Effectiveness of Dymista® in asthma patients with rhinitis

A pre-post cohort study evaluating the effectiveness of a novel combination therapy of antihistamine and intranasal corticosteroid (Dymista®) on asthma-related outcomes among patients with allergic rhinitis and asthma multi-morbidity

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1.0 Content Page

PROTOCOL SIGNATURE PAGE

Study Name: A pre-post cohort study evaluating the effectiveness of a novel combination therapy of antihistamine and intranasal corticosteroid (Dymista) on asthma-related outcomes among patients with allergic rhinitis and asthma multi-morbidity.

Study Number: OPRI-1824

The Sponsor and Chief Investigator have approved the protocol version v.1.0 dated DD/MM/YYYY, and confirm hereby to conduct the study according to the protocol and the Sponsor's SOPs, the current version of the World Medical Association Declaration of Helsinki, International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and the applicable regulatory requirements.

Chief Investigator:

Professor David Brendan Price		29/05/2019
Name	Signature	Date

2.0 Background

Allergic rhinitis is a symptomatic disorder of the nose induced by an immunoglobulin E (IgE)-mediated inflammation of the membranes lining the nose after exposure to allergens [1]. This symptomatic disorder is a global health problem that causes major illness and disability worldwide, because its affects social life, sleep, school and work [2]. Moreover, it has been recognised that allergic rhinitis comprises more than the classical symptoms of sneezing, rhinorrhoea and nasal obstruction.

Since the nasal airways are an integral part of the respiratory tract [1, 3-5], allergic rhinitis and asthma are often comorbidities. Over 80% of asthma patients have rhinitis and 10–40% of patients with rhinitis have asthma [1, 6]. For patients with co-morbid asthma, the presence of allergic rhinitis also predicts poor asthma control [7], suggesting the concept of 'one airway one disease', although there are differences between rhinitis and asthma [8,9] This concept of 'one airway one disease' emphasises the need to treat rhinitis and asthma symptoms concomitantly [1].

Since June 2013, a combination therapy comprising an intranasal antihistamine (azelastine hydrochloride) and intranasal corticosteroid (fluticasone propionate), Dymista®, has been approved in the United Kingdom (UK) for treatment of rhinitis [10]. Several studies have shown that patients with moderate-to-severe seasonal allergic rhinitis and those with chronic rhinitis treated with Dymista® provided relief from nasal symptoms and had rapid sustained symptom control compared to the ones treated with either intranasal antihistamine or glucocorticoid as a monotherapy [11-16].

Next to this, Dymista® has been shown to reduce healthcare costs in patients with comorbid rhinitis and asthma [17]. However, based on combined data from three pivotal randomised, double-blind clinical trials, patients with mild intermittent asthma who were treated with Dymista® had similar improvements in their nasal symptoms scores and health-related quality of life scores compared with scores for patients not diagnosed with asthma [18].

Currently, a single centre, double-blind, placebo-controlled, adaptive design, cross-over trial is assessing the additive effects of using Dymista® on airway hyper-responsiveness. Compared to the previous study, this trial included patients with persistent asthma and allergic rhinitis [19]. Findings of this trail will be presented in the near future.

Although all data about the effectiveness of Dymista® are not available, it has been hypothesised that the combination therapy of intranasal corticosteroids and antihistamines may improve the asthma-related outcomes in patients with allergic rhinitis and asthma multi-morbidity. However, the impact of initiating Dymista® therapy on asthma-related outcomes in patients with allergic rhinitis and asthma multi-morbidity in daily practice has not yet been investigated.

3.0 Study Aims & Objectives

3.1 Study Aim

The aim of the study is to examine the effectiveness of a novel combination therapy of antihistamine and intranasal corticosteroid (Dymista®) for allergic rhinitis in terms of improving asthma control in patients with allergic rhinitis and asthma multi-morbidity

3.2 Study Objective

To examine the effectiveness of Dymista® in terms of improving asthma control by comparing the number of acute respiratory events and other measures of asthma control in the year before and after initiation of Dymista®

4.0 Methods

4.1 Study Cohort and Exposure

The study cohort comprises patients with active asthma, aged ≥12 years, who initiate Dymista® for treatment of allergic rhinitis. The date of the first prescription of Dymista® is the date of initiation.
Dymista® is the combination therapy of antihistamine (azelastine hydrochloride) and intranasal corticosteroid (fluticasone propionate).
Active asthma will be defined as a diagnostic read code for asthma ever recorded prior to the date of initiation of Dymista® and ≥1 prescription for asthma therapy (reliever and/or controller medication) in the year prior to and including the date of initiation of Dymista®. A list of diagnostic read codes for asthma and product codes for Dymista® are presented in Appendix 8.1 and 8.2, respectively.

4.2 Study Design

A pre-post cohort study will be carried out using a database containing data from UK general practitioners, including asthma patients, aged ≥12 years who initiated Dymista® for treatment of allergic rhinitis (Figure 1).

- **Index prescription date (IPD):** is defined as the date at which patients with active asthma receive the first prescription for the combination therapy of antihistamine (azelastine hydrochloride) and intranasal corticosteroid (fluticasone propionate) (Dymista®).

- **Baseline period or pre-initiation period:** is used to describe patient characteristics, and to measure the change in asthma outcomes from baseline to outcome year. The baseline period is at least one-year prior to and including the IPD.
- **Outcome period or post-initiation period:** all patients will be followed one-year after the IPD for measurement of outcome variables.

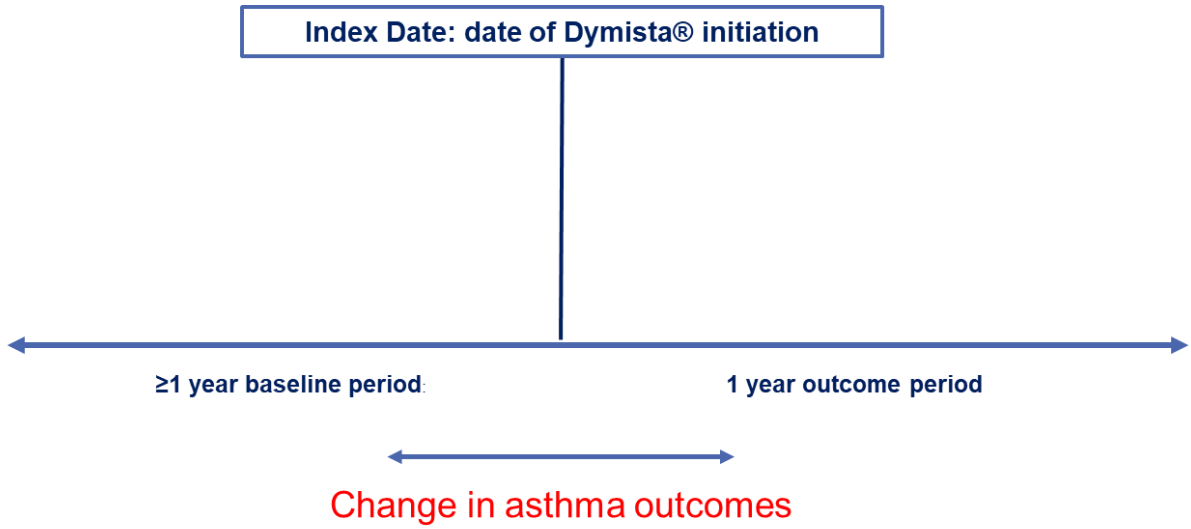

Figure 1 A pre-post design within a cohort of patients with allergic rhinitis and asthma multi-morbidity, aged ≥12 years who initiated Dymista®

4.3 Subgroup analyses

In order to evaluate asthma outcomes based on real-life prescriptions for allergic rhinitis prior to initiation of Dymista®, the following sub-groups will be defined and analysed:

1. *Intranasal corticosteroid switchers* will be defined as patients with another type of nasal steroid prescribed in the last 45 days before initiation of Dymista®
2. *Intranasal corticosteroid naïve patients* will be defined as patients who had never had nasal steroids prescribed before initiation of Dymista®

Other potential sub-groups will be defined following baseline characterisation of patients initiating Dymista® in UK clinical practice.

4.4 Study Population

4.4.1 Inclusion Criteria

- Initiation of Dymista® (patients receive ≥1 prescription of Dymista® any time);
- Diagnosis of asthma ever: diagnostic read code ever following the Quality Outcomes Framework (QOF)[*] ;
- Age ≥12 years at IPD;
- Active asthma, defined as ≥1 prescription for an inhaler (reliever or controller) in the year prior to and including IPD
- Continuous electronic medical data for ≥1 year prior to IPD
- ≥1 year of electronic medical data after IPD

4.4.2 Exclusion Criteria

- Patients with only a diagnosis of chronic obstructive pulmonary disease (COPD); QOF read codes).
- Patients with maintenance oral corticosteroids in the year prior to initiation of Dymista®

4.5 Data Sources

This study will use data from the continuous electronic health record database, Optimum Patient Care Research Database (OPCRD). The OPCRD, a clinical research database contains records of approximately 5.8 million patients from over 700 primary care centres across the UK (http://opcrd.co.uk/). The database contains anonymised routine, patient-level diagnostic, clinical and prescribing information extracted via dedicated software interface. OPCRD has received a favourable opinion from the NHS Health Research Authority for anonymous research use (REC reference: 15/EM/0150). Governance is provided by the Anonymised Data Ethics and Protocols Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG, http://www.effectivenessevaluation.org/) to govern the standard of research conducted on internationally recognised databases.

[*] register of patients with asthma, which GP practices in the UK maintain for the Quality Outcomes Framework (see http://www.hscic.gov.uk/qof for details).

5.0 Study variables

5.1 Baseline characteristics

Patient characteristics in the baseline period will be described for the variables listed below.

Demographics

- Age at IPD, years, mean (standard deviation (SD)), median (interquartile range (IQR)) and categorised as:
    - 12– 17
    - 18 – 64
    - ≥65, n (%)
- Sex, n (%)
- Smoking Status closest to IPD and including within 5 years[†], n (%)
    - Current smokers
    - Former smokers
    - Never smokers
- Body Mass Index (BMI), kg/m^2 closest to and including IPD within 5 years[‡], mean (SD) and mean (IQR), and categorised as:
    - Underweight, <18.5
    - Normal Weight, ≥18.5 and <25
    - Overweight, ≥25 and <30
    - Obese, ≥30

Comorbidities

At least one diagnostic read code prior to and including IPD, n (%) for:

- Eczema diagnosis
    - Never
    - Active[§]
    - Ever, not active
- Nasal polyps (ever/never)
- Chronic rhinosinusitis (ever/never)
- Gastroesophageal reflux disease (GERD) (ever/never)

[†] Recording closest to ID within a window of 5 years prior to IPD
[‡] Recording closest to ID within a window of 5 years prior to IPD
[§] 'Active' refers to those for which a diagnosis or active treatment was recorded in the baseline year. 'Ever' refers to diagnostic Read code at any time before or during the baseline period

- Diabetes Mellitus (ever/never)
- Osteoporosis (ever/never)
- Hypertension (ever/never)
- Cardiovascular disease (ever/never)
- Any cardiovascular disease, and more specific diagnoses:
    - Ischaemic heart disease
    - Heart failure
    - Myocardial infarction
- Chronic kidney disease (ever/never), stage 3-5
- Depression/anxiety (ever/never)
- Pneumonia (ever/never)
- Obstructive Sleep apnoea (ever/never)
- Charlson co-morbidity index: based on diagnoses (ever/never) and will be categorised as:
    - ≤1
    - 2-4
    - ≥5

Disease control and severity indicators in the baseline year

- Rhinitis treatment (yes/no), n (%)
    - Oral antihistamines (AH)
    - Intranasal corticosteroids (INCS)
    - Leukotriene receptor antagonist (LTRA) prescribed during a consultation for rhinitis
    - Oral decongestants
    - Non-steroidal nasal sprays defined by BNF section 12.2, including:
        - Antihistamines
        - Decongestants
        - Chromones
        - Ipratropium bromide
        - Saline
    - Eye drops for allergic conjunctivitis,
- Age of asthma onset (where data is available), year, mean (SD) and median (IQR)
- Blood eosinophil count in steady state of the disease (no steroid use 2 weeks prior to measurement) closest to IPD within 5 years[**], mean (SD) and median (IQR), and categorised as:

[**] Recording closest to IPD within a window of 5 years prior to IPD

- $<0.25 \times 10^9$/L
- $\geq 0.25 \times 10^9$/L

- Asthma control:
  - Risk Domain asthma control (RDAC) (yes/no), defined as absence of all of the following events in the baseline year
    - Acute respiratory event (primary outcome as defined above), *and*
    - Asthma-related outpatient department visit [20]
  - Overall asthma control (OAC) (yes/no), defined as absence of all of the following events in the baseline year:
    - Acute respiratory event (primary outcome), *and*
    - Asthma-related outpatient department visit, *and*
    - Average daily dose of SABA >200 µg salbutamol/ >500 µg terbutaline [20]
- Asthma treatment:
  - GINA steps of asthma management, n (%) (Appendix 8.3)[††]
  - Average daily dose of inhaled corticosteroids (ICS) consumed, beclomethasone dipropionate (BDP) equivalent in µg/day (0, >0-≤250, >250-500, >500), n (%) (Appendix 8.4)
  - Last intended dose of ICS in the baseline year, beclometasone dipropionate equivalent in µg/day, mean (SD) and median (IQR), n (%)
  - Total number of ICS inhalers, (0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, ≥12), n (%)
  - Any prescription of treatment (yes/no), n (%)
    - ICS
    - long-acting muscarinic antagonist (LAMA)
    - short-acting beta agonist (SABA)
    - short-acting muscarinic antagonist (SAMA)
    - ICS + long-acting beta agonist (LABA)
    - LTRA
    - Theophylline
    - Anti-IgE treatment (Omalizumab (Xolair®)
    - Anti-Interleukin-5 (IL-5) treatment (Mepolizumab)
    - IL-4 treatment
    - IL-13 treatment
    - Macrolides
    - Sodium cromoglicate

[††] From the Global Strategy for Asthma Management and Prevention, 2018. Available from www.ginasthma.org

        - Nedocromil
    - Add-on treatment prescriptions (≥1 prescription in baseline year (yes/no) on top of ICS), n (%):
        - LABA
        - Theophylline
        - LTRA
        - LAMA
        - Anti-IgE treatment
        - IL-5 treatment
        - IL-4 treatment
        - IL-13 treatment
        - Macrolides
    - Reliever medications: average daily dose of SABA, salbutamol equivalent in µg/day, mean (SD) and median (IQR) and categorised as 0, 1-100, 101-200, 201-300, 301-400, >400, n (%)
    - The number of acute OCS courses, categorised as 0, 1, 2, 3 and ≥4, n (%)
    - ICS and ICS + LABA adherence, measured as, n (%):
      Medication Possession Ratio (MPR), i.e. the Refill rate (%) = (Total ICS pack days / Number of prescription days) * 100, using the following cut points
        - <50%
        - 50 to <80%
        - ≥80%, n (%)
- Lung function, in terms of percent predicted Peak Expiratory Flow (PEF), last recorded value closest to IPD prior to 5 years (>18 years old) or last recorded value closest to IPD prior to 2 years (15-18 years old), categorised as, n (%):
    - Green (≥80)
    - Yellow (≥50)
    - Red (<50)[‡‡], n (%)
- Forced Expiratory Flow in one second (FEV_1) predicted, last recorded value closest to IPD prior to 5 years, described as mean (SD) and median (IQR) and categorised as, n (%):
    - <30%
    - 30 – 49%
    - 50 – 79%

‡‡ Peak flow readings are classified into 3 zones of measurement (green, yellow and red) according to American Lung Association.

    - ≥80%
- FEV_1/FVC ration, last recorded value closest to IPD prior to 5 years, described as mean (SD) and median (IQR)
- The number of respiratory-related hospital admissions, mean (SD) and median (IQR), and will be presented as:
    - 0
    - 1
    - ≥2
- The number of asthma-related emergency attendance, mean (SD) and median (IQR), and will be presented as:
    - 0
    - 1
    - ≥2

5.2 Study Outcomes

The primary, secondary and exploratory study outcomes will be assessed in both baseline and outcome year.

5.2.1 Primary outcome

Change in the number of acute respiratory events (an ordinal endpoint), defined as occurrence of any of the following events separately or together (occurrences within 14 days of each other are considered to belong to the same event):

- Asthma-related hospital admission, *and/or*
- Asthma-related Accident and Emergency (A&E) attendance, *and/or*
- Acute course of oral corticosteroids, *and/or*
- Antibiotics course with evidence of respiratory consultation,

and will be presented as n (%):

- 0
- 1
- 2
- 3
- 4
- 5
- 6

- 7
- 8
- ≥9 (categories will be presented as long as we have ≥5 patients)

5.2.2 Secondary outcome

1. Change in the number of asthma exacerbations (ordinal end point), defined as the occurrence of any of the following events separately or together, based on the American Thoracic Society/European Respiratory Society (ATS/ERS) Force definition (occurrences within 14 days of each other are considered to belong to the same event):
   - Asthma-related hospital admission, *and/or*
   - Asthma-related A&E attendance, *and/or*
   - Acute course of oral corticosteroids,

and will be presented as n (%):

- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- ≥9 (categories will be presented as long as we have ≥5 patients)

5.2.3 Exploratory outcomes

1. Change in asthma treatment step, following the GINA guidelines (GINA step 1, 2, 3, 4 and 5)
2. Change in average daily dose of SABA prescribed (Salbutamol equivalent)[§§]
3. Change in Risk Domain Asthma Control (yes/no) (see definition in paragraph 5.1)
4. Change in Overall Asthma Control (yes/no), (see definition in paragraph 5.1)
5. Change in the control of asthma symptoms, using the following variables:
   a. Three Royal College of Physicians (RCP) questions, which are part of the annual review of patients with asthma in the UK within the QOF framework (Appendix 8.6) and >2 puffs of SABA per week

[§§] Average daily dose: (number of inhalers prescribed in year * doses in pack) / 365) * mcg strength)

b. GINA control status, categorised as well-controlled, partly controlled, uncontrolled (Appendix 8.7)

6.0 Statistical Analysis

6.1 Baseline characteristics

The following descriptive statistics will be used for all baseline variables:

1. Frequency statistics for categorical variables: number and percentage;
2. Mean (SD) and median (IQR; 25th and 75th percentiles) for continuous variables and categorical distribution for count variables;
3. Dichotomous variable for variables yes vs. no (e.g. presence of comorbidities)

The number and percentage of the population with non-missing information will be described in case of missing data. Data will be presented for patients with non-missing information.

6.2 Confounding assessment

The self-controlled study design ensures that patient characteristics that are stable over the study period cannot affect the associations of interest. However, it is still possible that some characteristics, and especially those affecting asthma control, might be different from the baseline to the outcome period. In case e.g. the initiation of Dymista is associated with a change in asthma therapy, we cannot assess the true effect that Dymista initiation has on asthma outcomes, without taking such factors into account. Potential confounders will be assessed at a theoretical level through expert opinion and by a data driven technique using a balance statistic, the standardised mean differences. Expert opinion will decide what set of baseline characteristics will be adjusted for and/or evaluated for their balance between the baseline and outcome periods. Identified confounders will be introduced into the models iteratively to avoid collinearity by verifying variance inflation.

6.3 Outcome Analyses

Count outcomes: To examine the effectiveness of Dymista® on asthma-related outcomes, the number of, for instance, acute respiratory events in the year after IPD will be compared with the number of events in the year prior to IPD by the Wilcoxon signed rank test (for paired data). A conditional negative binomial regression will be used in case we need to adjust for confounders. The result will be reported as rate ratio and corresponding 95% confidence interval (CI).

Binary outcomes: For outcomes such as the exploratory outcomes of asthma control ('controlled' vs. 'uncontrolled'), the McNemar's test will be performed. In case of controlling for confounders, a conditional logistic regression will be used. Findings will be reported as odds ratio (OR) and 95% CI.

Multinomial outcomes: For outcomes with more than two categories (e.g. Gina step), conditional multinomial logistic regression will be used. For this analysis the relative risk ratio (RRR) and 95% CI will be presented.

6.4 Feasibility: OPCRD

A feasibility assessment applying the inclusion/exclusion criteria has been conducted in the OPCRD data, resulting in a total of at least 1,188 eligible patients with allergic rhinitis and asthma multi-morbidity, aged ≥12 years who initiated Dymista®. Ever recorded information on the exploratory outcome 'severity of asthma symptoms (RCP-questions)' are estimated to be available for more than 80% of patients.

6.5 Statistical power analysis

We have used the Wilcoxon's sum rank test for paired data to calculate the number of patients we need to detect a difference in the number of acute respiratory events between before and after initiation of Dymista® with an effect size of 0.1 and 90% statistical power at a significance level of 0.05. We will need 1,103 patients in our study.

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Table 1. Characteristics of patients with allergic rhinitis and asthma multi-morbidity before initiation of Dymista®

	Patients with allergic rhinitis and asthma multi-morbidity N = 1,188
Age, year, n (%)	
Mean (SD)	
Median (IQR)	
12 – 17	
18 – 64	
≥65	
Sex, n (%)	
Men	
Women	
Smoking status, n (%)	
Non-missing, n (%)	
Current smokers	
Former smokers	
Non-smokers	
Body Mass Index, kg/m^2, n (%)	
Non-missing, n (%)	
Mean (SD)	
Median (IQR)	
Underweight: <18.5	
Normal weight: 18.5 - <25	
Overweight: 25 - <30	
Obese: >30	
Presence of comorbidities ever prior to prescription index date, n (%)	
Eczema diagnosis	
Never	
Active	
ever, not active	

	Patients with allergic rhinitis and asthma multi-morbidity N = 1,188
Chronic Obstructive Pulmonary Disease	
Never	
Active	
ever, not active	
Nasal polyps	
Chronic rhinosinusitis	
Gastroesophageal reflux disease	
Diabetes Mellitus	
Osteoporosis	
Hypertension	
Cardiovascular disease	
Ischaemic heart disease	
Heart failure	
Myocardial infarction	
Chronic kidney disease, stage 3 – 5	
Depression/ Anxiety	
Pneumonia	
Obstructive sleep apnoea	
Charlson co-morbidity index, n (%)	
≤1	
2 – 4	
≥5	

SD: standard deviation; IQR: interquartile range; index prescription date: the date at which patients with active asthma receive the first prescription for Dymista®.

Table 2. Disease control and severity indicators among patients with allergic rhinitis and asthma multi morbidity in the year before initiation of Dymista®

Disease control and severity indicators	**Patients with allergic rhinitis and asthma multi-morbidity N = 1,188**
Rhinitis treatment, n (%)	
Oral antihistamines	
Intranasal corticosteroids	
LTRA*	
Oral decongestants	
Non-steroidal nasal sprays**	
Eye drops for allergic conjunctivitis	
Age of asthma onset, year (where data is available)	
Non-missing, n (%)	
Mean (SD)	
Mean (IQR)	
Blood eosinophil count measured at state of the disease (no steroid use 2 weeks prior to measurement) closest to IPD within 5 years, n (%)	
Non-missing	
Mean (SD)	
Median (IQR)	
$<0.25 \times 10^9$/L	
$\geq 0.25 \times 10^9$/L	
Asthma treatment, n (%)	
GINA treatment step	
1	
2	
3	
4	
5	
Total number of ICS inhalers prescribed, n(%)	
Mean (SD)	
Median (IQR)	

Number of ICS inhalers prescribed, n (%)	
0	
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
≥12	
Average daily dose of ICS consumed, beclometasone dipropionate equivalent in µg/day, n (%)	
Mean (SD)	
Median (IQR)	
None: 0	
Low dose: >0 - ≤250‡	
Medium dose: >250 - ≤500	
High dose: >500	
Last intended dose of ICS beclometasone dipropionate equivalent in µg/day	
Mean (SD)	
Median (IQR)	
Any prescription of treatment (yes), n (%)	
ICS	
LAMA	
SABA	
SAMA	
ICS + LABA	
LTRA	
Theophylline	
Anti-IgE treatment	

Anti-Interleukin-5 (IL-5) treatment	
IL-4 treatment	
IL-13 treatment	
Macrolides	
Sodium cromoglicate	
Nedocromil	
Add on treatment prescriptions on top of ICS, n(%)	
LABA	
LAMA	
LTRA	
Theophylline	
Anti-IgE treatment	
IL-5 treatment	
IL-4 treatment	
IL-13 treatment	
Macrolides	
Acute OCS courses, n (%)	
0	
1	
2	
3	
≥4	
ICS adherence, %, n (%)‡‡	
<50	
50 - <80	
≥80	
ICS + LABA adherence, %, n (%)‡‡	
<50	
50 - <70	
70 - <80	
≥80	
Peak expiratory flow§, n (%)	
Non-missing, n (%)	
Mean (SD)	
Median (IQR)	

Green	
Yellow	
Red	
FEV_1 % predicted, n (%)	
Non-missing, n (%)	
Mean (SD)	
Median (IQR)	
<30	
30 – 49	
50 – 79	
≥80	
FEV_1/FVC ratio	
Non-missing, n (%)	
Mean (SD)	
Median (IQR)	
Respiratory-related hospital admissions, n (%)	
Mean (SD)	
Median (IQR)	
0	
1	
≥2	
Asthma-related ED attendance, n (%)	
Mean (SD)	
Median (IQR)	
0	
1	
≥2	

LTRA: leukotriene receptor antagonist; IPD: index prescription date (date of initiation of Dymista®); SD: standard deviation; IQR: interquartile range; ICS: inhaled corticosteroids; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonists; SABA: short-acting beta agonist; SAMA: short-acting muscarinic antagonists; ED: emergency department; FEV^1: Forced Expiratory Flow in one second; FVC: Forced Vital Capacity

*prescribed during a consultation for rhinitis

**including antihistamines, decongestants, chromones, ipratropium bromide and saline

‡Based on the Global Initiative for Asthma definitions of low, medium and high dose of inhaled corticosteroids for adolescents and adults.

‡‡Adherence calculated by the Medication Possession Ratio, i.e. the refill rate (%) = (total ICS pack days/number of prescription days) * 100

§Last recorded value closest to IPD prior to 5 years (>18 years old) or last recorded value closest to IPD prior to 2 years (15-18 years old). Peak flow reading are classified into 3 zones of measurement (green, yellow and red) according to American Lung Association.

Table 3. Change in asthma-related outcomes in the period before and after initiation of Dymista® among patients with allergic rhinitis and asthma multi-morbidity

Asthma-related outcomes	**Patients at pre-initiation Dymista® N = 1,188**	**Patients at post-initiation Dymista® N = 1,188**	**P-value[§]**
Primary outcome			
Number of acute respiratory events, n (%)			
0			
1			
2			
≥3			
Secondary outcome			
Number of asthma exacerbations, based on ATS/ERS Force definition, n (%)			
0			
1			
2			
≥3			
Exploratory outcomes			
Asthma treatment: GINA step, n (%)			
1			
2			
3			
4			
5			
Stable GINA step			
Any step-up in GINA step			
Any step-down in GINA step			
Any step-up/step-down GINA step			
Average daily dose of SABA prescribed, salbutamol equivalent in µg/day, n (%)			

0			
>0 – 100			
101 – 200			
201 – 300			
301 – 400			
>400			
Risk domain asthma control*, n (%)			
controlled			
uncontrolled			
Overall asthma control**, n (%)			
controlled			
uncontrolled			
Control of asthma symptoms, defined by:			
1.Three Royal College of Physicians (RCP) questions‡			
Response to one of the following questions, n (%)			
Have you had difficulty sleeping because of your asthma symptoms in the last month?			
Non-missing, n(%)			
Yes			
No			
Have you had your usual symptoms during the day in the last month?			
Non-missing, n(%)			
Yes			
No			
Has your asthma interfered with your usual activities in the last month?			
Non-missing, n (%)			
Yes			
No			

The number of "yes" responses to RCP questions, n (%)			
Non-missing			
0			
1			
2			
3			
2. >2 puffs of SABA per week, n (%)			
Gina level control, n (%)‡‡			
Non-missing			
controlled			
partly controlled			
uncontrolled			

ATS/ERS: American Thoracic Society/European Respiratory Society; SABA: short-acting beta agonist

*Risk Domain asthma control (RDAC) (yes/no), defined as absence of any of the following events in the baseline year

1. Acute respiratory event (primary outcome as defined above), *and*
2. Asthma-related outpatient department visit [20]

**Overall asthma control (OAC) (yes/no), defined as absence of any of the following events in the baseline year:

1. Acute respiratory event (primary outcome), *and*
2. Asthma-related outpatient department visit, *and*
3. Average daily dose of SABA >200 µg salbutamol/ >500 µg terbutaline [20]

‡Response "yes" to one of the three Royal College of Physicians (RCP) questions, which are part of the annual review of patients with asthma in the UK within the QOF framework

‡‡Poor asthma symptom control is defined as 3 out of 4 of the following:

1) "yes" to 3 RCP questions
2) >2 puffs of SABA per week

Controlled = none of the questions have a "yes" response; Partly controlled = 1-2 of the questions have a "yes" response; Uncontrolled = 3-4 of the questions have a "yes" response

§the differences between pre-initiation and post-initiation of each outcome will be calculated by the Wilcoxon signed-ranks test for categorical outcomes and the McNemar test for dichotomous outcomes

Table 4. Change in asthma-related outcomes in the period before and after initiation of Dymista® among patients with allergic rhinitis and asthma multi-morbidity

Asthma-related outcomes		**P-value**
Primary outcome		
Change in the number of acute respiratory events	**RR (95% CI)**	
Secondary outcome		
Change in the number of asthma exacerbations, based on ATS/ERS Force definition	**RR (95% CI)**	
Exploratory outcomes		
Asthma treatment: change in GINA step	**OR (95% CI)**	
No change in GINA step	Reference	
Change in GINA step		
Average daily dose of SABA prescribed, salbutamol equivalent in µg/day	**RR (95% CI)**	
Risk domain asthma control*	**OR (95% CI)**	
controlled	Reference	
uncontrolled		
Overall asthma control**	**OR (95% CI)**	
controlled	Reference	
uncontrolled		
GINA level control§	**RRR (95% CI)**	
controlled	Reference	
partly controlled		
uncontrolled		

ATS/ERS: American Thoracic Society/European Respiratory Society; SABA: short-acting beta agonist; RR: rate ratio; CI: confidence interval; OR: odds ratio; RRR: relative risk ratio

[*]Risk Domain asthma control (RDAC) (yes/no), defined as absence of any of the following events in the baseline year

1. Acute respiratory event (primary outcome as defined above), *and*
2. Asthma-related outpatient department visit [20]

[**]Overall asthma control (OAC) (yes/no), defined as absence of any of the following events in the baseline year:

1. Acute respiratory event (primary outcome), *and*
2. Asthma-related outpatient department visit, *and*
3. Average daily dose of SABA >200 µg salbutamol/ >500 µg terbutaline [20]

[§]Poor asthma symptom control is defined as 3 out of 4 of the following:

1) "yes" to 3 Royal College of Physicians (RCP) questions (questions are described in table 3)
2) >2 puffs of SABA per week

Controlled = none of the questions have a "yes" response; Partly controlled = 1-2 of the questions have a "yes" response; Uncontrolled = 3-4 of the questions have a "yes" response

Table 5. Characteristics of patients with allergic rhinitis and asthma multi-morbidity and who switched to intranasal corticosteroids before initiation of Dymista®*

	Patients with allergic rhinitis and asthma multi-morbidity who switched to intranasal corticosteroids* **N =**
Age, year, n (%)	
Mean (SD)	
Median (IQR)	
12 – 17	
18 – 64	
≥65	
Sex, n (%)	
Men	
Women	
Smoking status, n (%)	
Non-missing, n (%)	
Current smokers	
Former smokers	
Non-smokers	
Body Mass Index, kg/m^2, n (%)	
Non-missing, n (%)	
Mean (SD)	
Median (IQR)	
Underweight: <18.5	
Normal weight: 18.5 - <25	
Overweight: 25 - <30	
Obese: >30	
Presence of comorbidities ever prior to prescription index date, n (%)	
Eczema diagnosis	

	Patients with allergic rhinitis and asthma multi-morbidity who switched to intranasal corticosteroids* **N =**
Never	
Active	
ever, not active	
Chronic Obstructive Pulmonary Disease	
Never	
Active	
ever, not active	
Nasal polyps	
Chronic rhinosinusitis	
Gastroesophageal reflux disease	
Diabetes Mellitus	
Osteoporosis	
Hypertension	
Cardiovascular disease	
Ischaemic heart disease	
Heart failure	
Myocardial infarction	
Chronic kidney disease, stage 3 – 5	
Depression/ Anxiety	
Pneumonia	
Obstructive sleep apnoea	
Charlson co-morbidity index, n (%)	
≤1	
2 – 4	
≥5	

SD: standard deviation; IQR: interquartile range; index prescription date: the date at which patients with active asthma receive the first prescription for Dymista®

* Patients with another type of intranasal steroid prescribed in the last 45 days before initiation of Dymista®

Table 6. Disease control and severity indicators among patients with allergic rhinitis and asthma multi morbidity and who switched to intranasal corticosteroids[§§] in the year before initiation of Dymista®

Disease control and severity indicators	**Patients with allergic rhinitis and asthma multi-morbidity who switched to intranasal corticosteroids[§§]** **N =**
Rhinitis treatment, n (%)	
Oral antihistamines	
Intranasal corticosteroids	
LTRA[*]	
Oral decongestants	
Non-steroidal nasal sprays[**]	
Eye drops for allergic conjunctivitis	
Age of asthma onset, year (where data is available)	
Non-missing, n (%)	
Mean (SD)	
Mean (IQR)	
Blood eosinophil count measured at state of the disease (no steroid use 2 weeks prior to measurement) closest to IPD within 5 years, n (%)	
Non-missing	
Mean (SD)	
Median (IQR)	
$<0.25 \times 10^9$/L	
$\geq 0.25 \times 10^9$/L	
Asthma treatment, n (%)	
GINA treatment step	
1	
2	
3	
4	

5	
Total number of ICS inhalers prescribed, n(%)	
Mean (SD)	
Median (IQR)	
Number of ICS inhalers prescribed, n (%)	
0	
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
≥12	
Average daily dose of ICS consumed, beclometasone dipropionate equivalent in µg/day, n (%)	
Mean (SD)	
Median (IQR)	
None: 0	
Low dose: >0 - ≤250‡	
Medium dose: >250 - ≤500	
High dose: >500	
Last intended dose of ICS beclometasone dipropionate equivalent in µg/day	
Mean (SD)	
Median (IQR)	
Any prescription of treatment (yes), n (%)	
ICS	
LAMA	
SABA	
SAMA	

ICS + LABA	
LTRA	
Theophylline	
Anti-IgE treatment	
Anti-Interleukin-5 (IL-5) treatment	
IL-4 treatment	
IL-13 treatment	
Macrolides	
Sodium cromoglicate	
Nedocromil	
Add on treatment prescriptions on top of ICS, n(%)	
LABA	
LAMA	
LTRA	
Theophylline	
Anti-IgE treatment	
IL-5 treatment	
IL-4 treatment	
IL-13 treatment	
Macrolides	
Acute OCS courses, n (%)	
0	
1	
2	
3	
≥4	
ICS adherence, %, n (%)‡‡	
<50	
50 - <80	
≥80	
ICS + LABA adherence, %, n (%)‡‡	
<50	
50 - <70	
70 - <80	
≥80	

Peak expiratory flow[§], n (%)	
Non-missing, n (%)	
Mean (SD)	
Median (IQR)	
Green	
Yellow	
Red	
FEV_1 % predicted, n (%)	
Non-missing, n (%)	
Mean (SD)	
Median (IQR)	
<30	
30 – 49	
50 – 79	
≥80	
FEV_1/FVC ratio	
Non-missing, n (%)	
Mean (SD)	
Median (IQR)	
Respiratory-related hospital admissions, n (%)	
Mean (SD)	
Median (IQR)	
0	
1	
≥2	
Asthma-related ED attendance, n (%)	
Mean (SD)	
Median (IQR)	
0	
1	
≥2	

LTRA: leukotriene receptor antagonist; IPD: index prescription date (date of initiation of Dymista®); SD: standard deviation; IQR: interquartile range; ICS: inhaled corticosteroids; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonists; SABA: short-acting beta agonist; SAMA: short-acting muscarinic antagonists; ED: emergency department; FEV^1: Forced Expiratory Flow in

one second; FVC: Forced Vital Capacity

[*]prescribed during a consultation for rhinitis

[**] including antihistamines, decongestants, chromones, ipratropium bromide and saline

[‡]Based on the Global Initiative for Asthma definitions of low, medium and high dose of inhaled corticosteroids for adolescents and adults.

[‡‡]Adherence calculated by the Medication Possession Ratio, i.e. the refill rate (%) = (total ICS pack days/number of prescription days) * 100

[§]Last recorded value closest to IPD prior to 5 years (>18 years old) or last recorded value closest to IPD prior to 2 years (15-18 years old).Peak flow reading are classified into 3 zones of measurement (green, yellow and red) according to American Lung Association.

[§§]Patients with another type of intranasal steroid prescribed in the last 45 days before initiation of Dymista®

Table 7. Change in asthma-related outcomes in the period before and after initiation of Dymista® among patients with allergic rhinitis and asthma multi-morbidity and who switched to intranasal corticosteroids[§§] before Dymista® initiation

Asthma-related outcomes	Patients at pre-initiation Dymista® N =	Patients at post-initiation Dymista® N =	P-value[§]
Primary outcome			
Number of acute respiratory events, n (%)			
0			
1			
2			
≥3			
Secondary outcome			
Number of asthma exacerbations, based on ATS/ERS Force definition, n (%)			
0			
1			
2			
≥3			
Exploratory outcomes			
Asthma treatment: GINA step, n (%)			
1			
2			
3			
4			
5			
Stable GINA step			
Any step-up in GINA step			
Any step-down in GINA step			
Any step-up/step-down GINA step			

Average daily dose of SABA prescribed, salbutamol equivalent in µg/day, n (%)			
Non-missing			
0			
>0 – 100			
101 – 200			
201 – 300			
301 – 400			
>400			
Risk domain asthma control*, n (%)			
controlled			
uncontrolled			
Overall asthma control**, n (%)			
controlled			
uncontrolled			
Control of asthma symptoms, defined by:			
1.Three Royal College of Physicians (RCP) questions‡			
Response to one of the following questions, n (%)			
Have you had difficulty sleeping because of your asthma symptoms in the last month?			
Non-missing, n(%)			
Yes			
No			
Have you had your usual symptoms during the day in the last month?			
Non-missing, n(%)			
Yes			
No			
Has your asthma interfered with your usual activities in the last month?			
Non-missing, n (%)			

Yes			
No			
The number of "yes" responses to RCP questions, n (%)			
Non-missing			
0			
1			
2			
3			
2. >2 puffs of SABA per week, n (%)			
Gina level control, n (%)‡‡			
Non-missing			
controlled			
partly controlled			
uncontrolled			

ATS/ERS: American Thoracic Society/European Respiratory Society; SABA: short-acting beta agonist

*Risk Domain asthma control (RDAC) (yes/no), defined as absence of any of the following events in the baseline year

1. Acute respiratory event (primary outcome as defined above), *and*
2. Asthma-related outpatient department visit [20]

**Overall asthma control (OAC) (yes/no), defined as absence of any of the following events in the baseline year:

1. Acute respiratory event (primary outcome), *and*
2. Asthma-related outpatient department visit, *and*
3. Average daily dose of SABA >200 µg salbutamol/ >500 µg terbutaline [20]

‡Response "yes" to one of the three Royal College of Physicians (RCP) questions, which are part of the annual review of patients with asthma in the UK within the QOF framework

‡‡Poor asthma symptom control is defined as 3 out of 4 of the following:

1) "yes" to 3 RCP questions
2) >2 puffs of SABA per week

Controlled = none of the questions have a "yes" response; Partly controlled = 1-2 of the questions have a "yes" response; Uncontrolled = 3-4 of the questions have a "yes" response

§the differences between pre-initiation and post-initiation of each outcome will be calculated by the Wilcoxon signed-ranks test for categorical outcomes and the McNemar test for dichotomous outcomes

[§§]Patients with another type of intranasal steroid prescribed in the last 45 days before initiation of Dymista®

Table 8. Change in asthma-related outcomes in the period before and after initiation of Dymista® among patients with allergic rhinitis and asthma multi-morbidity and who switched to intranasal corticosteroids[§§] before Dymista® initiation

Asthma-related outcomes		**P-value**
Primary outcome		
Change in the number of acute respiratory events	**RR (95% CI)**	
Secondary outcome		
Change in the number of asthma exacerbations, based on ATS/ERS Force definition	**RR (95% CI)**	
Exploratory outcomes		
Asthma treatment: change in GINA step	**OR (95% CI)**	
No change in GINA step	Reference	
Change in GINA step		
Average daily dose of SABA prescribed, salbutamol equivalent in µg/day	**RR (95% CI)**	
Risk domain asthma control[*]	**OR (95% CI)**	
controlled	Reference	
uncontrolled		
Overall asthma control[**]	**OR (95% CI)**	
controlled	Reference	
uncontrolled		
GINA level control[§]	**RRR (95% CI)**	
controlled	Reference	
partly controlled		
uncontrolled		

ATS/ERS: American Thoracic Society/European Respiratory Society; SABA: short-acting beta agonist; RR: rate ratio; CI: confidence interval; OR: odds ratio; RRR: relative risk ratio

[*]Risk Domain asthma control (RDAC) (yes/no), defined as absence of any of the following events in the baseline year

1. Acute respiratory event (primary outcome as defined above), *and*
2. Asthma-related outpatient department visit [20]

[**]Overall asthma control (OAC) (yes/no), defined as absence of any of the following events in the baseline year:

1. Acute respiratory event (primary outcome), *and*
2. Asthma-related outpatient department visit, *and*
3. Average daily dose of SABA >200 µg salbutamol/ >500 µg terbutaline [20]

[§]Poor asthma symptom control is defined as 3 out of 4 of the following:

1) "yes" to 3 Royal College of Physicians (RCP) questions (questions are described in table 3)
2) >2 puffs of SABA per week

Controlled = none of the questions have a "yes" response; Partly controlled = 1-2 of the questions have a "yes" response; Uncontrolled = 3-4 of the questions have a "yes" response

[§§]Patients with another type of intranasal steroid prescribed in the last 45 days before initiation of Dymista®

Table 9. Characteristics of patients with allergic rhinitis and asthma multi-morbidity and who were intranasal corticosteroid naïve[*] before initiation of Dymista®

	Intranasal corticosteroid naïve patients with allergic rhinitis and asthma multi-morbidity[*] **N =**
Age, year, n (%)	
Mean (SD)	
Median (IQR)	
12 – 17	
18 – 64	
≥65	
Sex, n (%)	
Men	
Women	
Smoking status, n (%)	
Non-missing, n (%)	
Current smokers	
Former smokers	
Non-smokers	
Body Mass Index, kg/m^2, n (%)	
Non-missing, n (%)	
Mean (SD)	
Median (IQR)	
Underweight: <18.5	
Normal weight: 18.5 - <25	
Overweight: 25 - <30	
Obese: >30	
Presence of comorbidities ever prior to prescription index date, n (%)	
Eczema diagnosis	
Never	

	Intranasal corticosteroid naïve patients with allergic rhinitis and asthma multi-morbidity* **N =**
Active	
ever, not active	
Chronic Obstructive Pulmonary Disease	
Never	
Active	
ever, not active	
Nasal polyps	
Chronic rhinosinusitis	
Gastroesophageal reflux disease	
Diabetes Mellitus	
Osteoporosis	
Hypertension	
Cardiovascular disease	
Ischaemic heart disease	
Heart failure	
Myocardial infarction	
Chronic kidney disease, stage 3 – 5	
Depression/ Anxiety	
Pneumonia	
Obstructive sleep apnoea	
Charlson co-morbidity index, n (%)	
≤1	
2 – 4	
≥5	

SD: standard deviation; IQR: interquartile range; prescription index date: the date at which patients with active asthma receive the first prescription for Dymista®

* Patients who never had intranasal steroids prescribed before initiation of Dymista®

Table 10. Disease control and severity indicators among patients with allergic rhinitis and asthma multi morbidity and who were intranasal corticosteroid naïve[§§] in the year before initiation of Dymista®

Disease control and severity indicators	**Intranasal corticosteroid naïve patients with allergic rhinitis and asthma multi-morbidity[§§] N =**
Rhinitis treatment, n (%)	
Oral antihistamines	
Intranasal corticosteroids	
LTRA[*]	
Oral decongestants	
Non-steroidal nasal sprays[**]	
Eye drops for allergic conjunctivitis	
Age of asthma onset, year (where data is available)	
Non-missing, n (%)	
Mean (SD)	
Mean (IQR)	
Blood eosinophil count measured at state of the disease (no steroid use 2 weeks prior to measurement) closest to IPD within 5 years, n (%)	
Non-missing	
Mean (SD)	
Median (IQR)	
$<0.25 \times 10^9$/L	
$\geq 0.25 \times 10^9$/L	
Asthma treatment, n (%)	
GINA treatment step	
1	
2	
3	
4	
5	

Total number of ICS inhalers prescribed, n(%)	
Mean (SD)	
Median (IQR)	
Number of ICS inhalers prescribed, n (%)	
0	
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
≥12	
Average daily dose of ICS consumed, beclometasone dipropionate equivalent in µg/day, n (%)	
Mean (SD)	
Median (IQR)	
None: 0	
Low dose: >0 - ≤250‡	
Medium dose: >250 - ≤500	
High dose: >500	
Last intended dose of ICS beclometasone dipropionate equivalent in µg/day	
Mean (SD)	
Median (IQR)	
Any prescription of treatment (yes), n (%)	
ICS	
LAMA	
SABA	
SAMA	
ICS + LABA	

LTRA	
Theophylline	
Anti-IgE treatment	
Anti-Interleukin-5 (IL-5) treatment	
IL-4 treatment	
IL-13 treatment	
Macrolides	
Sodium cromoglicate	
Nedocromil	
Add on treatment prescriptions on top of ICS, n(%)	
LABA	
LAMA	
LTRA	
Theophylline	
Anti-IgE treatment	
IL-5 treatment	
IL-4 treatment	
IL-13 treatment	
Macrolides	
Acute OCS courses, n (%)	
0	
1	
2	
3	
≥4	
ICS adherence, %, n (%)‡‡	
<50	
50 - <80	
≥80	
ICS + LABA adherence, %, n (%)‡‡	
<50	
50 - <70	
70 - <80	
≥80	
Peak expiratory flow§, n (%)	

Non-missing, n (%)	
Mean (SD)	
Median (IQR)	
Green	
Yellow	
Red	
FEV_1 % predicted, n (%)	
Non-missing, n (%)	
Mean (SD)	
Median (IQR)	
<30	
30 – 49	
50 – 79	
≥80	
FEV_1/FVC ratio	
Non-missing, n (%)	
Mean (SD)	
Median (IQR)	
Respiratory-related hospital admissions, n (%)	
Mean (SD)	
Median (IQR)	
0	
1	
≥2	
Asthma-related ED attendance, n (%)	
Mean (SD)	
Median (IQR)	
0	
1	
≥2	

LTRA: leukotriene receptor antagonist; IPD: index prescription date (date of initiation of Dymista®); SD: standard deviation; IQR: interquartile range; ICS: inhaled corticosteroids; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonists; SABA: short-acting beta agonist; SAMA: short-acting muscarinic antagonists; ED: emergency department; FEV^1: Forced Expiratory Flow in one second; FVC: Forced Vital Capacity

[*]prescribed during a consultation for rhinitis

[**] including antihistamines, decongestants, chromones, ipratropium bromide and saline

[‡]Based on the Global Initiative for Asthma definitions of low, medium and high dose of inhaled corticosteroids for adolescents and adults.

[‡‡]Adherence calculated by the Medication Possession Ratio, i.e. the refill rate (%) = (total ICS pack days/number of prescription days) * 100

[§]Last recorded value closest to IPD prior to 5 years (>18 years old) or last recorded value closest to IPD prior to 2 years (15-18 years old).Peak flow reading are classified into 3 zones of measurement (green, yellow and red) according to American Lung Association.

[§§]Patients who never had intranasal steroids prescribed before initiation of Dymista®

Table 11. Change in asthma-related outcomes in the period before and after initiation of Dymista® among patients with allergic rhinitis and asthma multi-morbidity and who were intranasal corticosteroid naïve[§§] before Dymista® initiation

Asthma-related outcomes	**Patients at pre-initiation Dymista® N =**	**Patients at post-initiation Dymista® N =**	**P-value[§]**
Primary outcome			
Number of acute respiratory events, n (%)			
0			
1			
2			
≥3			
Secondary outcome			
Number of asthma exacerbations, based on ATS/ERS Force definition, n (%)			
0			
1			
2			
≥3			
Exploratory outcomes			
Asthma treatment: GINA step, n (%)			
1			
2			
3			
4			
5			
Stable GINA step			
Any step-up in GINA step			
Any step-down in GINA step			
Any step-up/step-down GINA step			

Average daily dose of SABA prescribed, salbutamol equivalent in µg/day, n (%)			
Non-missing			
Mean (SD)			
Median (IQR)			
0			
>0 – 100			
101 – 200			
201 – 300			
301 – 400			
>400			
Risk domain asthma control*, n (%)			
controlled			
uncontrolled			
Overall asthma control**, n (%)			
controlled			
uncontrolled			
Control of asthma symptoms, defined by:			
1.Three Royal College of Physicians (RCP) questions‡			
Response to one of the following questions, n (%)			
Have you had difficulty sleeping because of your asthma symptoms in the last month?			
Non-missing, n(%)			
Yes			
No			
Have you had your usual symptoms during the day in the last month?			
Non-missing, n(%)			
Yes			
No			

Has your asthma interfered with your usual activities in the last month?			
Non-missing, n (%)			
Yes			
No			
The number of "yes" responses to RCP questions, n (%)			
Non-missing			
0			
1			
2			
3			
2. >2 puffs of SABA per week, n (%)			
Gina level control, n (%)‡‡			
Non-missing			
controlled			
partly controlled			
uncontrolled			

ATS/ERS: American Thoracic Society/European Respiratory Society; SABA: short-acting beta agonist

*Risk Domain asthma control (RDAC) (yes/no), defined as absence of any of the following events in the baseline year

1. Acute respiratory event (primary outcome as defined above), *and*
2. Asthma-related outpatient department visit [20]

**Overall asthma control (OAC) (yes/no), defined as absence of any of the following events in the baseline year:

1. Acute respiratory event (primary outcome), *and*
2. Asthma-related outpatient department visit, *and*
3. Average daily dose of SABA >200 µg salbutamol/ >500 µg terbutaline [20]

‡Response "yes" to one of the three Royal College of Physicians (RCP) questions, which are part of the annual review of patients with asthma in the UK within the QOF framework

‡‡Poor asthma symptom control is defined as 3 out of 4 of the following:

1) "yes" to 3 RCP questions
2) >2 puffs of SABA per week

Controlled = none of the questions have a "yes" response; Partly controlled = 1-2 of the questions have a "yes" response; Uncontrolled = 3-4 of the questions have a "yes" response

[§]the differences between pre-initiation and post-initiation of each outcome will be calculated by the Wilcoxon signed-ranks test for categorical outcomes and the McNemar test for dichotomous outcomes

[§§]Patients who never had intranasal steroids prescribed before initiation of Dymista®

Table 12. Change in asthma-related outcomes in the period before and after initiation of Dymista® among patients with allergic rhinitis and asthma multi-morbidity and who were intranasal corticosteroid naïve[§§] before Dymista® initiation

Asthma-related outcomes		**P-value**
Primary outcome		
Change in the number of acute respiratory events	**RR (95% CI)**	
Secondary outcome		
Change in the number of asthma exacerbations, based on ATS/ERS Force definition	**RR (95% CI)**	
Exploratory outcomes		
Asthma treatment: change in GINA step	**OR (95% CI)**	
No change in GINA step	Reference	
Change in GINA step		
Average daily dose of SABA prescribed, salbutamol equivalent in µg/day	**RR (95% CI)**	
Risk domain asthma control[*]	**OR (95% CI)**	
controlled	Reference	
uncontrolled		
Overall asthma control[**]	**OR (95% CI)**	
controlled	Reference	
uncontrolled		
GINA level control[§]	**RRR (95% CI)**	
controlled	Reference	
partly controlled		
uncontrolled		

[*]Risk Domain asthma control (RDAC) (yes/no), defined as absence of any of the following events in the baseline year

1. Acute respiratory event (primary outcome as defined above), *and*
2. Asthma-related outpatient department visit [20]

[**]Overall asthma control (OAC) (yes/no), defined as absence of any of the following events in the baseline year:

1. Acute respiratory event (primary outcome), *and*
2. Asthma-related outpatient department visit, *and*
3. Average daily dose of SABA >200 µg salbutamol/ >500 µg terbutaline [20]

[§]Poor asthma symptom control is defined as 3 out of 4 of the following:

1) "yes" to 3 Royal College of Physicians (RCP) questions (questions are described in table 3)
2) >2 puffs of SABA per week

Controlled = none of the questions have a "yes" response; Partly controlled = 1-2 of the questions have a "yes" response; Uncontrolled = 3-4 of the questions have a "yes" response

[§§]Patients who never had intranasal steroids prescribed before initiation of Dymista®

8.0 Appendices

8.1 List of read codes for asthma

Read code	read_term_v2	read_term_v3
173A.	Exercise induced asthma	Exercise-induced asthma
H3120	Chronic asthmatic bronchitis	Chronic asthmatic bronchitis
H3120	Chronic asthmatic bronchitis	Chronic asthmatic bronchitis
H33..	Asthma	Asthma
H33..	Asthma	Asthma
H330.	Extrinsic (atopic) asthma	Asthma: [extrins - atop][allerg][pollen][childh][+ hay fev]
H330.	Extrinsic (atopic) asthma	Asthma: [extrins - atop][allerg][pollen][childh][+ hay fev]
H330.	Extrinsic (atopic) asthma	Asthma: [extrins - atop][allerg][pollen][childh][+ hay fev]
H330.	Extrinsic (atopic) asthma	Asthma: [extrins - atop][allerg][pollen][childh][+ hay fev]
H330.	Extrinsic (atopic) asthma	Asthma: [extrins - atop][allerg][pollen][childh][+ hay fev]
H3300	Extrinsic asthma without status asthmaticus	(Hay fever + asthma) or (extr asthma without status asthmat)
H3300	Extrinsic asthma without status asthmaticus	(Hay fever + asthma) or (extr asthma without status asthmat)
H3301	Extrinsic asthma with status asthmaticus	Extrins asthma with: [asthma attack] or [status asthmaticus]
H3301	Extrinsic asthma with status asthmaticus	Extrins asthma with: [asthma attack] or [status asthmaticus]
H330z	Extrinsic asthma NOS	Extrinsic asthma NOS
H331.	Intrinsic asthma	(Intrinsic asthma) or (late onset asthma)
H331.	Intrinsic asthma	(Intrinsic asthma) or (late onset asthma)
H3310	Intrinsic asthma without status asthmaticus	Intrinsic asthma without status asthmaticus
H3311	Intrinsic asthma with status asthmaticus	Intrins asthma with: [asthma attack] or [status asthmaticus]
H3311	Intrinsic asthma with status asthmaticus	Intrins asthma with: [asthma attack] or [status asthmaticus]
H331z	Intrinsic asthma NOS	Intrinsic asthma NOS
H332.	Mixed asthma	Mixed asthma
H334.	Brittle asthma	

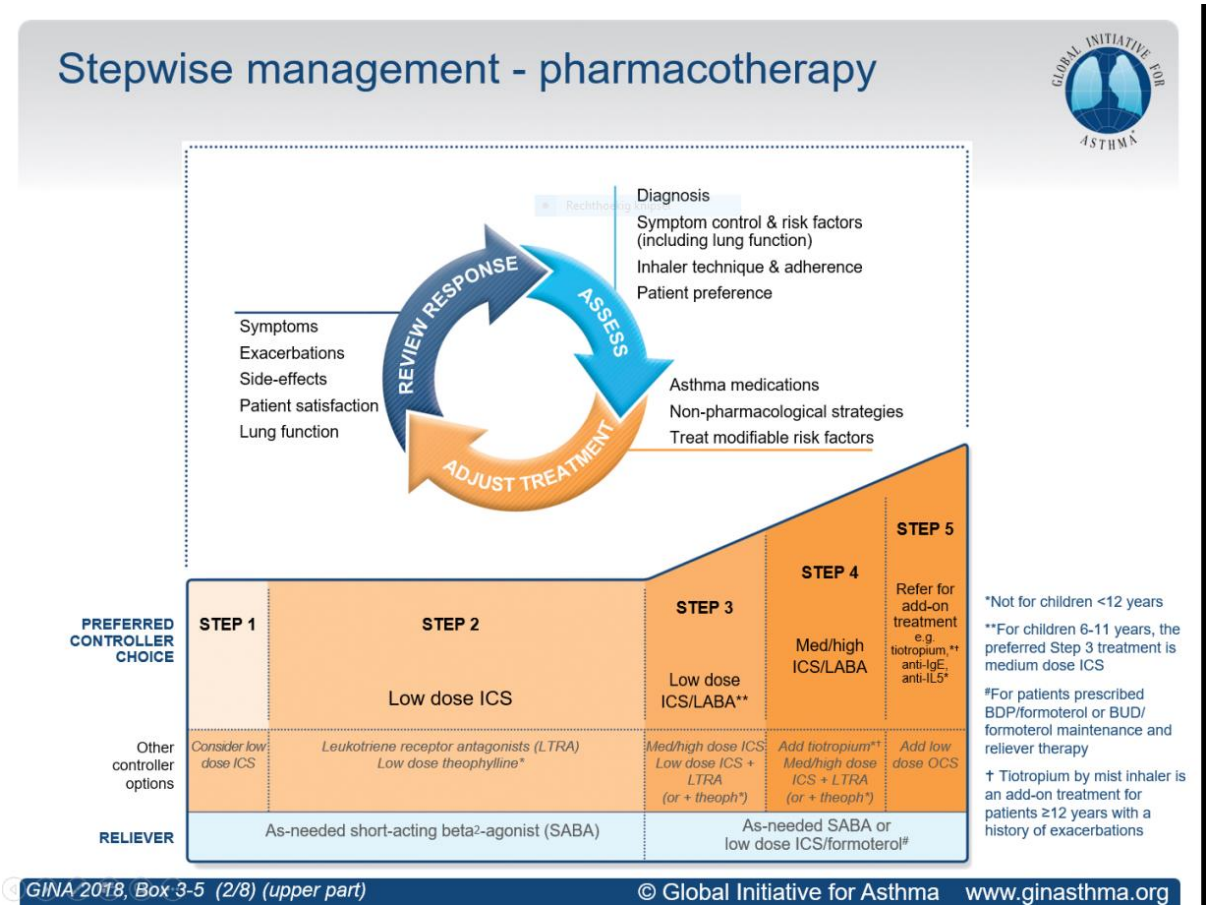
H335.	Chronic asthma with fixed airflow obstruction	Chronic asthma with fixed airflow obstruction
H33z.	Asthma unspecified	Asthma unspecified
H33z.	Asthma unspecified	Asthma unspecified
H33z0	Status asthmaticus NOS	(Severe asthma attack) or (status asthmaticus NOS)
H33z0	Status asthmaticus NOS	(Severe asthma attack) or (status asthmaticus NOS)
H33z1	Asthma attack	Asthma attack (& NOS)
H33z1	Asthma attack	Asthma attack (& NOS)
H33z2	Late-onset asthma	
H33zz	Asthma NOS	(Asthma:[exerc ind][allerg NEC][NOS]) or (allerg bronch NEC)
H33zz	Asthma NOS	(Asthma:[exerc ind][allerg NEC][NOS]) or (allerg bronch NEC)
H33zz	Asthma NOS	(Asthma:[exerc ind][allerg NEC][NOS]) or (allerg bronch NEC)
H33zz	Asthma NOS	(Asthma:[exerc ind][allerg NEC][NOS]) or (allerg bronch NEC)
H3B..	Asthma-chronic obstructive pulmonary disease overlap syndrom	
Ua1AX		Brittle asthma
X101t		Childhood asthma
X101u		Late onset asthma
X101x		Allergic asthma
X101y		Extrinsic asthma with asthma attack
X101z		Allergic asthma NEC
X1020		Hay fever with asthma
X1021		Allergic non-atopic asthma
X1022		Intrinsic asthma with asthma attack
X1024		Aspirin-sensitive asthma with nasal polyps
X102D		Status asthmaticus
XE0YQ		Allergic atopic asthma
XE0YR		Extrinsic asthma without status asthmaticus
XE0YS		Extrinsic asthma with status asthmaticus
XE0YT		Non-allergic asthma
XE0YU		Intrinsic asthma with status asthmaticus
XE0YV		Status asthmaticus NOS
XE0YW		Asthma attack
XE0YX		Asthma NOS

XE0ZP	Extrinsic asthma - atopy (& pollen)
XE0ZR	Asthma: [intrinsic] or [late onset]
XE0ZT	Asthma: [NOS] or [attack]
XM0s2	Asthma attack NOS
Xa0lZ	Asthmatic bronchitis
Xa9zf	Acute asthma
XaLPE	Nocturnal asthma
Xaa7B	Chronic asthma with fixed airflow obstruction
Xac33	Asthma-chronic obstructive pulmonary disease overlap syndrom
Xafdj	Acute severe exacerbation of asthma
Xafdy	Moderate acute exacerbation of asthma
Xafdz	Life threatening acute exacerbation of asthma

8.2 List of read codes for Dymista®

Read code	read_term_v2	read_term_v3
l8E..	AZELASTINE HYDROCHLORIDE+FLUTICASONE PROPIONATE	AZELASTINE HYDROCHLORIDE+FLUTICASONE PROPIONATE
l8E1.	DYMISTA 137micrograms/50micrograms nasal spray	DYMISTA 137micrograms/50micrograms nasal spray
l8E2.	AZELASTINE HCL+FLUTICASONE PROPION 137mcg/50mcg nasal spray	AZELASTINE HCL+FLUTICASONE PROPION 137mcg/50mcg nasal spray

8.3 GINA steps of asthma management



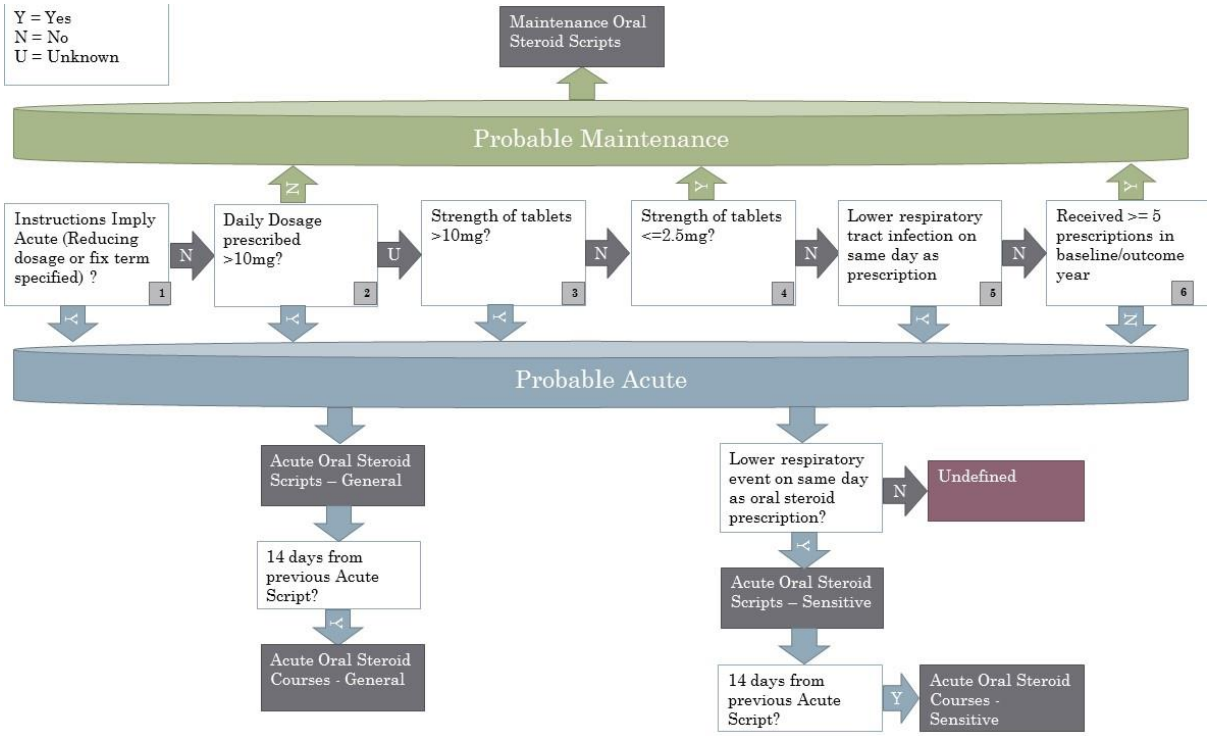
8.4 GINA definitions of low, medium and high dose ICS

Box 8. Low, medium and high daily doses of inhaled corticosteroids (mcg)

Inhaled corticosteroid	Adults and adolescents			Children 6–11 years		
	Low	Medium	High	Low	Medium	High
Beclometasone dipropionate (CFC)*	200–500	>500–1000	>1000	100–200	>200–400	>400
Beclometasone dipropionate (HFA)	100–200	>200–400	>400	50-100	>100-200	>200
Budesonide (DPI)	200–400	>400–800	>800	100–200	>200–400	>400
Budesonide (nebules)				250–500	>500–1000	>1000
Ciclesonide (HFA)	80–160	>160–320	>320	80	>80-160	>160
Fluticasone furoate (DPI)	100	n.a.	200	n.a.	n.a.	n.a.
Fluticasone propionate(DPI)	100–250	>250–500	>500	100–200	>200–400	>400
Fluticasone propionate (HFA)	100–250	>250–500	>500	100–200	>200–500	>500
Mometasone furoate	110–220	>220–440	>440	110	≥220–<440	≥440
Triamcinolone acetonide	400–1000	>1000–2000	>2000	400–800	>800–1200	>1200

CFC: chlorofluorocarbon propellant; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant. *Included for comparison with older literature.

8.5 Algorithm for definition of probably acute versus probable chronic oral corticosteroids prescriptions



8.6 Royal College of Physicians 3 Questions for Asthma

Royal College of Physicians 3 Questions for Asthma

No to all questions consistent with controlled asthma

In the last month	YES	NO
"Have you had difficulty sleeping because of your asthma symptoms (including cough)?"	☐	☐
"Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)?"	☐	☐
"Has your asthma interfered with your usual activities (e.g. housework, work, school, etc)?"	☐	☐

8.7 Definition of asthma control status, following the GINA guidelines

Box 2-2. GINA assessment of asthma control in adults, adolescents and children 6–11 years

A. Asthma symptom control		Level of asthma symptom control		
In the past 4 weeks, has the patient had:		**Well controlled**	**Partly controlled**	**Uncontrolled**
• Daytime asthma symptoms more than twice/week?	Yes☐ No☐	None of these	1–2 of these	3–4 of these
• Any night waking due to asthma?	Yes☐ No☐			
• Reliever needed for symptoms* more than twice/week?	Yes☐ No☐			
• Any activity limitation due to asthma?	Yes☐ No☐			