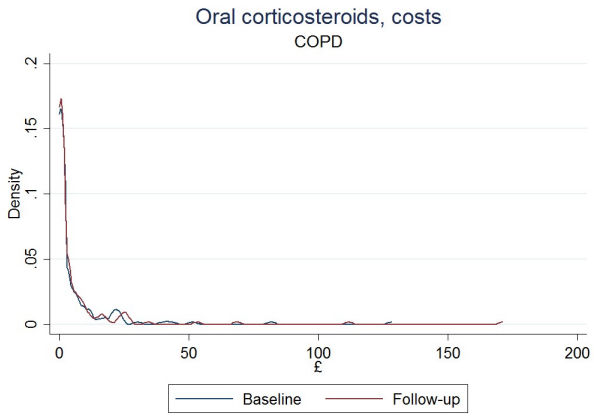
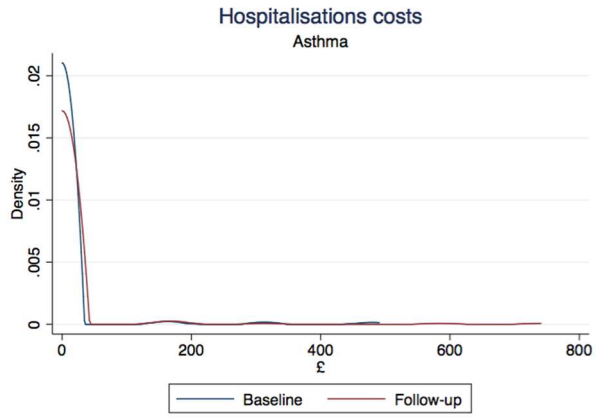
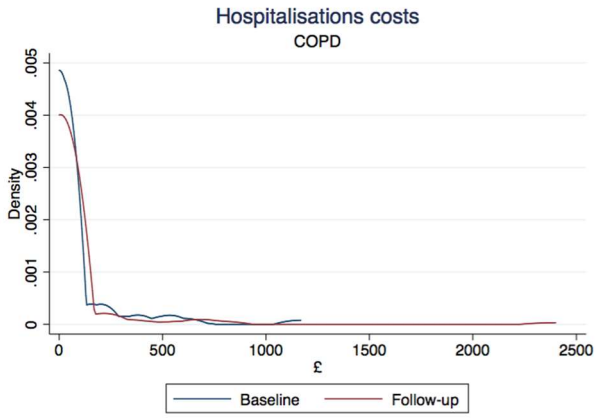
.02
.04
.06
0
50
100
150
200
250
£
Baseline
Follow-up

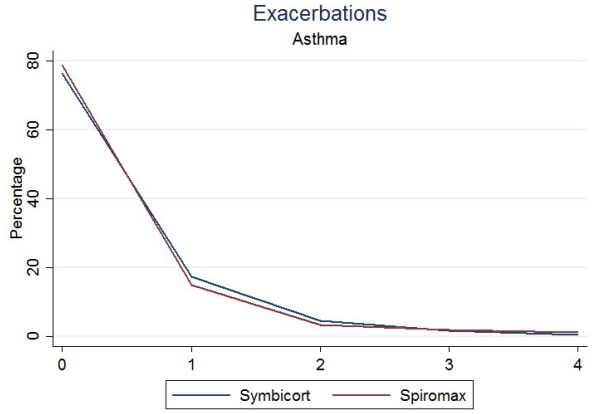

SABA, costs
COPD
Density
0
.01
.02
.03
0
50
100
150
£
Baseline
Follow-up

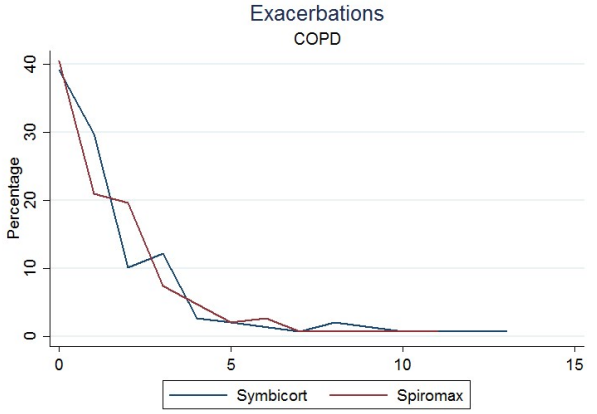

Oral corticosteroids, costs
Asthma
Density
0
.05
.1
.15
.2
0
20
40
60
£
Baseline
Follow-up

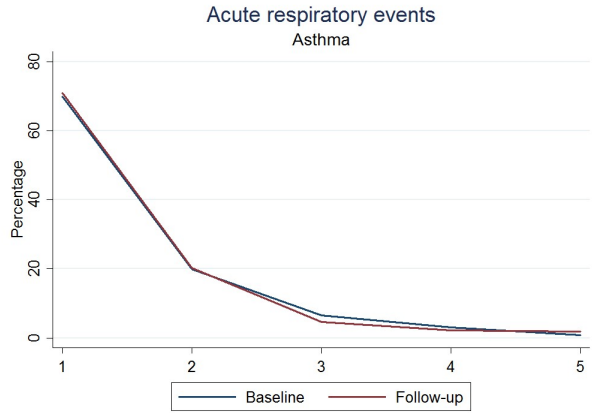

Oral corticosteroids, costs
COPD
Density
0
.05
.1
.15
.2
0
50
100
150
200
£
Baseline
Follow-up


Hospitalisations costs
Asthma
Density
0
.005
.01
.015
.02
0
200
400
600
800
£
Baseline
Follow-up


Hospitalisations costs
COPD
Density
0
.001
.002
.003
.004
.005
0
500
1000
1500
2000
2500
£
Baseline
Follow-up


Exacerbations
Asthma
Percentage
0
20
40
60
80
0
1
2
3
4
Symbicort
Spiromax


Exacerbations
COPD
Percentage
0
10
20
30
40
0
5
10
15
Symbicort
Spiromax


Acute respiratory events
Asthma
Percentage
0
20
40
60
80
1
2
3
4
5
Baseline
Follow-up

14.5 Phase 4 matched outcome listings – asthma

Variable	Category	DuoResp	Turbohaler	P
Acute OCS prescriptions	N (% non-missing)	253 (100.0)	743 (100.0)	0.1821
	0, n (%)	205 (81.0)	572 (77.0)	
	1, n (%)	34 (13.4)	97 (13.1)	
	2, n (%)	7 (2.8)	45 (6.1)	
	3, n (%)	3 (1.2)	20 (2.7)	
	4, n (%)	4 (1.6)	7 (0.9)	
	6, n (%)	0 (0.0)	2 (0.3)	
Acute OCS courses	N (% non-missing)	253 (100.0)	743 (100.0)	0.1590
	0, n (%)	205 (81.0)	572 (77.0)	
	1, n (%)	34 (13.4)	111 (14.9)	
	2, n (%)	9 (3.6)	38 (5.1)	
	3, n (%)	2 (0.8)	19 (2.6)	
	4, n (%)	3 (1.2)	2 (0.3)	
	5, n (%)	0 (0.0)	1 (0.1)	
Maintenance OCS prescriptions	N (% non-missing)	253 (100.0)	743 (100.0)	0.7250
	0, n (%)	247 (97.6)	718 (96.6)	
	1, n (%)	0 (0.0)	4 (0.5)	
	2, n (%)	1 (0.4)	1 (0.1)	
	3, n (%)	0 (0.0)	1 (0.1)	
	4, n (%)	1 (0.4)	1 (0.1)	
	5, n (%)	0 (0.0)	3 (0.4)	
	6, n (%)	1 (0.4)	4 (0.5)	
	7, n (%)	0 (0.0)	1 (0.1)	
	8, n (%)	0 (0.0)	3 (0.4)	
	9, n (%)	0 (0.0)	1 (0.1)	
	11, n (%)	1 (0.4)	1 (0.1)	
	12, n (%)	0 (0.0)	1 (0.1)	
	13, n (%)	0 (0.0)	2 (0.3)	
	14, n (%)	2 (0.8)	1 (0.1)	
	15, n (%)	0 (0.0)	1 (0.1)	
Total OCS prescriptions	N (% non-missing)	253 (100.0)	743 (100.0)	0.3780
	0, n (%)	202 (79.8)	555 (74.7)	
	1, n (%)	32 (12.6)	97 (13.1)	
	2, n (%)	7 (2.8)	44 (5.9)	
	3, n (%)	2 (0.8)	17 (2.3)	
	4, n (%)	4 (1.6)	7 (0.9)	
	5, n (%)	2 (0.8)	4 (0.5)	
	6, n (%)	1 (0.4)	6 (0.8)	
	7, n (%)	0 (0.0)	2 (0.3)	
	8, n (%)	0 (0.0)	3 (0.4)	
	9, n (%)	0 (0.0)	2 (0.3)	
	11, n (%)	0 (0.0)	1 (0.1)	
	12, n (%)	1 (0.4)	1 (0.1)	
	13, n (%)	0 (0.0)	2 (0.3)	
	14, n (%)	2 (0.8)	1 (0.1)	
	18, n (%)	0 (0.0)	1 (0.1)	
Antibiotic courses, lower resp	N (% non-missing)	253 (100.0)	743 (100.0)	0.1726
	0, n (%)	210 (83.0)	576 (77.5)	
	1, n (%)	35 (13.8)	109 (14.7)	

Variable	Category	DuoResp	Turbohaler	P
	2, n (%)	4 (1.6)	32 (4.3)	
	3, n (%)	2 (0.8)	14 (1.9)	
	4, n (%)	0 (0.0)	8 (1.1)	
	5, n (%)	1 (0.4)	2 (0.3)	
	6, n (%)	1 (0.4)	2 (0.3)	
Outpatient hospital visits	N (% non-missing)	253 (100.0)	743 (100.0)	0.6728
	0, n (%)	250 (98.8)	734 (98.8)	
	1, n (%)	2 (0.8)	8 (1.1)	
	2, n (%)	1 (0.4)	1 (0.1)	
Inpatient hospital admissions	N (% non-missing)	253 (100.0)	743 (100.0)	0.9852
	0, n (%)	252 (99.6)	740 (99.6)	
	1, n (%)	1 (0.4)	3 (0.4)	
FDC inhalers prescribed	N (% non-missing)	253 (100.0)	743 (100.0)	<0.0001
	2, n (%)	4 (1.6)	14 (1.9)	
	3, n (%)	1 (0.4)	27 (3.6)	
	4, n (%)	16 (6.3)	38 (5.1)	
	5, n (%)	8 (3.2)	34 (4.6)	
	6, n (%)	28 (11.1)	58 (7.8)	
	7, n (%)	7 (2.8)	42 (5.7)	
	8, n (%)	20 (7.9)	55 (7.4)	
	9, n (%)	2 (0.8)	38 (5.1)	
	10, n (%)	21 (8.3)	63 (8.5)	
	11, n (%)	10 (4.0)	60 (8.1)	
	12, n (%)	22 (8.7)	81 (10.9)	
	13, n (%)	3 (1.2)	52 (7.0)	
	14, n (%)	19 (7.5)	70 (9.4)	
	15, n (%)	4 (1.6)	26 (3.5)	
	16, n (%)	16 (6.3)	14 (1.9)	
	17, n (%)	4 (1.6)	8 (1.1)	
	18, n (%)	8 (3.2)	16 (2.2)	
	19, n (%)	1 (0.4)	3 (0.4)	
	20, n (%)	10 (4.0)	7 (0.9)	
	21, n (%)	2 (0.8)	1 (0.1)	
	22, n (%)	7 (2.8)	6 (0.8)	
	23, n (%)	0 (0.0)	2 (0.3)	
	24, n (%)	5 (2.0)	2 (0.3)	
	25, n (%)	1 (0.4)	2 (0.3)	
	26, n (%)	15 (5.9)	6 (0.8)	
	27, n (%)	0 (0.0)	2 (0.3)	
	28, n (%)	6 (2.4)	6 (0.8)	
	30, n (%)	4 (1.6)	0 (0.0)	
	32, n (%)	3 (1.2)	4 (0.5)	
	33, n (%)	0 (0.0)	2 (0.3)	
	34, n (%)	0 (0.0)	1 (0.1)	
	35, n (%)	1 (0.4)	0 (0.0)	
	36, n (%)	0 (0.0)	1 (0.1)	
	37, n (%)	1 (0.4)	0 (0.0)	
	40, n (%)	2 (0.8)	1 (0.1)	
	44, n (%)	0 (0.0)	1 (0.1)	
	56, n (%)	1 (0.4)	0 (0.0)	
	64, n (%)	1 (0.4)	0 (0.0)	

Variable	Category	DuoResp	Turbohaler	P
ICS inhalers prescribed	N (% non-missing)	253 (100.0)	743 (100.0)	0.9241
	0, n (%)	249 (98.4)	730 (98.3)	
	1, n (%)	1 (0.4)	2 (0.3)	
	2, n (%)	1 (0.4)	1 (0.1)	
	3, n (%)	1 (0.4)	1 (0.1)	
	4, n (%)	1 (0.4)	4 (0.5)	
	5, n (%)	0 (0.0)	2 (0.3)	
	6, n (%)	0 (0.0)	1 (0.1)	
	10, n (%)	0 (0.0)	1 (0.1)	
	13, n (%)	0 (0.0)	1 (0.1)	
Asthma related GP consultations	N (% non-missing)	253 (100.0)	743 (100.0)	0.0101
	0, n (%)	91 (36.0)	223 (30.0)	
	1, n (%)	131 (51.8)	326 (43.9)	
	2, n (%)	26 (10.3)	110 (14.8)	
	3, n (%)	3 (1.2)	39 (5.2)	
	4, n (%)	1 (0.4)	21 (2.8)	
	5, n (%)	1 (0.4)	13 (1.7)	
	6, n (%)	0 (0.0)	3 (0.4)	
	7, n (%)	0 (0.0)	2 (0.3)	
	8, n (%)	0 (0.0)	1 (0.1)	
	9, n (%)	0 (0.0)	2 (0.3)	
	10, n (%)	0 (0.0)	1 (0.1)	
	15, n (%)	0 (0.0)	1 (0.1)	
	16, n (%)	0 (0.0)	1 (0.1)	
Exacerbations	N (% non-missing)	253 (100.0)	743 (100.0)	0.1204
	0, n (%)	204 (80.6)	568 (76.4)	
	1, n (%)	36 (14.2)	114 (15.3)	
	2, n (%)	8 (3.2)	38 (5.1)	
	3, n (%)	2 (0.8)	20 (2.7)	
	4, n (%)	3 (1.2)	2 (0.3)	
	5, n (%)	0 (0.0)	1 (0.1)	
Acute respiratory events	N (% non-missing)	253 (100.0)	743 (100.0)	0.1505
	0, n (%)	185 (73.1)	505 (68.0)	
	1, n (%)	49 (19.4)	142 (19.1)	
	2, n (%)	12 (4.7)	55 (7.4)	
	3, n (%)	2 (0.8)	27 (3.6)	
	4, n (%)	4 (1.6)	10 (1.3)	
	5, n (%)	1 (0.4)	4 (0.5)	
Respiratory A&E attendance	N (% non-missing)	253 (100.0)	743 (100.0)	0.6544
	0, n (%)	251 (99.2)	739 (99.5)	
	1, n (%)	2 (0.8)	4 (0.5)	

P = P-value for the Pearson's chi-square test of independent categories

14.6 Phase 4 matched outcome listings – COPD

Variable	Category	DuoResp	Turbohaler	P
Acute OCS prescriptions	N (% non-missing)	132 (100.0)	348 (100.0)	0.3299
	0, n (%)	73 (55.3)	185 (53.2)	
	1, n (%)	25 (18.9)	74 (21.3)	
	2, n (%)	13 (9.8)	40 (11.5)	
	3, n (%)	10 (7.6)	26 (7.5)	
	4, n (%)	4 (3.0)	16 (4.6)	
	5, n (%)	1 (0.8)	3 (0.9)	
	6, n (%)	2 (1.5)	3 (0.9)	
	7, n (%)	1 (0.8)	0 (0.0)	
	8, n (%)	1 (0.8)	0 (0.0)	
	9, n (%)	1 (0.8)	0 (0.0)	
	13, n (%)	0 (0.0)	1 (0.3)	
	15, n (%)	1 (0.8)	0 (0.0)	
Acute OCS courses	N (% non-missing)	132 (100.0)	348 (100.0)	0.6071
	0, n (%)	73 (55.3)	185 (53.2)	
	1, n (%)	26 (19.7)	83 (23.9)	
	2, n (%)	15 (11.4)	38 (10.9)	
	3, n (%)	9 (6.8)	25 (7.2)	
	4, n (%)	4 (3.0)	12 (3.4)	
	5, n (%)	1 (0.8)	3 (0.9)	
	6, n (%)	2 (1.5)	1 (0.3)	
	8, n (%)	1 (0.8)	0 (0.0)	
	11, n (%)	1 (0.8)	1 (0.3)	
Maintenance OCS prescriptions	N (% non-missing)	132 (100.0)	348 (100.0)	0.3632
	0, n (%)	124 (93.9)	312 (89.7)	
	1, n (%)	1 (0.8)	3 (0.9)	
	2, n (%)	0 (0.0)	1 (0.3)	
	3, n (%)	1 (0.8)	2 (0.6)	
	4, n (%)	0 (0.0)	1 (0.3)	
	5, n (%)	0 (0.0)	4 (1.1)	
	6, n (%)	1 (0.8)	2 (0.6)	
	7, n (%)	0 (0.0)	8 (2.3)	
	8, n (%)	2 (1.5)	2 (0.6)	
	9, n (%)	1 (0.8)	0 (0.0)	
	10, n (%)	0 (0.0)	3 (0.9)	
	11, n (%)	1 (0.8)	0 (0.0)	
	12, n (%)	0 (0.0)	2 (0.6)	
	13, n (%)	0 (0.0)	3 (0.9)	
	14, n (%)	0 (0.0)	2 (0.6)	
	17, n (%)	1 (0.8)	0 (0.0)	
	18, n (%)	0 (0.0)	1 (0.3)	
	21, n (%)	0 (0.0)	1 (0.3)	
	53, n (%)	0 (0.0)	1 (0.3)	
Total OCS prescriptions	N (% non-missing)	132 (100.0)	348 (100.0)	0.7175
	0, n (%)	70 (53.0)	165 (47.4)	
	1, n (%)	22 (16.7)	67 (19.3)	
	2, n (%)	13 (9.8)	39 (11.2)	
	3, n (%)	9 (6.8)	25 (7.2)	
	4, n (%)	4 (3.0)	14 (4.0)	

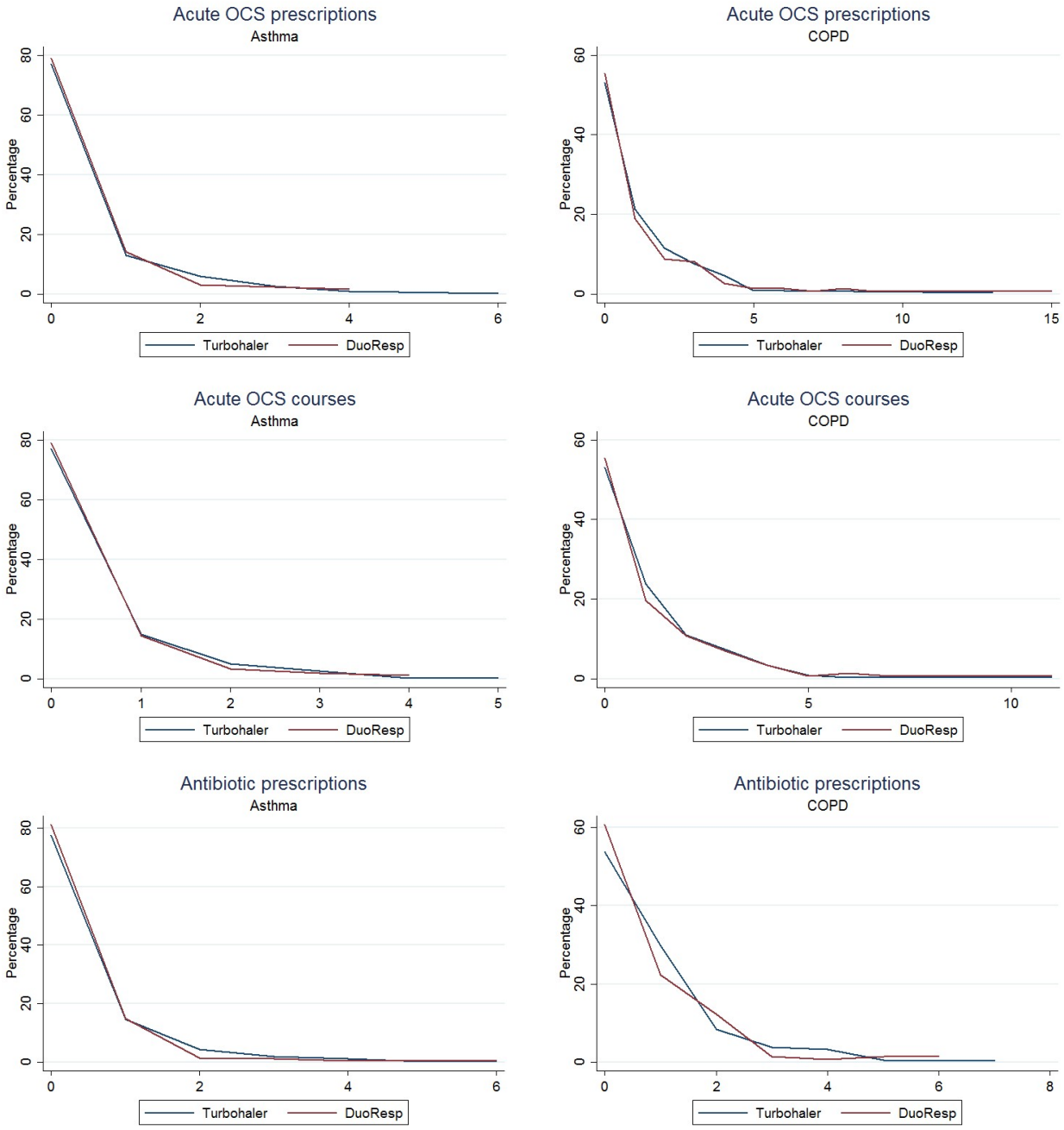
Variable	Category	DuoResp	Turbohaler	P
	5, n (%)	1 (0.8)	7 (2.0)	
	6, n (%)	3 (2.3)	4 (1.1)	
	7, n (%)	2 (1.5)	7 (2.0)	
	8, n (%)	2 (1.5)	5 (1.4)	
	9, n (%)	3 (2.3)	1 (0.3)	
	10, n (%)	0 (0.0)	1 (0.3)	
	11, n (%)	1 (0.8)	1 (0.3)	
	12, n (%)	0 (0.0)	1 (0.3)	
	13, n (%)	0 (0.0)	4 (1.1)	
	14, n (%)	0 (0.0)	2 (0.6)	
	15, n (%)	0 (0.0)	1 (0.3)	
	16, n (%)	1 (0.8)	0 (0.0)	
	18, n (%)	1 (0.8)	1 (0.3)	
	20, n (%)	0 (0.0)	1 (0.3)	
	21, n (%)	0 (0.0)	1 (0.3)	
	54, n (%)	0 (0.0)	1 (0.3)	
Antibiotic courses, lower resp	N (% non-missing)	132 (100.0)	348 (100.0)	0.0250
	0, n (%)	81 (61.4)	187 (53.7)	
	1, n (%)	29 (22.0)	104 (29.9)	
	2, n (%)	17 (12.9)	29 (8.3)	
	3, n (%)	1 (0.8)	13 (3.7)	
	4, n (%)	0 (0.0)	11 (3.2)	
	5, n (%)	2 (1.5)	2 (0.6)	
	6, n (%)	2 (1.5)	1 (0.3)	
	7, n (%)	0 (0.0)	1 (0.3)	
Outpatient hospital visits	N (% non-missing)	132 (100.0)	348 (100.0)	0.4792
	0, n (%)	125 (94.7)	331 (95.1)	
	1, n (%)	4 (3.0)	9 (2.6)	
	2, n (%)	2 (1.5)	6 (1.7)	
	3, n (%)	1 (0.8)	0 (0.0)	
	5, n (%)	0 (0.0)	2 (0.6)	
Inpatient hospital admissions	N (% non-missing)	132 (100.0)	348 (100.0)	0.5777
	0, n (%)	128 (97.0)	338 (97.1)	
	1, n (%)	3 (2.3)	7 (2.0)	
	2, n (%)	0 (0.0)	1 (0.3)	
	3, n (%)	1 (0.8)	0 (0.0)	
	4, n (%)	0 (0.0)	1 (0.3)	
	6, n (%)	0 (0.0)	1 (0.3)	
FDC inhalers prescribed	N (% non-missing)	132 (100.0)	348 (100.0)	0.0005
	2, n (%)	1 (0.8)	7 (2.0)	
	3, n (%)	0 (0.0)	7 (2.0)	
	4, n (%)	3 (2.3)	5 (1.4)	
	5, n (%)	3 (2.3)	14 (4.0)	
	6, n (%)	4 (3.0)	17 (4.9)	
	7, n (%)	5 (3.8)	14 (4.0)	
	8, n (%)	3 (2.3)	20 (5.7)	
	9, n (%)	6 (4.5)	17 (4.9)	
	10, n (%)	5 (3.8)	25 (7.2)	
	11, n (%)	10 (7.6)	23 (6.6)	
	12, n (%)	13 (9.8)	43 (12.4)	
	13, n (%)	16 (12.1)	57 (16.4)	

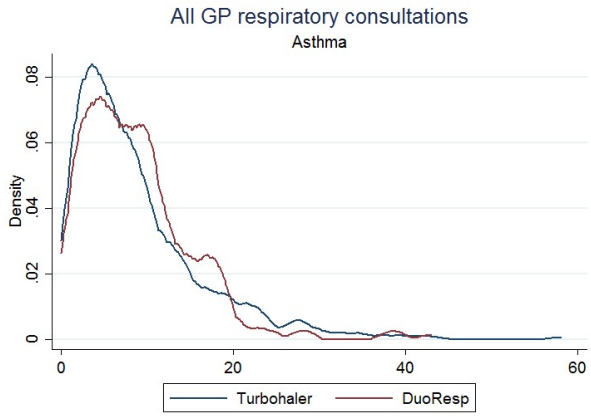
Variable	Category	DuoResp	Turbohaler	P
	14, n (%)	15 (11.4)	43 (12.4)	
	15, n (%)	6 (4.5)	14 (4.0)	
	16, n (%)	2 (1.5)	7 (2.0)	
	17, n (%)	0 (0.0)	2 (0.6)	
	18, n (%)	6 (4.5)	5 (1.4)	
	19, n (%)	2 (1.5)	2 (0.6)	
	20, n (%)	1 (0.8)	3 (0.9)	
	22, n (%)	3 (2.3)	4 (1.1)	
	23, n (%)	0 (0.0)	2 (0.6)	
	24, n (%)	11 (8.3)	3 (0.9)	
	25, n (%)	1 (0.8)	0 (0.0)	
	26, n (%)	10 (7.6)	7 (2.0)	
	27, n (%)	0 (0.0)	2 (0.6)	
	28, n (%)	3 (2.3)	3 (0.9)	
	30, n (%)	3 (2.3)	0 (0.0)	
	34, n (%)	0 (0.0)	1 (0.3)	
	44, n (%)	0 (0.0)	1 (0.3)	
ICS inhalers prescribed	N (% non-missing)	132 (100.0)	348 (100.0)	0.4374
	0, n (%)	131 (99.2)	345 (99.1)	
	1, n (%)	0 (0.0)	1 (0.3)	
	2, n (%)	1 (0.8)	0 (0.0)	
	3, n (%)	0 (0.0)	1 (0.3)	
	5, n (%)	0 (0.0)	1 (0.3)	
COPD related GP consultations	N (% non-missing)	132 (100.0)	348 (100.0)	0.8507
	0, n (%)	29 (22.0)	75 (21.6)	
	1, n (%)	60 (45.5)	150 (43.1)	
	2, n (%)	19 (14.4)	55 (15.8)	
	3, n (%)	12 (9.1)	23 (6.6)	
	4, n (%)	3 (2.3)	22 (6.3)	
	5, n (%)	4 (3.0)	10 (2.9)	
	6, n (%)	1 (0.8)	2 (0.6)	
	7, n (%)	2 (1.5)	3 (0.9)	
	8, n (%)	1 (0.8)	2 (0.6)	
	10, n (%)	0 (0.0)	1 (0.3)	
	11, n (%)	0 (0.0)	1 (0.3)	
	12, n (%)	1 (0.8)	0 (0.0)	
	16, n (%)	0 (0.0)	1 (0.3)	
	17, n (%)	0 (0.0)	1 (0.3)	
	18, n (%)	0 (0.0)	1 (0.3)	
	28, n (%)	0 (0.0)	1 (0.3)	
Exacerbations	N (% non-missing)	132 (100.0)	348 (100.0)	0.2326
	0, n (%)	53 (40.2)	129 (37.1)	
	1, n (%)	28 (21.2)	104 (29.9)	
	2, n (%)	27 (20.5)	52 (14.9)	
	3, n (%)	10 (7.6)	35 (10.1)	
	4, n (%)	5 (3.8)	17 (4.9)	
	5, n (%)	3 (2.3)	6 (1.7)	
	6, n (%)	4 (3.0)	2 (0.6)	
	8, n (%)	1 (0.8)	1 (0.3)	
	9, n (%)	0 (0.0)	1 (0.3)	
	11, n (%)	1 (0.8)	1 (0.3)	

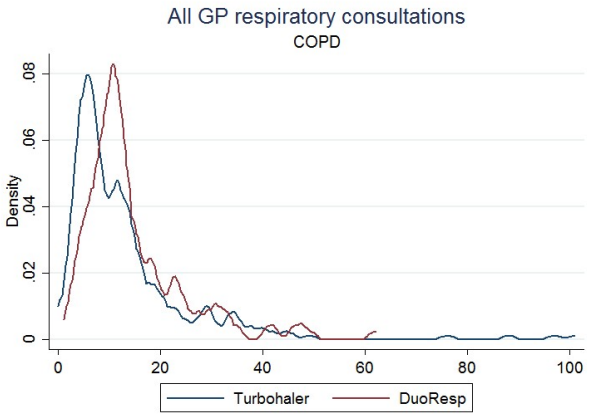
Variable	Category	DuoResp	Turbohaler	P
Respiratory A&E attendance	N (% non-missing)	132 (100.0)	348 (100.0)	0.8273
	0, n (%)	127 (96.2)	335 (96.3)	
	1, n (%)	4 (3.0)	11 (3.2)	
	2, n (%)	1 (0.8)	1 (0.3)	
	6, n (%)	0 (0.0)	1 (0.3)	

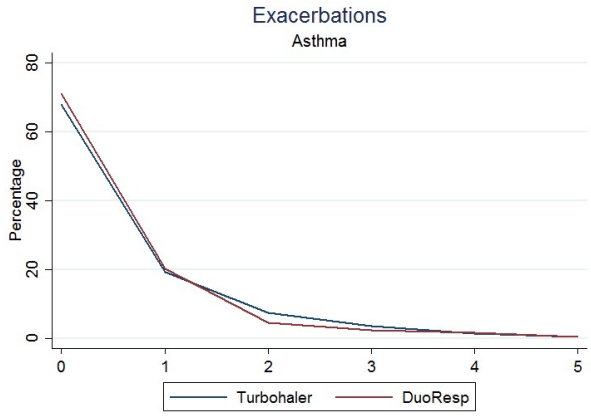
P = P-value for the Pearson's chi-square test of independent categories

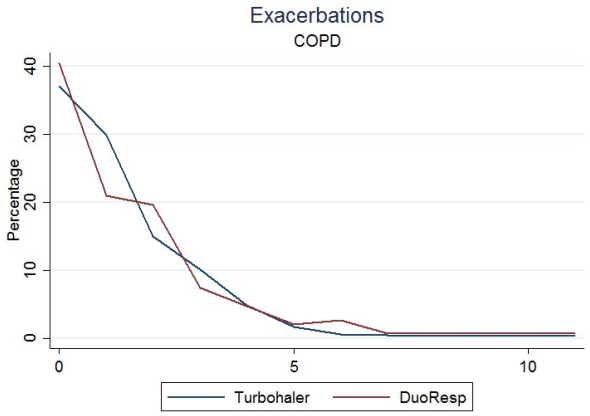
14.7 Phase 4 outcome distributions

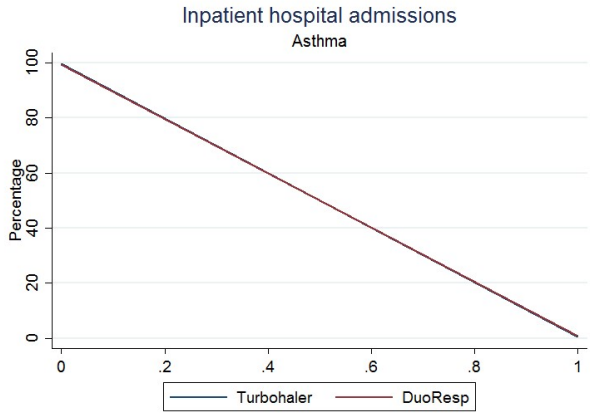


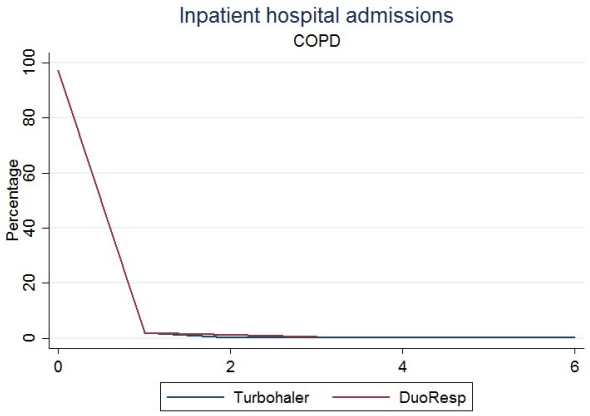

All GP respiratory consultations
Asthma
Density
0
.02
.04
.06
.08
0
20
40
60
Turbohaler
DuoResp

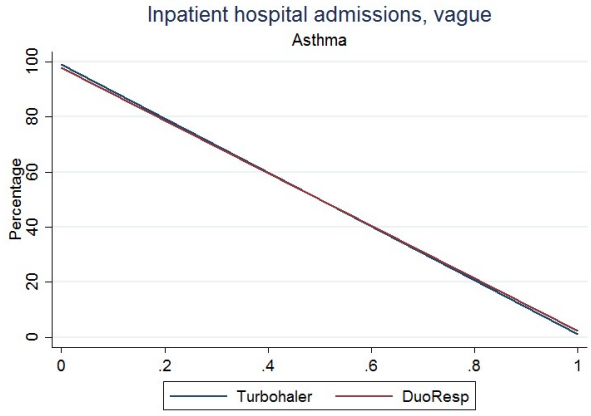

All GP respiratory consultations
COPD
Density
0
.02
.04
.06
.08
0
20
40
60
80
100
Turbohaler
DuoResp

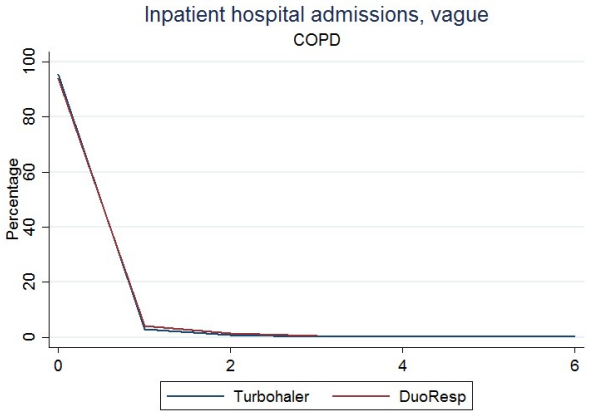

Exacerbations
Asthma
Percentage
0
20
40
60
80
0
1
2
3
4
5
Turbohaler
DuoResp

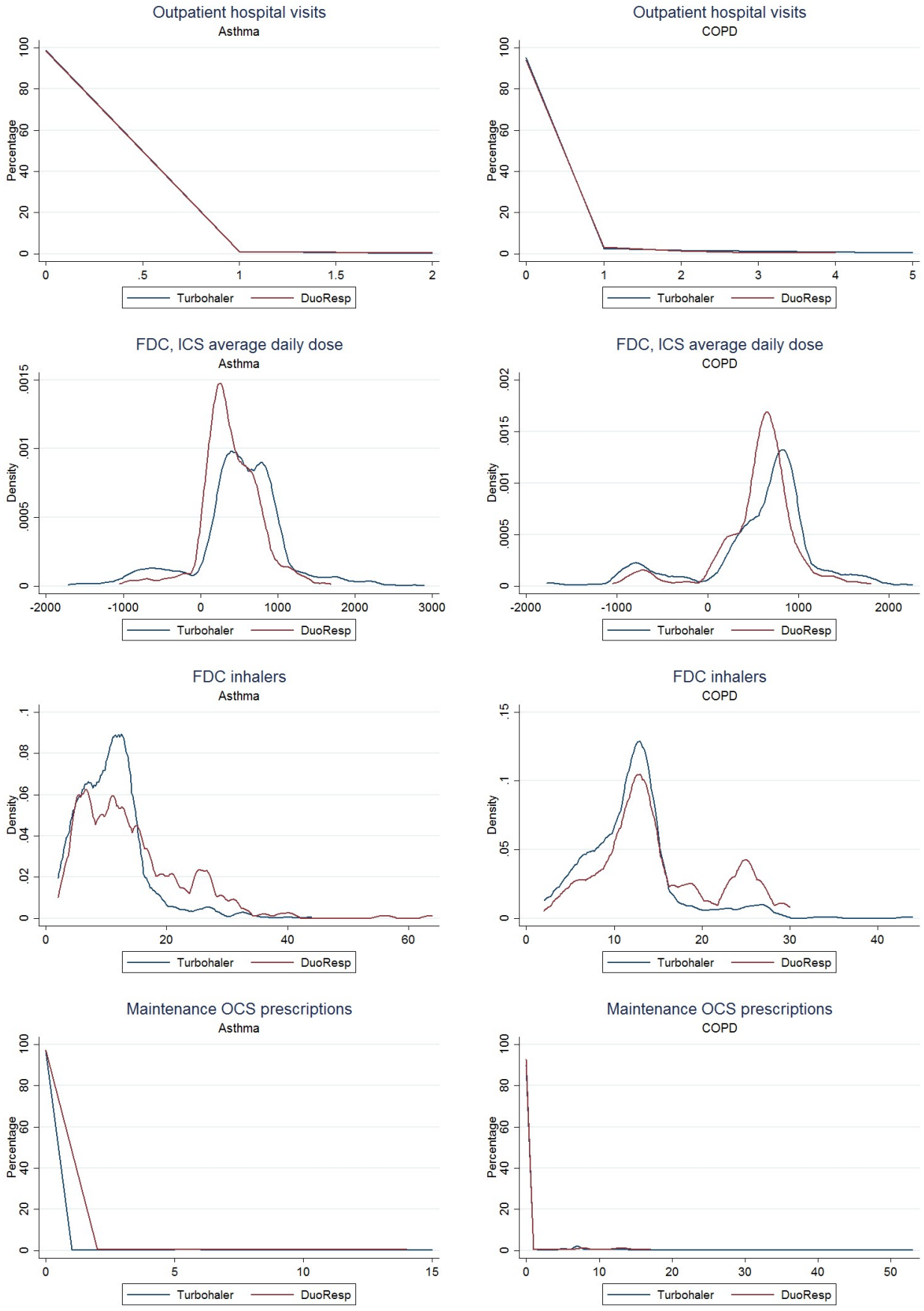

Exacerbations
COPD
Percentage
0
10
20
30
40
0
5
10
Turbohaler
DuoResp

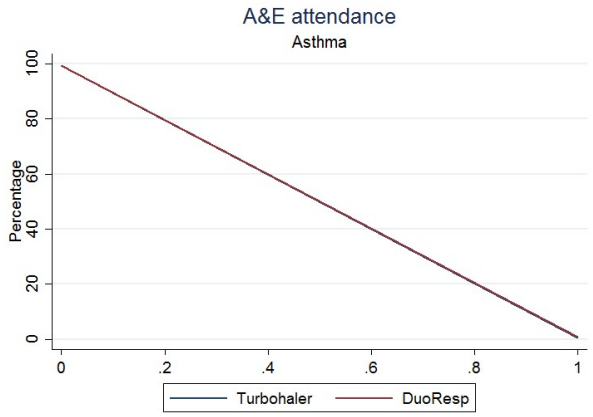

Inpatient hospital admissions
Asthma
Percentage
0
20
40
60
80
100
0
.2
.4
.6
.8
1
Turbohaler
DuoResp

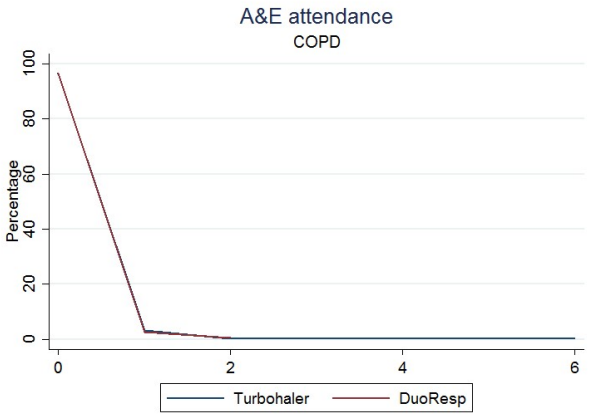

Inpatient hospital admissions
COPD
Percentage
0
20
40
60
80
100
0
2
4
6
Turbohaler
DuoResp

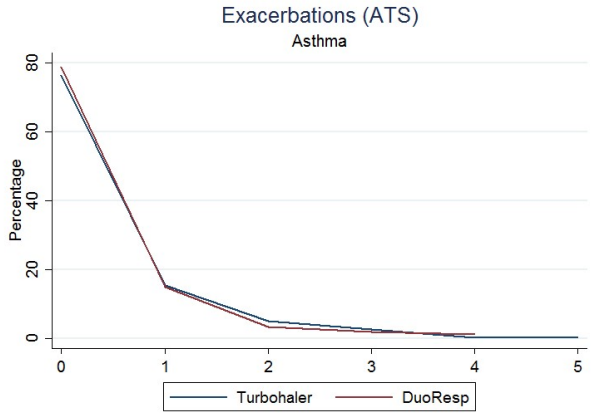

Inpatient hospital admissions, vague
Asthma
Percentage
0
20
40
60
80
100
0
.2
.4
.6
.8
1
Turbohaler
DuoResp

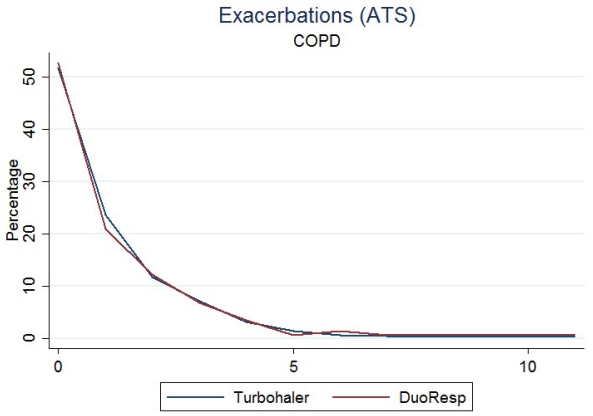

Inpatient hospital admissions, vague
COPD
Percentage
0
20
40
60
80
100
0
2
4
6
Turbohaler
DuoResp

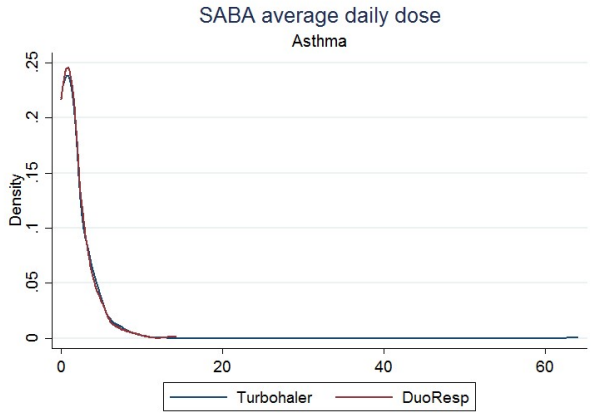

Outpatient hospital visits
Asthma
Percentage
0
20
40
60
80
100
0
.5
1
1.5
2
Turbohaler
DuoResp
Outpatient hospital visits
COPD
Percentage
0
20
40
60
80
100
0
1
2
3
4
5
Turbohaler
DuoResp
FDC, ICS average daily dose
Asthma
Density
0
.0005
.001
.0015
-2000
-1000
0
1000
2000
3000
Turbohaler
DuoResp
FDC, ICS average daily dose
COPD
Density
0
.0005
.001
.0015
.002
-2000
-1000
0
1000
2000
Turbohaler
DuoResp
FDC inhalers
Asthma
Density
0
.02
.04
.06
.08
.1
0
20
40
60
Turbohaler
DuoResp
FDC inhalers
COPD
Density
0
.05
.1
.15
0
10
20
30
40
Turbohaler
DuoResp
Maintenance OCS prescriptions
Asthma
Percentage
0
20
40
60
80
100
0
5
10
15
Turbohaler
DuoResp
Maintenance OCS prescriptions
COPD
Percentage
0
20
40
60
80
100
0
10
20
30
40
50
Turbohaler
DuoResp

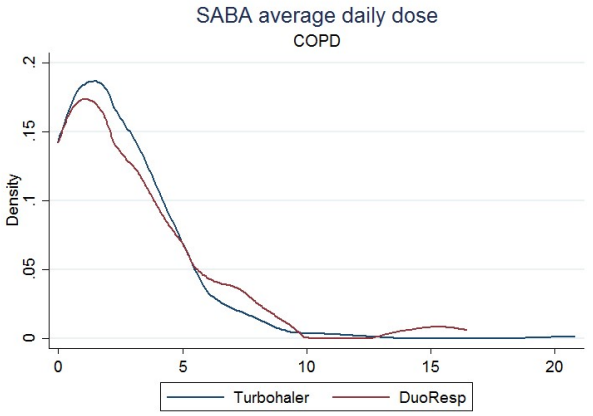

A&E attendance
Asthma
Percentage
0
20
40
60
80
100
0
.2
.4
.6
.8
1
Turbohaler
DuoResp

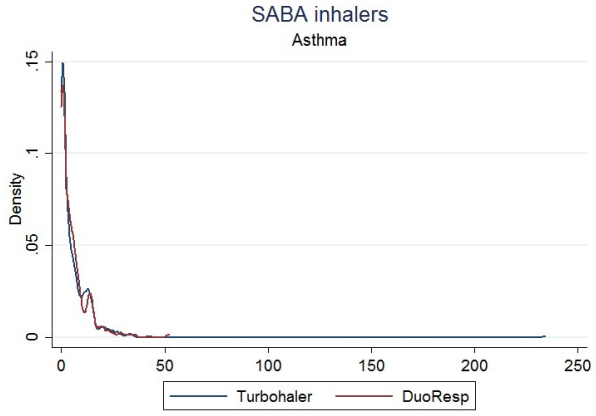

A&E attendance
COPD
Percentage
0
20
40
60
80
100
0
2
4
6
Turbohaler
DuoResp

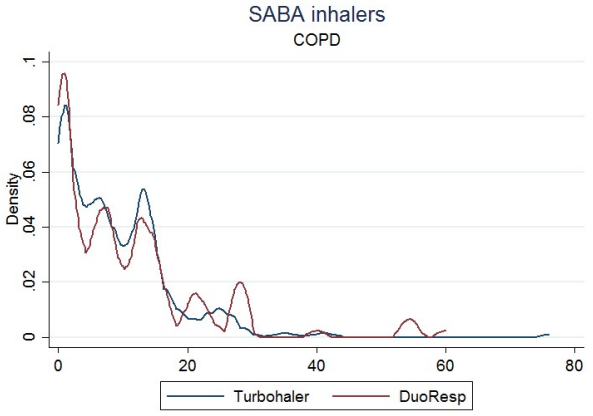

Exacerbations (ATS)
Asthma
Percentage
0
20
40
60
80
0
1
2
3
4
5
Turbohaler
DuoResp

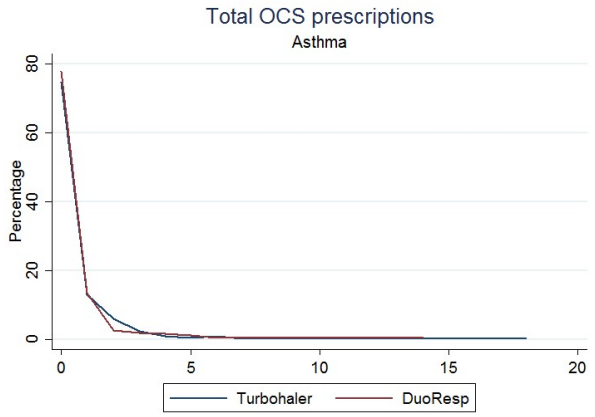

Exacerbations (ATS)
COPD
Percentage
0
10
20
30
40
50
0
5
10
Turbohaler
DuoResp

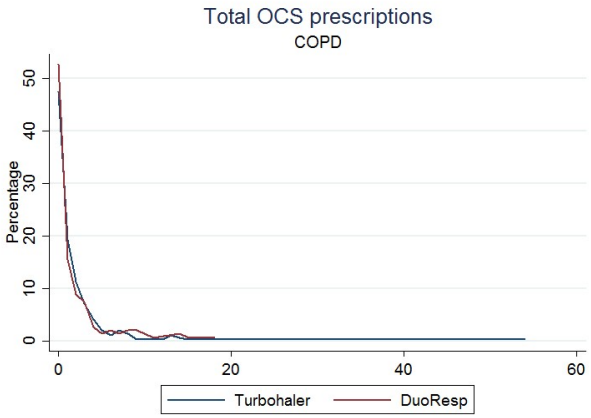

SABA average daily dose
Asthma
Density
0
.05
.1
.15
.2
.25
0
20
40
60
Turbohaler
DuoResp

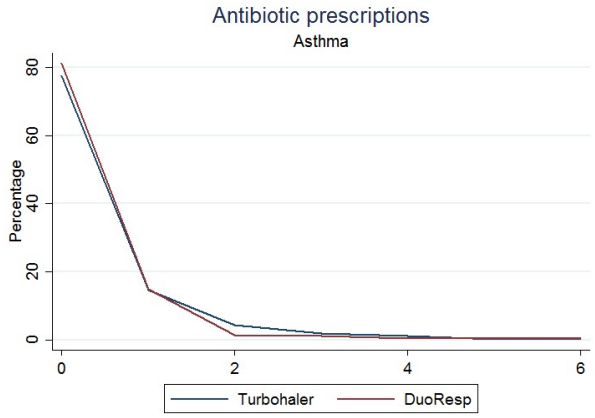

SABA average daily dose
COPD
Density
0
.05
.1
.15
.2
0
5
10
15
20
Turbohaler
DuoResp

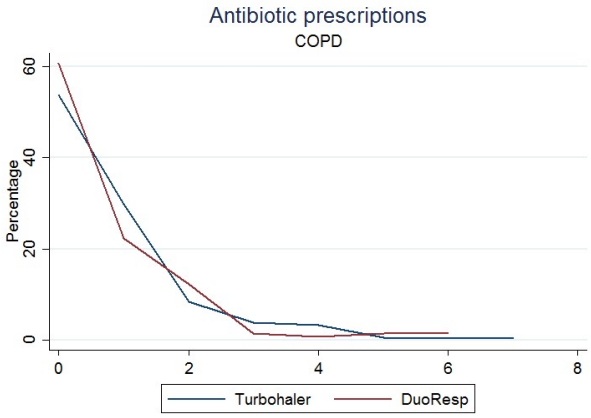

SABA inhalers
Asthma
Density
0
.05
.1
.15
0
50
100
150
200
250
Turbohaler
DuoResp


SABA inhalers
COPD
Density
0
.02
.04
.06
.08
.1
0
20
40
60
80
Turbohaler
DuoResp


Total OCS prescriptions
Asthma
Percentage
0
20
40
60
80
0
5
10
15
20
Turbohaler
DuoResp


Total OCS prescriptions
COPD
Percentage
0
10
20
30
40
50
0
20
40
60
Turbohaler
DuoResp


Antibiotic prescriptions
Asthma
Percentage
0
20
40
60
80
0
2
4
6
Turbohaler
DuoResp


Antibiotic prescriptions
COPD
Percentage
0
20
40
60
0
2
4
6
8
Turbohaler
DuoResp