
Observational Study Protocol

| | |
|------------|-------------------|
| Study Code | << D589BR00053 >> |
| Version | 6.5 |
| Date | 01/28/22 |

The burden of intermittent OCS use in asthma

An observational cohort study to describe intermittent OCS utilisation and its association with adverse outcomes and healthcare resource use and costs in asthma using the OPCR and CPRD databases.

Sponsor: AstraZeneca

Author: Professor David Price
Professor of Primary Care Respiratory Medicine and OPC Global Director
5a Coles Lane
Oakington
Cambridge
CB24 3BA
United Kingdom
M: +44 7787 905 057
david@optimumpatientcare.org

| | PAGE |
|--|-------------|
| TABLE OF CONTENTS | 2 |
| LIST OF ABBREVIATIONS AND DEFINITION OF TERMS | 3 |
| RESPONSIBLE PARTIES | 5 |
| PROTOCOL SYNOPSIS | 6 |
| 1. BACKGROUND AND RATIONALE | 12 |
| 1.1 Background | 12 |
| 1.2 OCS Literature Review | 13 |
| 1.3 Rationale | 14 |
| 1.4 Feasibility | 14 |
| 2. OBJECTIVES AND HYPOTHESES | 15 |
| 2.1 Hypothesis..... | 15 |
| 2.2 Primary Objective(s) & Hypothesis(es)..... | 15 |
| 3. METHODOLOGY | 16 |
| 3.1 Study Design | 16 |
| 3.2 Inclusion Criteria | 17 |
| 3.3 Study Design | 17 |
| 3.4 Study Population | 23 |
| 3.5 Inclusion Criteria | 23 |
| 3.6 Exclusion Criteria | 23 |
| 3.7 Participant Follow-up..... | 24 |
| 4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS | 24 |
| 4.1 Exposures | 24 |
| 4.2 Outcomes | 25 |
| 4.3 Other Variables and Covariates | 30 |
| 5. STUDY CONDUCT AND REGULATORY DETAILS | 36 |
| 5.1 Data Management | 36 |
| 5.2 Study Conduct..... | 36 |
| 5.3 Protection of Human Subjects..... | 38 |
| 5.4 Communication Plan..... | 38 |
| 6. LIST OF REFERENCES | 39 |
| 7. APPENDICES | 42 |

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation or special term | Explanation |
|-------------------------------------|--|
| ADEPT | Anonymised Data Ethics & Protocol Transparency Committee |
| A&E | Accident and Emergency |
| AE | Adverse Event |
| ATC | Anatomical Therapeutic Chemical classification system of medication |
| AZ | AstraZeneca |
| BEC | Blood Eosinophil Count |
| BMI | Body Mass Index |
| BTS | British Thoracic Society |
| CPRD | Clinical Practice Research Datalink |
| DDD | Defined daily dose |
| EMR | Electronic Medical Record |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| FEV ₁ | Forced Expiratory Flow in one second |
| FVC | Forced Vital Capacity |
| GINA | Global Initiative for Asthma |
| GP | General Practitioner |
| HES | Hospital Episode Statistics |
| HRU | Healthcare Resource Utilisation |
| ICD-10 | International Classification of Disease v10 |
| ICS | Inhaled Corticosteroids |
| ID | Index Date |
| IQR | Inter Quartile Range |
| ISAC | Independent Scientific Advisory Committee |
| LABA | Long Acting β adrenoceptor Agonists |
| LAMA | Long-Acting Muscarinic Receptor Antagonists |
| LRTI | Lower Respiratory Tract Infection |
| LTRA | Leukotriene Receptor Antagonist |
| NRAD | National Review of Asthma Deaths |
| NHS | National Health Service |
| OCS | Oral Corticosteroids |

| Abbreviation or special term | Explanation |
|-------------------------------------|--|
| OPC | Optimum Patient Care |
| OPCRD | Optimum Patient Care Research Database |
| OPRI | Observational and Pragmatic Research Institute |
| PEFR | Peak Expiratory Flow |
| RCP3 | Royal College of Physicians 3 Questions for asthma |
| SABA | Short-Acting Beta-Agonists |
| SAMA | Short-Acting Muscarinic Antagonist |
| SCS | Systemic Corticosteroids |
| SD | Standard Deviation |
| SIGN | Scottish Intercollegiate Guidelines Network |
| UK | United Kingdom |

RESPONSIBLE PARTIES

| Name | Professional Title | Role in Study | Affiliation | Email Address |
|-------------------|---------------------------------------|------------------------|-------------|-----------------------------------|
| Dr. Trung N. Tran | TA Strategy and Evidence Lead, Asthma | AZ Research Lead | AZ | trung.tran1@astrazeneca.com |
| Ekaterina Maslova | Associate Director, Epidemiology | AZ Support | AZ | ekaterina.maslova@astrazeneca.com |
| Prof. David Price | Professor | Chief Investigator | OPRI | david@opri.sg |
| Victoria Carter | Research Director | Management | OPRI | victoria@opri.sg |
| Dr. Heath Heatley | Senior Researcher | Project Research Lead | OPRI | heath@opri.sg |
| Brooklyn Stanley | Data Analytics Manager | Data Analytics Support | OPRI | brooklyn@opri.sg |
| Derek Skinner | Senior Data Analyst | Data Analytics Support | OPRI | derek@optimumpatientcare.org |

Proposed Steering committee members

| Name | Affiliation | Email Address |
|--------------------------|---|-------------------------------|
| Prof. Arnaud Bourdin | Centre Hospitalier Universitaire de Montpellier, France | arnaud01009157@gmail.com |
| Dr. David Jackson | Faculty of Medicine, National Heart & Lung Institute, Imperial College London, UK | david.jackson@gstt.nhs.uk |
| Prof. Andrew Menzies-Gow | Royal Brompton & Harefield NHS Foundation Trust, UK | A.Menzies-Gow@rbht.nhs.uk |
| Prof David Price | Professor of Primary Care Respiratory Medicine and OPC Global Director | david@opri.sg |
| Prof. Josef Smolen | Internal Medicine, Medical University of Vienna, Austria | josef.smolen@meduniwien.ac.at |
| Dr. Trung N. Tran | TA Strategy and Evidence Lead, Asthma, AZ | trung.tran1@astrazeneca.com |

PROTOCOL SYNOPSIS

An observational cohort study to describe intermittent OCS utilisation and its association with adverse outcomes and healthcare resource use and costs in asthma using the OPCR and CPRD databases.

Background/Rationale:

Oral corticosteroids (OCS) are frequently prescribed for patients with respiratory conditions such as asthma. Despite evidence on the adverse outcomes of OCS, their use remains part of the clinical guidelines for asthma. There is evidence showing that relatively low cumulative doses of OCS can increase the risk of adverse outcomes and there is a wide consensus among physicians and researchers that the use of OCS should be limited to a minimum and should only be used when no other treatment option is available. Despite this OCS are still widely prescribed for patients with mild asthma.

Whilst there is evidence showing increased risk of adverse events related to cumulative OCS dose there is little showing how patterns of intermittent OCS use are related to adverse events and related healthcare costs. There is also a paucity of data exploring the longitudinal patterns of intermittent OCS use in asthmatic patients.

Objectives:

1. To classify intermittent OCS prescriptions for patients with asthma and to describe longitudinal patterns of intermittent (acute) OCS use by Global Initiative for Asthma (GINA) step, and Inhaled Corticosteroids (ICS) and Short-Acting Beta-Agonists (SABA) use.
2. To assess the association between differing patterns of intermittent OCS use and OCS-related adverse events (AE) in patients with asthma
3. To describe the impact of different patterns of intermittent OCS use on the frequency of healthcare resource utilisation (HRU) in patients with asthma.
4. To describe the AE for patients with an average annual OCS dose of 250-499mg, 500-999mg, or $\geq 1g$ of OCS during the follow up.
5. To describe the longitudinal patterns of intermittent OCS use in the last five years of follow-up among those who had more than one year of follow-up and were frequent OCS users in their final year of follow-up, and to identify factors that are

independently associated with frequent OCS use. Analyses are stratified by blood eosinophil counts closest to the index date.

Methods:

Study design

The most recent extraction of Electronic Medical Record (EMR) data from Optimum Patient Care Research Database (OPCRD) and Clinical Practice Research Datalink (CPRD) general practices will be used for this analysis. The index date (ID) will be defined for patients aged ≥ 4 years of age, the ID will be the first acute OCS prescription with concurrent evidence of asthma event (medication, asthma consultation and/or asthma diagnosis) within a 3-month period. The index date will be the patients first prescription of OCS within 3 months, either before or after, an asthma related event (medication, asthma consultation and/or asthma diagnosis). Patients will be excluded if they have ever had a diagnosis of a chronic condition* treated with OCS. Patients will be categorised into OCS prescribing patterns.

Demographics, clinical characteristics, including asthma severity and control and HRU, will be described for different prescribing patterns over their follow up period.

For objective 4, to describe the AE for patients with an average annual OCS dose of 250-499mg, 500-999mg, or ≥ 1 g of OCS during the follow up. These patients will be monitored to determine OCS-related AEs.

Data Source(s)

Optimum Patient Care Research Database (OPCRD) and Clinical Practice Research Datalink (CPRD) with linked Hospital Episode Statistics (HES) data.

Study Population:

Inclusion Criteria

1. OCS Arm - Patients with a prescription of an OCS with a concurrent (within 3 months) asthma event defined as an asthma QOF diagnosis or asthma QOF prescription. This will be the index date.
2. Non-OCS Arm - Patients with no OCS prescription at any time
3. Patients with at least 12 months baseline period (prior to index date)
4. Patients aged 4 or over at the index date

Exclusion Criteria

* Patients aged ≥ 18 : Ankylosing spondylitis, Sjogren's syndrome, Systemic lupus erythematosus, Temporal arteritis, Ulcerative colitis, Psoriatic arthritis, Multiple sclerosis, Polymyalgia rheumatica, Crohn's disease, Cancer of respiratory system, Patients aged >4 & <18 : Analysis of concurrent OCS and diagnoses will determine exclusion conditions

1. Patients with a diagnosis, ever, for a chronic condition treated with OCS
2. Patients with a chronic AE outcome prior to the index date will be excluded from the analysis. This will ensure that the first chronic condition is the post index date incident event.

Feasibility:

Feasibility of using OCS prescribing patterns was explored in the OPCR dataset. A total of 653,548 patients met the study criteria stated above. Forty percent of these patients received only one prescription of OCS during their follow-up period, 39% of patients had periods of frequent OCS prescribing (frequent or mixed prescribing including frequent OCS prescription with gaps of less than 90 days). Twenty percent of patients were found to have periods of sporadic OCS prescribing (sporadic or mixed including sporadic OCS prescriptions with gaps of greater than 365 days).

Exposure(s):

Exposure will be defined as an OCS prescription prescribed with a concurrent asthma event. OCS exposures will cease at the time of the patients first AE.

Outcome(s):

Objective 1: Baseline patient characteristics will be collected according to patients OCS patterns of use. These include:

- a) patient characteristics described prior to index date
- b) length of patient record prior and after index date
- c) age of onset of asthma (age at first asthma diagnosis ever)
- d) time from first asthma diagnosis date to index date
- e) ICS and SABA use in the year prior to index date
- f) patient's treatment by Global Initiative for Asthma (GINA) (2020) treatment step prior to index date

Objective 2: The following adverse events for OCS will be studied: type 2 diabetes mellitus, osteoporosis/osteoporotic fractures, hypertension, glaucoma, sleep apnoea, weight gain and depression/anxiety, pneumonia, cataracts, sleep disorders, cardiovascular disease, chronic kidney disease, dyslipidaemia and peptic ulcer disease, and in the adolescent population we will look for growth suppression and behavioural disorders.

Objective 3: Annualised healthcare resource utilisation and related costs will be determined in terms of primary care consultation costs, specialist consultations, hospitalisations, and Accident and Emergency (A&E) attendances.

Objective 4: To describe the AE for patients with an average annual OCS dose of 250-499mg, 500-999mg, or =>1g of OCS during the follow up.

Objective 5: To describe the the longitudinal patterns of intermittent OCS use in the last five years of follow-up among patients who had at least one year of follow-up and were frequent

OCS users in their final year of follow-up, and to identify factors that are independently associated with frequent OCS use.

Statistical Analysis:

Objective 1: Baseline characteristics will be described in the baseline period for patients according to their longitudinal patterns of intermittent (acute) OCS use by GINA step, and ICS and SABA use. To describe the distribution of variables among the OCS prescribing patterns.

Objective 2: A matched historical cohort study will be performed with an assessment of potential confounders during a baseline period prior to the index date. Patients will be excluded if they had a record of the adverse event prior to their index date and categorised according to their patterns of OCS prescribing. To address potential differences between OCS groups, patients will be matched initially on gender, age, and the index date. Other potential confounders (listed in 4.1.1) will be identified during the analysis, using potential bias assessments of covariates.

Objective 3: HRU events will be described over the follow up period using the CPRD dataset. HRU events will be described in the baseline period and during the follow up for both asthma-related and all-cause events. CPRD HES linked data will be used to describe hospital admissions, A&E attendances, and Outpatient visits

Objective 4: To describe the AE for patients with an average annual OCS dose of 250-499mg, 500-999mg, or =>1g of OCS during the follow up.

Objective 5: To describe the the longitudinal patterns of intermittent OCS use in the last five years of follow-up among patients who had more than one year of follow-up and were frequent OCS users in their final year of follow-up. Intermittent OCS use is described and classified using the system developed in Objective 1 (one-off, sporadic, infrequent, moderately frequent, and frequent). Factors that are independently associated with frequent OCS use will be identified using multivariable Cox regression with consideration of time-varying covariates. Analyses will be stratified by blood eosinophil counts closest to the index date.

Observational Study Protocol
Study Code << D589BR00053 >>
Version 6.5
Date 01/28/22

AMENDMENT HISTORY

| Date | Section of study protocol | | Amendment or update | Reason |
|-------------|----------------------------------|--------|--|--|
| 06/05/20 | Various | v3 -v5 | Various (detailed in version with reviewers' comments) | Amendment following MEORT Review |
| 11/08/20 | Various | v6.1 | Various (detailed in version with reviewers' comments) | Amendment following AZ and RTI review |
| 07/01/22 | Various | v6.4 | Various | Amendment following addition of Objective 5 |
| 28/01/22 | Various | v6.5 | Various | Amendment of objective 5 following AZ review |

MILESTONES

| Milestone | Planned date |
|-----------------------|---------------------|
| OPCRD Dataset Created | August 2020 |
| Analysis of OPCRD | September 2020 |
| Arrival of CPRD | October 2020 |
| CPRD Dataset created | October 2020 |
| Analysis of CPRD | November 2020 |
| Final Study Report | January 2021 |

ADDITIONAL MILESTONES

| Milestone | Planned date |
|---|---------------------|
| Protocol amendment submitted to ADEPT | January 2022 |
| OPCRD Dataset Updated | January 2022 |
| Statistical Analyses: Objective 1 (Study Slide-set) | January 2022 |
| Final Study Slide-deck | January 2022 |

1. BACKGROUND AND RATIONALE

1.1 Background

Asthma currently affects an estimated 358 million individuals worldwide and poses a substantial burden on healthcare systems.¹ Longstanding asthma medications are not optimally used to treat asthma. Patients often receive large numbers of SABA prescriptions despite United Kingdom (UK) asthma guidelines stating use at least three times a week is a marker for potentially poor control and a predictor of future risk of asthma attacks and death.² The National Review of Asthma Deaths (NRAD) recommended that prescription of more than one Short-Acting Beta-Agonists (SABA) per month should trigger an asthma review. Underuse of Inhaled Corticosteroids (ICS) has also contributed to asthma deaths.³ New treatment regimens for patients with asthma are being recommended for both the milder and severe asthma populations, e.g. amendments to GINA treatments steps and the development of biological therapies, respectively. The biological agents mepolizumab, reslizumab and benralizumab which target the interleukin-5 molecules or their receptors to reduce eosinophils have been demonstrated to reduce asthma attacks and improve symptoms in patients with severe, uncontrolled eosinophilic asthma. They also have the potential to reduce patient exposure to high dosages of ICS and oral corticosteroids (OCS) and thereby, OCS related adverse effects.⁴⁻⁷

Despite the more widespread use of newer treatment regimens, oral corticosteroids are still widely used in patients with asthma. In a recent systematic literature review, 58 studies reported short-term OCS/Systemic corticosteroid (SCS) use for patients with asthma. Short-term OCS/SCS use ranged from 2.1% (international study of SCS use for patients aged ≥ 12 years with asthma requiring GINA Step 2 treatment or greater) to 92.6% (U.K. study of OCS use for patients with severe asthma).

Asthma management guidelines recommend the use of oral corticosteroids in the management of severe asthma exacerbations. Chronic or long-term oral corticosteroids can be used as a continuous, or frequent use, for a small number of patients who are not controlled on high-dose ICS therapies. These patients should remain under the care of a specialist asthma service. Intermittent or burst oral steroid are recommended to prevent mortality, relapses, subsequent hospital admission and requirement for $\beta 2$ agonist therapy. The British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) recommends an intermittent OCS dose of 40-50mg prednisolone, daily for a minimum of 5 days and a maintenance dose at the lowest dose providing adequate control.⁸ GINA recommends 40-50mg prednisolone, daily for 5-7 days and a maintenance dose of ≤ 7.5 mg.²

Systematic literature reviews of studies evaluating the use of OCS show an increased risk of adverse outcomes which increase with dose.^{9,10} A recent Observational and Pragmatic Research Institute (OPRI) study examining a broad UK asthma population initiating OCS (including all doses of intermittent and chronic use) over a medium period of over 7 years found that increasing cumulative exposure to OCS places patients at a high risk of OCS-related adverse outcomes ranging from acute complications such as infections to chronic complications such as

metabolic and cardiovascular events. The onset of some outcomes was associated with cumulative OCS exposure of only 0.5–<1 g.¹¹

Most epidemiological studies examining the impact of OCS use are inclined to place more emphasis on maintenance OCS use in patients with severe asthma. In clinical practice, however, most patients have mild to moderate disease and it is unclear to what extent intermittent use of OCS will increase the risk of adverse outcomes.¹² A cohort study performed in the UK CPRD reported that over 60% of patients with asthma have mild asthma (British Thoracic Society (BTS) steps ½ [Appendix 8.1]) and that these patients often have suboptimal symptom control. Whilst exacerbation rates increase with severity, 9.3 exacerbations for patients at BTS step 5, this study reported that patients with the mildest asthma (BTS step 1) experienced 2.4 exacerbations per 10 person years.¹³ A US longitudinal, open-cohort, observational study using health insurance claims data (1997-2013: Medicaid) from several US states found that a high proportion of mild asthma patients are prescribed intermittent bursts of OCS (1 in 4).¹⁴ A UK retrospective analysis of patients from 46 GP surgeries examined prescription rates of OCS in relation to asthma treatment steps (according to the BTS Guidelines). This study reported that the mean number of OCS courses per year ranged from 1.2 to 2.1 at Steps 1 to 4, and 5.3 at Step 5 (maintenance OCS therapy).¹⁵ Additionally, the aforementioned studies of intermittent OCS prescriptions only reported gross prescription rates over a set time period, without exploration of longitudinal prescription patterns. There thus remain many areas worthy of investigation pertinent to intermittent OCS use in asthmatic patients.

1.2 OCS Literature Review

A literature review was undertaken to determine how previous studies classified OCS use. Patterns of short-term OCS use are defined by terms such as being ‘intermittent’, ‘acute’, ‘burst’ and ‘for asthma exacerbations’. Long term OCS use have been defined as being ‘daily’, ‘continuous’, ‘maintenance’, ‘chronic’, used as ‘controller medication’ or ‘high use’. This protocol will use the phrase intermittent and maintenance OCS use.

A search of the literature within PubMed to identify English-language articles using the following search terms: “Adrenal Cortex Hormones”[nm][†] AND oral corticosteroid NOT inhalation AND asthma AND (burst OR Intermittent OR Acute). Abstracts and full-text articles were screened to determine their relevance.

The measures used in these studies to classify patients OCS use varied between studies. Methods used to categorise OCS use included:

- a) The number of days of continuous OCS prescribing (e.g. from >15 days,¹⁶ => 30days,¹⁷ =>60 days¹⁸, >90 days¹⁹)
- b) Periods covered with OCS without gaps (e.g. =<14 days²⁰)
- c) The average number of days covered over a time period (e.g. >=50% of days covered²¹)
- d) Prescribing instruction including titration patterns (>14 days with no titration pattern¹⁵)

[†] [nm] – Mesh Heading

- e) Cumulative and Average daily dosage over time periods ($\geq 1600\text{mg/year}$ [4.4mg/d/y]²² and $\geq 2.5\text{mg/d}$ over a year,²³ $\geq 5\text{mg/d}$ over a year²⁴)

This literature review found that OCS prescriptions were categorised based on aggregate measures over a time period rather than prescribing patterns. The review suggested that cumulative OCS/SCS exposure may not be an ideal measure because of possible variations among patients with regard to factors such as disease duration and severity.²⁵ This study intends to improve by firstly categorise OCS prescriptions as being intermittent or maintenance use based upon prescribing information including dosing instructions, daily dose, tablet strength, concurrent diagnoses and asthma medications, number of scripts per year, and other concurrent asthma medication.

In addition to the prescribing information the patient's asthma treatments will be extracted and categorised into GINA 2020 treatment steps (appendix 8.2). Patients at GINA step 5 receiving OCS would therefore be expected to be in receipt of maintenance OCS.

Secondly, patients receiving intermittent OCS prescriptions will be categorised according to the patterns of prescribing rather than the average dose or number of prescriptions over a time period.

1.3 Rationale

Systematic literature reviews of studies evaluating the use of OCS show an increased risk of adverse outcomes which increase in dose.^{9,10} A recent OPRI study examining a broad UK asthma population initiating OCS the onset of some outcomes was associated with cumulative OCS exposure starting at $0.5 < 1\text{ g}$.¹⁰ However, there was no evidence on whether patients with intermittent use are associated with adverse outcomes and associated increased healthcare resource costs. Additionally, little is known about the longitudinal patterns of intermittent OCS prescription in asthmatic patients, and these patterns' relations with blood eosinophil counts.

1.4 Feasibility

Initial analysis to better understand which OCS patterns should be considered for use in this analysis reported patterns for patients meeting the inclusion and exclusion criteria and receiving intermittent OCS prescriptions within OPCR. D.

Prescribing of OCS were categorised as either a) one off – patients with only one OCS prescription, b) sporadic – prescriptions with gaps 365 days or over, c) Infrequent – prescription with gaps of between 182 – 365 days, d) Moderately infrequent - prescription with gaps of between 90 and 182 days, e) Frequent – prescription gaps of less than 90 days and f) Mixed – Patients with a mixture of the patterns listed above.

Most patients were found to have either one-off OCS prescriptions or mixed patterns (Table 1).

Table 1 - OCS Prescribing patterns for patients in OPCR

| Prescribing Patterns | Numbers of Patients | % |
|--|---------------------|-------|
| One Off | 263,430 | 40.3% |
| Frequent or Mixed prescribing including frequent | 256,866 | 39.3% |
| Sporadic or Mixed including sporadic | 130,605 | 20.0% |
| Only Infrequent | 1,685 | 0.3% |
| Only Moderately Frequent | 871 | 0.1% |
| Total | 653,457 | |

2. OBJECTIVES AND HYPOTHESES

2.1 Hypothesis

Patients with a more frequent OCS prescribing patterns will suffer an increase in adverse events and increased healthcare costs.

2.2 Primary Objective(s) & Hypothesis(es)

1. To classify intermittent OCS prescriptions for patients with asthma and to describe longitudinal patterns of intermittent (acute) OCS use by GINA step, and ICS and SABA use.
2. To assess the association between patterns of intermittent OCS use and OCS-related adverse outcomes in patients with asthma.
3. To describe the impact of different patterns of intermittent OCS use on the frequency of healthcare resource utilisation in patients with asthma.
4. To describe the AE for patients with an average annual OCS dose of 250-499mg, 500-999mg, or $\geq 1g$ of OCS during the follow up. The index date will be the patients first prescription of OCS within 3 months, either before or after, an asthma related event (medication, asthma consultation and/or asthma diagnosis)

2.3 Exploratory analysis

5. To describe the longitudinal patterns of intermittent OCS use in the last five years of follow-up among those who had more than one year of follow-up and were frequent OCS users in their final year of follow-up, and to identify factors that are independently associated with frequent OCS use. Analyses are stratified by blood eosinophil counts closest to the index date.

3. METHODOLOGY

3.1 Study Design

3.1.1 Data Sources

A historical longitudinal descriptive cohort study using patients' electronic medical records extracted from general practices from the Optimum Patient Care Research Database (OPCRD) and Clinical Practice Research Datalink (CPRD).

The OPCRD comprises data extracted through the Optimum Patient Care (OPC) Clinical Service Evaluation. At the time of writing, OPCRD contains anonymized, research-quality data for approximately 7 million patients across the UK. Dates of last data collection from general practices range from 2008 to 2019, with almost half of the data being uploaded in 2019 and 79% in the last 5 years.²⁶

The CPRD database is an ongoing primary care database of anonymized medical records from general practitioners, with coverage of over 11 million patients from 674 practices in the UK.²⁷ At the time of writing CPRD HES linked data is available up to a maximum of March 2019.

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 CPRD records will be linked to Hospital Episode Statistics (HES), which records all utilization of UK hospitals.²⁷ This allows identification of any hospital admission, including admissions with asthma as the primary diagnosis. In addition, data is linked to HES outpatient data to identify outpatient visits and to HES A&E data to identify emergency department attendances.

For objective 3, only CPRD data will be used to describe HRU.

The OPCRD database is approved by the Health Research Authority for clinical research use (Research Ethics Committee reference: 15/EM/0150), is governed by the Anonymised Data Ethics & Protocol Transparency (ADEPT) Committee, and offers a high-quality data source that is used regularly in clinical, epidemiological and pharmaceutical research. CPRD database access will require approval from Independent Scientific Advisory Committee (ISAC).

For objective 5, only OPCRD data will be used to describe longitudinal patterns of intermittent OCS prescriptions.

3.2 Inclusion Criteria

3.2.1 Inclusion Criteria

1. OCS Arm - Patients with a prescription of an OCS with a concurrent (within 3 months) asthma event defined as an asthma QOF diagnosis or asthma QOF prescription. This will be the index date.
2. Non-OCS Arm - Patients with no OCS prescription at any time
3. Patients with at least 12 months baseline period (prior to index date)
4. Patients aged 4 or over at the index date

3.2.2 Exclusion Criteria

1. Patients with a diagnosis, ever, for a chronic condition treated with OCS^{‡§}
2. Patients with a chronic AE outcome prior to the index date will be excluded from the analysis. This will ensure that the first chronic condition is the post index date incident event.
3. For Objective 5, patients with only one year or shorter durations of follow-up will be excluded.

3.3 Study Design

Objective 1: To classify intermittent OCS prescriptions for patients with asthma and to describe longitudinal patterns of intermittent (acute) OCS use by Global Initiative for Asthma (GINA) step, and Inhaled Corticosteroids (ICS) and Short-Acting Beta-Agonists (SABA) use.

A historical follow-up study will be performed including a broad real-life population of patients with active asthma, registered at GP practices in the UK, using combined data from the OPCR and the CPRD.

The OPCR and CPRD datasets will be constructed separately and patients with duplicate data will be excluded before pooling for analyses. These two databases have been combined in multiple prior and current studies conducted by OPRI (Price et al., 2015; Israel et al., 2015; Roche et al., 2015).²⁸⁻³⁰ Hence, OPRI has expertise in identifying duplicate records of patients who are present in both OPCR and CPRD datasets (estimated to be in 2% of cases) by matching on a number of variables, such as the year of birth, gender and index date.

As CPRD and OPCR may contain identical data from a subset of patients extracted from the same primary care practice EMR systems, there is a risk of patient duplication. CPRD GOLD, which is the database to which we have requested access contains data from practices using Vision software only; OPCR contains data from a range of software providers including EMIS, iSoft, Microtest, SystemOne and Vision. For this study, we will take a conservative

[‡] For patients aged ≥ 18 Ankylosing spondylitis, Sjogren's syndrome, Systemic lupus erythematosus, Temporal arteritis, Ulcerative colitis, Psoriatic arthritis, Multiple sclerosis, Polymyalgia rheumatica, Crohn's disease, Cancer of respiratory system

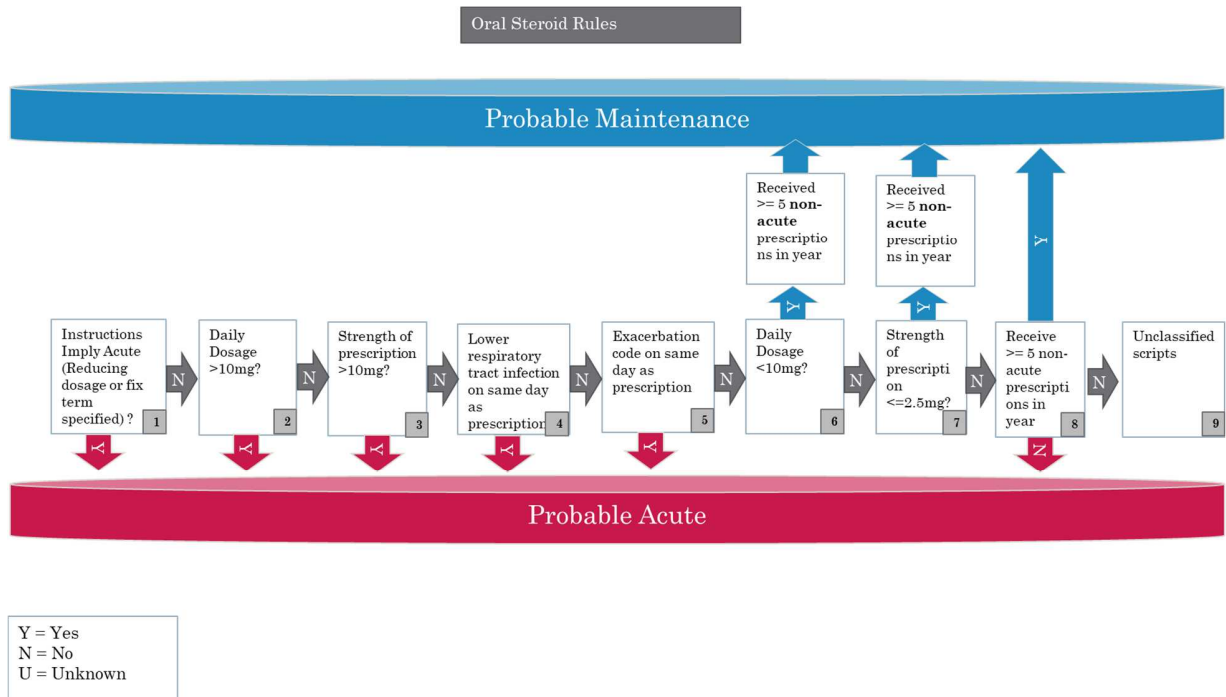
[§] Patients aged >4 & <18 : Analysis of concurrent OCS and diagnoses will determine exclusion conditions

approach and drop all data from Vision practices from the OPCRD database prior to commencing the study, to completely avoid overlap of GP practices with CPRD. Vision data constitutes about 12% of the OPRD database so we do not anticipate this will have a significant impact on final patient numbers.

Study inclusion and exclusion criteria listed above will be used to select the study population. Patients OCS prescriptions will then be classified as acute using an existing OPRI OCS algorithm (Figure 1).

The OPRI OCS algorithm uses information associated to the OCS prescriptions to determine whether they were likely an acute/intermittent or a maintenance script. This is done in a stepwise approach using the most definitive information first e.g. the dosing instructions. For prescriptions that do not enable a decision using the dosing instructions the next most definitive information is used, this being the daily dose. This approach has been used in previous OPRI studies to determine intermittent/maintenance OCS prescribing.

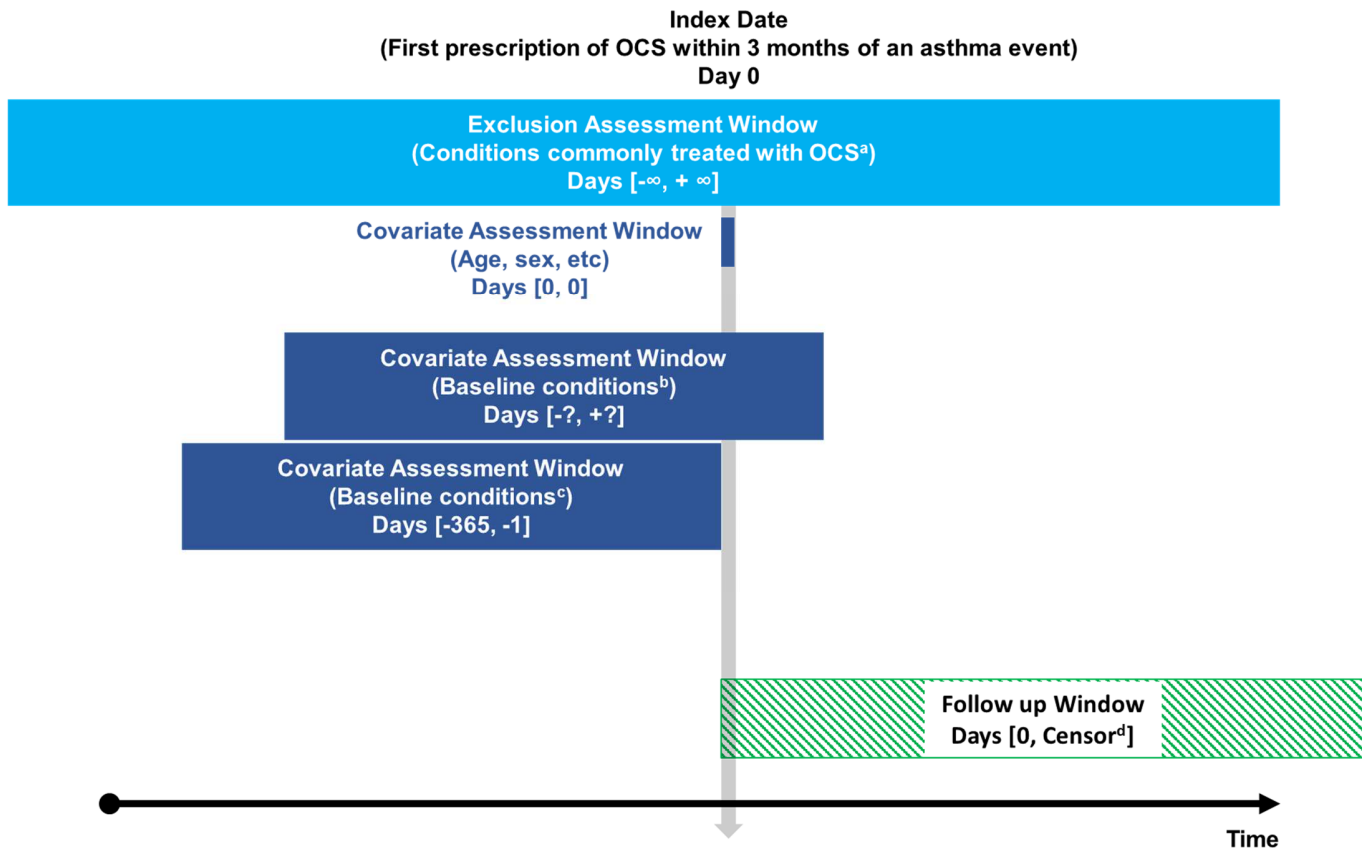
Figure 1 – OPRI OCS Algorithm to classify acute & maintenance (doses represent Prednisolone equivalent)



Inclusion and exclusion criteria will be used to define the patient population. Patients index date will be determined as their first OCS prescription with a concurrent (+/- 3 month i.e. 6-month interval) asthma event (Figure 2). Patients will be categorised according to their OCS patterns as defined previously (Table 1) and by demographic, clinical, and therapy indicators indicated below. Baseline patient characteristics to be described as part of Objective 1 include:

- patient characteristics described prior to index date
- length of patient record prior and after index date
- age of onset of asthma (age at first asthma diagnosis ever)
- time from first asthma diagnosis date to index date
- ICS and SABA use by OCS patterns and OCS patterns by ICS and SABA use
- patient’s treatment by GINA (2019) treatment step prior to index date

Figure 2 - Study Design



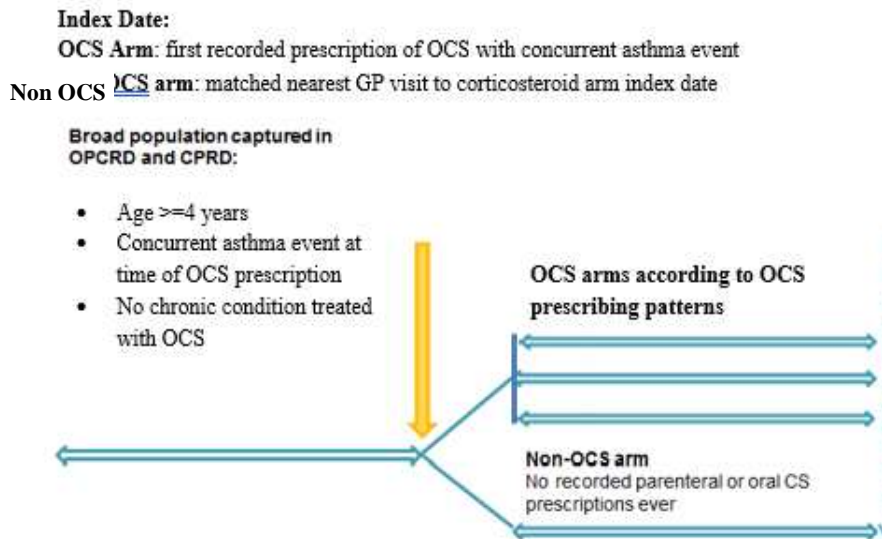
- Ankylosing spondylitis, Sjogren's syndrome, Systemic lupus erythematosus, Temporal arteritis, Ulcerative colitis, Psoriatic arthritis, Multiple sclerosis, Polymyalgia rheumatica, Crohn's disease, Cancer of respiratory system
- Baseline conditions included e.g. most recent Height & Body Mass Index etc
- Asthma Severity (GINA [2019] treatment step), BEC, Lung Function
- Censored due to patient receiving a maintenance OCS prescription, leaving the database (de-registration or death), last collection date, or first AE event

OCS = Oral Corticosteroid
 BEC = Blood Eosinophil Count

Objective 2: To assess the association between different patterns of intermittent OCS use and OCS-related adverse outcomes in patients with asthma

A matched historical cohort study will be performed among patients selected from two anonymised, real-life databases containing patient's electronic medical records extracted from general practices in the United Kingdom (UK). The duration of the study will be from the time of the patient's first OCS with concurrent asthma event until the end-of-records. The study will compare patients exposed to intermittent oral corticosteroids (OCS arm) and patients with asthma without any exposure to oral corticosteroids (non-OCS arm) (figure 3).

Figure 3 – Objective 2 Study design



The index date for the OCS arm will be the first recorded prescription of an OCS corticosteroid, while that of the non-OCS arm will be the nearest GP visit to the index date for the matched OCS arm patient. Patients within the two arms will be matched on gender

Primary outcome will be a diagnostic Read code for the following conditions: type 2 diabetes mellitus, osteoporosis/osteoporotic fractures, hypertension, glaucoma, sleep apnoea, weight gain** and depression/anxiety, pneumonia, cataracts, sleep disorders, cardiovascular disease, chronic kidney disease, dyslipidaemia and peptic ulcer disease, and in the adolescent population we will look for growth suppression and behavioural disorders.

Post hoc analysis will be undertaken to describe the rapidity of AE following OCS index.

** Weight gain - Defined as: Increase in Body Mass Index (BMI)h by at least 1 kg/m² compared to index date

Sample Size Estimations:

Diabetes: approximately 950 events will be needed to detect a 34% risk increase of diabetes onset for OCS patients,³¹ assuming a two-sided alpha level of 0.05, power of 90%, ratio of cases to controls 1:3 and a correlation to other covariates of 0.3. With a baseline cumulative incidence of diabetes of 4%, this would mean following up approximately 4,800 patients over a period of 5 years or 12,000 patients over 2 years.

Osteoporosis/fracture risk: approximately 1000 events will be needed to detect a 33% risk increase of fracture at any site for OCS patients,³² assuming a two-sided alpha level of 0.05, power of 90%, ratio of cases to controls 1:3 and a correlation to other covariates of 0.3. With a baseline cumulative incidence of osteoporosis of 1.6%, this would mean following up approximately 12,500 patients over a period of 5 years or 31,000 patients over 2 years.

Pneumonia: approximately 140 events will be needed to detect a 2.17-fold increase in pneumonia risk for OCS patients³³ assuming a two-sided alpha level of 0.05, power of 90%, ratio of cases to controls 1:3 and a correlation to other covariates of 0.3. With a baseline cumulative incidence of pneumonia of 0.45%, this would mean following up approximately 6,000 patients over a period of 5 years or 15,000 patients over 2 years.

A matched historical cohort study will be performed with an assessment of potential confounders during a baseline period prior to the index date. To address potential differences between treatment arms, patients will be matched initially on gender, and the index date. Other potential confounders (listed in 4.1.1) will be identified during the model building, using potential bias assessments of covariates, together with expert input.

For each risk cohort, patients are excluded if they had a record of the condition of interest before the index date.

Objective 3: To describe the impact of different patterns of intermittent OCS use on the frequency of healthcare resource utilisation in patients with asthma.

CPRD HES linked data will be used to describe hospital admissions, A&E attendances, and Outpatient visits

All HRU events and asthma specific events will be described for eight HRU categories described further below. These will be described for each of the prescribing pattern categories.

1. Physician office visits, categorized as 0, 1-4, 5-8, 9-12, 12-24, ≥ 25 :

- a. General Practitioner (GP) consultations, all-cause
- b. Respiratory-related GP consultations
2. Outpatient visits (CPRD-HES only):
 - a. Referrals to specialist, all-cause
 - b. Referrals for asthma or other lower respiratory conditions
3. A&E attendances (CPRD-HES only):
 - a. All-cause,
 - b. Respiratory-related^{††}
4. Hospital attendances, number of spells, *including day cases*:
 - a. All-cause
 - b. Asthma (ICD-10 J45/J46) as primary diagnosis
 - c. Asthma (ICD-10 J45/J46) at any diagnostic position
 - d. Respiratory conditions (ICD-10 J00-J99) as primary diagnosis
5. Hospital attendances, number of spells, *excluding day cases*:
 - a. All-cause
 - b. Asthma (ICD-10 J45/J46) as primary diagnosis
 - c. Asthma (ICD-10 J45/J46) at any diagnostic position
 - d. Respiratory conditions (ICD-10 J00-J99) as primary diagnosis
6. Hospital attendance, length of stay, *overall*: cumulative number of days per patient (including values of zero for patients not admitted to hospital)
 - a. All-cause
 - b. Asthma (ICD-10 J45/J46) as primary diagnosis
 - c. Asthma (ICD-10 J45/J46) at any diagnostic position
 - d. Respiratory conditions (ICD-10 J00-J99) as primary diagnosis
7. Hospital attendances, length of stay, ≥ 1 *overnight*: cumulative number of days per patient, only reported for patients who remained overnight
 - a. All-cause
 - b. Asthma (ICD-10 J45/J46) as primary diagnosis
 - c. Asthma (ICD-10 J45/J46) at any diagnostic position
 - d. Respiratory conditions (ICD-10 J00-J99) as primary diagnosis
8. Day cases, number of spells (discharge date = admission date):
 - a. All-cause
 - b. Asthma (ICD-10 J45/J46) as primary diagnosis
 - c. Asthma (ICD-10 J45/J46) at any diagnostic position
 - d. Respiratory conditions (ICD-10 J00-J99) as primary diagnosis

Objective 4: To describe the AE for patients with an average annual OCS dose of 250-499mg, 500-999mg, or ≥ 1 g of OCS during the follow up.

The unadjusted incidence rate of each adverse outcome in the OCs categories (250-499mg, 500-999mg, or ≥ 1 g) and non-OCS arms, as cases per 100 patient-years of follow-up (100 pt-yr), will be compared using the incidence rate difference and the incidence rate ratio (IRR)

^{††} HES variables DIAG2 = 25 (Respiratory conditions) or DIAG = 'AST%' or DIAG2 = 'J4%'

with 95% CIs. Each patient will be followed until the first occurrence of the outcome of interest and will be censored at death or the end of available records.

Objective 5: To describe the the longitudinal patterns of intermittent OCS use in the last five years of follow-up among patients who had more than one year of follow-up and were frequent OCS users in their final year of follow-up, and to identify factors that are independently associated with frequent OCS use. Analyses will be stratified by blood eosinophil counts closest to the index date.

The longitudinal patterns of intermittent OCS prescriptions in the last five years of follow-up will be described for those who had more than one year of follow-up and were frequent OCS users in their final year of follow-up. Patients with one year or shorter duration of follow-up will be excluded from this objective's analyses. The system developed in Objective 1 (one-off, sporadic, infrequent, moderately frequent, and frequent) will be used for describing the aforementioned longitudinal patterns. These patterns may be categorized, and the numbers and characteristics of patients for each pattern category may be described. The cumulative dosage of OCS used in the final year of follow-up will also be described for these patients.

Furthermore, factors that are independently associated with frequent OCS use will be identified. The analytic results will be further stratified by the blood eosinophil counts measured closest to the index date (<150 per mL, 150-300 per mL, and >300 per mL). A sensitivity analysis will also be performed, in which patients without baseline asthma treatments will be excluded.

3.4 Study Population

The most recent extraction of EMR data from OPCR and CPRD with linked HES data (HES data is currently upto March 2019) general practices for patients diagnosed with asthma, with no asthma resolved code to the latest available data.

The index date will be the patients first prescription of OCS within 3 months of an asthma related event (medication, asthma consultation and/or asthma diagnosis). Patients will be followed until the end of their EMR or their first prescription of a maintenance OCS. A 3-month window around the initial OCS date was included to help ensure that the OCS prescription related to an asthma clinical event.

3.5 Inclusion Criteria

The index date (ID) will be defined as the first OCS prescription for patients aged 4 or over within the study period with evidence of asthma (medication, asthma consultation and/or asthma diagnosis) in a 3-month window (either before or after the OCS prescription). Patients will also require at least 12 months baseline data (prior to index date) (Figure 2).

3.6 Exclusion Criteria

Asthma patients will be excluded if they have a chronic condition that is commonly treated with Oral Corticosteroids (i.e. ankylosing spondylitis, Sjogren's syndrome, systemic lupus

erythematosus, temporal arteritis, ulcerative colitis, psoriatic arthritis, multiple sclerosis, polymyalgia rheumatica, Crohn's disease, cancer of respiratory system) recorded in at any time in the database.

Patients with a chronic AE outcome prior to the index date will be excluded from the analysis. This will ensure that the first chronic condition is the post index date incident event.

Patients in receipt of maintenance therapy will be excluded from the analysis as per the OPRI OCS algorithm.

3.7 Participant Follow-up

Data will be right censored at the end of data availability

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

4.1 Exposures

Exposure will be defined as a prescription of oral corticosteroids, which is prescribed for the treatment of a condition of interest (medication, asthma consultation and/or asthma diagnosis) during the calendar year of analysis.

The systemic corticosteroids contributing to OCS exposure in this study are shown in Table 2. Doses will be converted into prednisolone equivalents using the defined daily dose (DDD) obtained from the ATC/DDD classification system.³⁴

Table 2 - Oral corticosteroid drugs

| Drug name | Prednisolone equivalent conversion factor | ATC code systemic use | DDD |
|--------------------|--|------------------------------|------------|
| Betamethasone | 6.67 | H02AB01 | 1.5 |
| Cortisone | 0.27 | H02AB10 | 37.5 |
| Deflazacort | 0.67 | H02AB13 | 15 |
| Dexamethasone | 6.67 | H02AB02 | 1.5 |
| Hydrocortisone | 0.33 | H02AB09 | 30 |
| Methylprednisolone | 1.33 | H02AB04 | 7.5 |
| Prednisolone | 1.0 | H02AB06 | 10 |
| Prednisone | 1.0 | H02AB07 | 10 |
| Triamcinolone | 1.33 | H02AB08 | 7.5 |

OCS utilisation will be classified into periods of distinctive utilisation patterns. OCS utilisation patterns based on the spacing of OCS bursts until an event date will be used to classify OCS patterns. These patterns described previously (table 1) are:

- a) One off – patients with only one OCS prescription,
- b) Sporadic – prescriptions with gaps 365 days or over,
- c) Infrequent – prescription with gaps of between 182 – 365 days,
- d) Moderately infrequent - prescription with gaps of between 90 and 182 days,
- e) Frequent – prescription gaps of less than 90 days and
- f) Mixed – Patients with a mixture of the patterns listed above.

Feasibility analysis described have already described the OCS patterns within the OPCRCD data (1.4). The patterns for analysis in this study will include:

Patients that received a single OCS prescription,

Patients that received frequent or frequent and other mixed prescribing patterns

Patients that received sporadic or sporadic including other prescribing patterns

Sensitivity analysis will be included in these analyses following expert input from the steering committee.

4.1.1 Covariates/potential confounders add into analysis

Other covariates/potential confounders to be investigated include but not limited to:

- Baseline demographic variables
- Asthma severity (GINA treatment (2020))
- Inhaled corticosteroid use

4.2 Outcomes

Objective 1: To classify intermittent OCS prescriptions for patients with asthma and to describe longitudinal patterns of intermittent (acute) OCS use by GINA step, and ICS and SABA use.

Patients in receipt of maintenance therapy will be excluded from this analysis, baseline patient characteristics to be described as part of Objective 1 include:

- patient characteristics (age, gender, BMI, asthma control RCP3, blood eosinophil count, lung function) described prior to index date

- length of patient record prior and after index date
- age of onset of asthma (age at first asthma diagnosis ever)
- time from first asthma diagnosis date to index date
- ICS and SABA use prior to index date
- patient's treatment by GINA (2019) treatment step prior to index date

Objective 2: To assess the association between different patterns of intermittent OCS use and OCS-related adverse outcomes in patients with asthma

Patients in receipt of maintenance therapy will be excluded from this analysis. For each corticosteroid-related conditions, a multivariable Cox proportional hazard model will be fitted for each of the intermittent OCS patterns.³⁵ Conditional regression will be used to compare OCS use with non-OCS use in the matched populations. Regular Cox regression will be used to assess the hazard ratios of exposure in the OCS-arm only, either as continuous (dose/year) or categorical variables. Time to event will be defined as the time between index date and the onset of an AE. Patients without an AE will be censored at the end of follow-up.

Each analysis will be adjusted for the variables identified as confounders in the post-matching baseline analysis (section 4.1.1). Since it can be expected that variables can have similar associations with exposure and/or outcome, we will assess their bias conditional on the variables already in the model. Starting with a model containing the exposure measure and the variables that were forced into the model, all available covariates will be assessed on their bias potential (the relative change in coefficient they cause by being added to the model). The variable with the highest bias potential of at least 2% will be added to the model. Then, this process is repeated until either no more candidate confounders are available, or all available covariates show a bias potential of less than 2%.

Different time-dependent treatment measures (SABA use, ICS, and other maintenance use to determine GINA step) will be explored as covariates, as have been applied in previous studies: cumulative dose (g) and average daily exposure (mg/day).

A patient's cumulative dose will be calculated as the sum of all prednisolone, or equivalent, doses (g) prescribed from index date up until the outcome event. In case of time-varying exposure, this will be assessed at the occurrence of each new prescription. In case of assessment at the end of follow-up, this will be assessed at the moment of the onset of the condition of interest, or the end of follow-up. Average daily exposure will be calculated by dividing the cumulative OCS dose received by a patient, by the time since index date.

Primary Outcome Variables

Onset will only be examined in the group of patients without a recorded clinician diagnosed condition prior to the index date.

1. Type 2 diabetes mellitus onset

Defined as:

- i. Diagnosis of type 2 diabetes mellitus (Read code post index date) AND/OR
- ii. Antidiabetic medication prescriptions in outcome period AND/OR
- iii. HbA1c \geq 6.5% in outcome period (Read code post index date)

2. Osteoporosis/osteoporotic fracture onset

Defined as:

- i. Osteoporosis diagnostic code in outcome period (Read codes) AND/OR
- ii. Osteoporotic fractures (hip, wrist or spinal fracture types only will be considered). A recurring fracture of the same site within 8 weeks of the previous fracture date will be counted as the same fracture. However, the patient will still be at risk of a fracture at a different site any time after the date of previous fracture

3. Hypertension onset

Defined as: Hypertension diagnostic code in outcome period (Read codes)

4. Glaucoma onset

Defined as:

- i. Glaucoma diagnostic code in outcome period (Read codes) AND/OR
- ii. Treatment for Glaucoma in the outcome period (section 4.1.7, Product/Read codes)

5. Sleep apnoea onset

Defined as:

- i. Sleep apnoea diagnostic code in outcome period (Read codes) AND/OR
- ii. Referral to sleep clinic in the outcome period AND
- iii. Usage of a continuous positive airway pressure (CPAP) device

6. Weight gain

Defined as:

Increase in Body Mass Index (BMI) by at least 1 kg/m² compared to index date in adults and more than 1% centile band.³⁶

7. Depression/anxiety onset

Defined as:

- i. Depression/anxiety diagnostic code in outcome period (Read codes) OR
- ii. Depression/anxiety diagnostic code in outcome period AND antidepressant medications in the outcome period (section 4.1.7, Product/Read codes)

8. Pneumonia onset

Defined as:

Pneumonia diagnostic code in outcome period (Read codes). A recurring diagnosis of pneumonia within 4 weeks of prior diagnosis will be considered as the same event.

9. Cataracts onset

Defined as:

- i. Cataract diagnostic code in outcome period (Read codes) AND/OR
- ii. Cataract surgery (Yes/No)

10. Sleep disorders onset

Defined as:

- i. Sleep disorder diagnostic code in outcome period (Read codes) AND/OR
- ii. Sleep disorder diagnostic code and hypnotic medications in the outcome period (Read codes)

11. Cardiovascular disease onset

Defined as:

Cardiovascular disease diagnostic code for myocardial infarction, heart failure or stroke in outcome period (Read codes)

12. Renal impairment onset

Defined as:

- i. Chronic kidney disease diagnostic code (only CKD stages 3a, 3b, 4 or 5 will be considered) AND/OR
- ii. eGFR <60 mL/min/1.73m² in outcome period (Read codes) AND/OR
- iii. Dialysis code in the outcome period (Read codes) AND/OR
- iv. Renal transplant code in the outcome period (Read codes)

13. Dyslipidaemia onset

Defined as:

- i. Total cholesterol readings >6.5 mmol/l in outcome period AND/OR
- ii. Low-density lipoprotein (LDL) readings >4 mmol/l in outcome period) AND/OR
- iii. Triglycerides readings ≥ 2.3 mmol/L in outcome period AND/OR
- iv. Diagnostic code for dyslipidaemia OR hyperlipidaemia OR hypercholesterolaemia OR hypertriglyceridaemia.

14. Peptic ulcer disease onset

Defined as:

Peptic ulcer disease diagnostic code (with endoscopy code for gastric ulcer and duodenal ulcer) in outcome period (Read codes)

15. Adolescent population – Behavioural disorders

Defined as:

Diagnostic code in outcome period to be determined by steering committee (Read codes)

16. Adolescent population - Growth suppression

Defined as:

Diagnostic code in outcome period (Read codes)

17. Mortality – Will be considered for inclusion at a later stage

Defined as:

Death certificate with AE (to be determined at a later stage) as the primary cause of death

Objective 3: To describe the impact of different patterns of intermittent OCS use on the frequency of healthcare resource utilisation in patients with asthma.

Patients in receipt of maintenance therapy will be excluded, outcomes are described as mean numbers \pm standard deviation (SD), as median numbers with the interquartile range (IQR) and as categorical variables (0, 1, 2, 3, ≥ 4) for hospital admissions, A&E attendances and outpatient visits and specified below for other variables. Length of stay in hospital will be described as mean days \pm standard deviation (SD), as median numbers with the interquartile range (IQR) and as categorical variables (0, 1, 2-7, 8-14, ≥ 14 days)

The HRU outcomes and associated costs will be calculated as annualised HRU and annualised costs for each of OCS pattern.

Annualised HRU will be calculated as:

$$\frac{\sum \text{Count of HRU: index date till end of records}}{\text{Total months: index date till end of records}} \times 12$$

Annualised cost will be calculated as:

$$\frac{\sum \text{Cost of HRU: index date till end of records}}{\text{Total months: index date till end of records}} \times 12$$

- Prices assigned to primary care consultation costs will be taken from the latest Personal Social Services Research Unit (PSSRU) document (<https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2018/>)
- Prices assigned to secondary care costs will be based on the national average hospital costs as found in PSSRU document
- Prices assigned to drugs will be taken from the Dictionary of Medicines and Devices browser (<http://dmd.medicines.org.uk/>). The electronic British National Formulary (eBNF) and the Medical Index of Medicinal Substances (MIMS) will be used to fill any gaps

HRU and associated costs will be assessed annually, and annual averages for the follow-up period will be calculated. We will estimate HRU-associated all-cause and cause-specific costs (2018 £) by multiplying HRU outcomes by the estimated unit costs associated with each HRU outcome from the Personal Social Services Research Unit, and the Dictionary of Medicines and Devices browser. Prescription costs will be obtained by multiplying cost by amount prescribed. Annualized HRU and healthcare costs will be reported for each OCS pattern.

Objective 4: To describe the AE for patients with an average annual OCS dose of 250-499mg, 500-999mg, or =>1g of OCS during the follow up.

The unadjusted incidence rate of each adverse outcome in the OCs categories (250-499mg, 500-999mg, or =>1g) and non-OCS arms, as cases per 100 patient-years of follow-up (100 pt-yr), will be compared using the incidence rate difference and the incidence rate ratio (IRR) with 95% CIs. Each patient will be followed until the first occurrence of the outcome of interest and will be censored at death or the end of available records.

Objective 5: To describe the the longitudinal patterns of intermittent OCS use in the last five years of follow-up among patients who had at least one year of follow-up and were frequent

OCS users in their final year of follow-up, and to identify factors that are independently associated with frequent OCS use. Analyses will be stratified by blood eosinophil counts closest to the index date.

The longitudinal patterns of intermittent OCS prescriptions in the last five years of follow-up will be described for those who had at least one year of follow-up and were frequent OCS users in their final year of follow-up. The system developed in Objective 1 (one-off, sporadic, infrequent, moderately frequent, and frequent) will be used. These patterns may be categorized, and the numbers and characteristics of patients for each pattern category may be described. The cumulative dosage of OCS used in the final year of follow-up will also be described for these patients.

Furthermore, factors that are independently associated with frequent OCS use will be identified. The analytic results will be further stratified by the blood eosinophil counts measured closest to the index date (<150 per mL, 150-300 per mL, and >300 per mL). A sensitivity analysis will also be performed, in which patients without baseline asthma treatments will be excluded.

4.3 Other Variables and Covariates

Table 2 - Variable measured at baseline

| Fixed variables measured at baseline | |
|--------------------------------------|---|
| Age | Age in years on index date. |
| Gender | Female or Male |
| Height | Measurement in metres (m) on reading closest to index date, in adulthood Defined as the ratio of weight (kg) to squared height (m ²) closest to the index date. Categorised as: <u>Adolescent</u> (<18yo) ³⁷ Calculated using UK reference population. Standardised BMI z-score based upon gender, weight, height and age |
| Body Mass Index (BMI) | <u>Adult</u> (18 and over) <ul style="list-style-type: none">• Underweight <18.5• Normal weight 18.5 to <25• Overweight 25 to <30• Obese 30 and over |
| Age of Asthma Onset | This will be estimated from the available patient history using appropriate algorithms |

| | |
|---|---|
| Asthma severity | Patients categorised by GINA Treatment Steps |
| Asthma Control using RCP3 questionnaire | RCP questions recorded as part of an asthma review. Categorised as: <ul style="list-style-type: none"> • Controlled • Not controlled |
| Blood eosinophil count (BEC) | Highest blood eosinophils (10^9 cells/L) in baseline year (or closest within 5 years of baseline). Categorised into groups of 10×10^9 cells/L (e.g. <0.05, 0.05-<0.25, 0.25-<0.35, etc) |
| Lung function | Percent predicted PEFR at index date. Percent predicted FEV ₁ at index date. |
| Total years of follow-up | Total follow-up time following index date |
| Number of SABA prescriptions (asthma control) | Total number of SABA prescriptions/inhalers/dose in baseline year (i.e. the year prior to the index date. Categorised e.g. by 0, 1-2, 3-11, 12+, and 0,1-2,3+ |
| Number of ICS prescriptions | Total number of ICS prescriptions/inhalers/dose in baseline year (i.e. the year prior to the index date. Categorised by maximum dose e.g. by 0 or 1+ etc |

Table 3 - Variable measured during follow up

| Time-varying variables measured during follow-up | |
|---|---|
| SABA | Cumulative sum of SABA prescriptions up until the end of follow-up/year |
| | Cumulative dose of SABA (number of inhalers) up until end of follow-up/year |
| ICS | Cumulative sum of ICS prescriptions up until the end of follow-up as a proportion of total years of follow-up, and/or |
| | Cumulative dose of ICS (number of inhalers) up until end of follow-up as a proportion of total years of follow-up |
| | (Includes ICS-only inhalers and ICS-combination inhalers) |
| Other maintenance therapy to determine GINA step of treatment | Prescriptions up until the end of follow-up as a proportion of total years of follow up for LABA, LAMA, LTRA, anti-IL-5, anti-IgE and anti-IL-13 medications (Long-acting beta-agonists (LABA), long acting muscarinic antagonist (LAMA), Leukotrine receptor antagonist (LTRA)) |

4.3.1 Missing Data

Imputation of Prescription Strength and Dose

| Missing value | Rule(s) |
|--|---|
| Date (days & months) | <ul style="list-style-type: none"> - Impute 15th of the month for missing days - Impute July 1st for missing days and months |
| Strength from generic active ingredient read codes | <ul style="list-style-type: none"> - Affects < 1% observations - Impute strength of branded/generic drug of the same active ingredient (by Read code) that is most frequently prescribed |
| Invalid quantity (number of units prescribed) | <ul style="list-style-type: none"> - Up to 35% invalid observations. Mostly quantity = 0 1. Impute most common strength of the same drug (by strength & Read code) for the patient 2. Impute most common quantity of drug of the same strength (by strength & Read code) prescribed for the OCS-related condition 3. Impute based on clinical input |

4.3.2 Strengths and Limitations

It is worth noting that this analysis aims to include patients that are definite intermittent OCS users and therefore may exclude some patients that are potentially intermittent OCS patients. This a strength of the study, since specificity of exposure is more important than sensitivity in studies aimed at evaluating safety.

This study will use all eligible patients in two large real-world databases. The real-life design of this study provides high generalisability of the results to primary care patients managed in actual primary care practice. Additionally, the long observation period is a strength of the OPCR and CPRD data for longitudinal studies.

This analysis will therefore likely be based on intermittent patients receiving a lower dose of OCS than those that are possible intermittent OCS patients, these results will therefore be conservative.

Exposure to OCS is estimated based on the number of prescriptions over time, which does not guarantee correct administration of OCS doses as prescribed.

Some of the study patients might have been exposed to systemic steroids outside the scope of the available medical record information, administered within a secondary care setting which isn't subsequently recorded on the patient's primary care EMR. Patients also move between GP practices which often makes their prior records inaccessible.

Using the first AE will underestimate the results as censoring patients after the onset of any outcome will exclude recurrent events.

Analysis of OPCRCD does not have a link to secondary care and emergency department data, therefore, exposure to OCS prescribed in hospital cannot be considered. However, we know from our previous work that the mean asthma-related hospitalisation rate is 0.02 per year, so it is unlikely that this will relevantly influence the results; some hospital admission exacerbation records may not be recorded in the primary care records.

While a sophisticated algorithm based on all available data will be used, and this will be validated using expert opinion, it is possible that some of the OCS prescription may be misclassified.

The datasets represent information collected for clinical and routine use rather than specifically for research purposes. The validity and completeness of individual patient records cannot be assessed.

This analysis may have residual confounding due to factors that were not considered.

5. STATISTICAL ANALYSIS PLAN

5.1 Statistical Methods – General Aspects

5.1.1 Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. descriptive statistics, hazard ratios, incidence rates, test/retest reliability)

The distribution of values at each decision step of the OPRI OCS algorithm (Figure 1) will be displayed as a histogram, expert opinion will review these histograms and determine whether the existing decision points are the most appropriate. Summary statistics will be provided for the prescriptions decisions.

Sequence and pattern analysis will be used to describe OCS prescribing patterns and determine OCS prescribing categories (e.g. absence, sporadic, infrequent, moderately frequent, frequent OCS bursts) that best describe the observed longitudinal OCS prescribing records.

Statistical analysis for the baseline variables for each of the OCS prescribing categories will be descriptive in nature. They will provide the absolute and relative number of subjects, mean, median, standard deviation, and interquartile range for continuous variables for the baseline variables.

Analyses will be completed in the total study population and stratified by asthma severity, measured by GINA treatment step (2019 version), SABA and ICS use for the following age subgroups:

- o $\geq 4 - 11$ years,
- o $\geq 12 - 17$ years,
- o $\geq 18 - 64$ years, and
- o $\geq 65+$ years

Latent class analysis of the annual OCS exposure starting at the index date for patients that have complete data will be undertaken. This will enable the most important patterns in the population to be determined and related to baseline characteristics.

5.1.2 Exploratory analyses in Objective 5

Analyses in Objective 5 will be stratified for blood eosinophil counts obtained closest to the index date, using the following subgroups:

- o < 150 per mL,
- o $150-300$ per mL, and
- o > 300 mL.

Additionally, factors that are independently associated with frequent OCS use will be identified using multivariable Cox regression with the time to frequent OCS use as the dependent variable, and with consideration of time-varying covariates. A sensitivity analysis will also be performed, in which patients without baseline asthma treatments will be excluded.

5.1.3 Missing Data

Missing data for BMI, smoking status and PEF % predicted will be imputed using multiple imputation techniques.

Missing dosing instructions for OCS and other medication groups will be imputed using modal daily doses at patient-drug level and drug level, respectively.

5.2 Bias

5.2.1 Methods to Minimize Bias

There could be misclassification of disease status due to either a limited availability of medical history in a patient's medical record, or incomplete registration by the GP. QOF helped ensure accurate recording of consultations, prescriptions and referrals related to specific conditions that fall within the QOF. Restricting analysis to a period after 2004 when the Quality and Outcomes Framework (QOF) came into effect in 2004 in the UK will help ensure misclassification of disease is restricted.²⁷

5.2.2 Strengths and Limitations

It is worth providing the caveat that this analysis aims to include patients that are definite intermittent OCS users and therefore may exclude some patients that are potentially intermittent OCS patients. This analysis will therefore likely be based on intermittent patients receiving a lower dose of OCS than those that are possible intermittent OCS patients.

Analysis of OPCRCD does not have a link to secondary care and emergency department data, therefore, exposure to OCS prescribed in hospital cannot be considered. However, we know from our previous work that the mean asthma-related hospitalisation rate is 0.02 per year, so it is unlikely that this will relevantly influence the results some hospital admission exacerbation records may not be recorded in the primary care records.

While a sophisticated algorithm based on all available data will be used, and this will be validated using expert opinion, it is possible that some of the OCS prescription may be misclassified.

The datasets represent information collected for clinical and routine use rather than specifically for research purposes. The validity and completeness of individual patient records cannot be assessed.

6. STUDY CONDUCT AND REGULATORY DETAILS

6.1 Data Management

CPRD data are delivered by AZ through their license. Database construction and analyses of data will be performed by OPRI.

6.2 Study Conduct

Analyses will be performed by the Observational & Pragmatic Research Institute.

A steering committee of respiratory research experts will be established to advise on the study.

Suggested members of the steering committee are:

- Josef Smolen (Internal Medicine, Medical University of Vienna, Austria)
- Andrew Menzies-Gow (Royal Brompton & Harefield NHS Foundation Trust, UK)
- David Jackson (Faculty of Medicine, National Heart & Lung Institute, Imperial College London, UK)
- Anaud Bourdin (Centre Hospitalier Universitaire de Montpellier, France)
- Prof David Price (OPRI)
- Dr Trung N. Tran (AZ)

6.2.1 Study Flow Chart and Plan

| TIMELINE PROJECTION TO STUDY COMPLETION | | |
|---|-------------------------|---------------------|
| Department/Activity | Estimated Delivery Time | Contracted Timeline |
| Draft Protocol to AZ (Objective 1) | | 03.08.2020 |
| Final Protocol to ADEPT & ISAAC (Objective 1) | +2 weeks (2 week) | 17.08.2020 |
| Dataset Created: OPCRD (Objective 1,2 & 4) | +2 week (4 weeks) | 31.08.2020 |
| Analysis OPCRD (Objective 1,2 & 4) | +5 week (9 weeks) | 05.10.2020 |
| Potential Arrival of CPRD data | (9 weeks) | 05.10.2020 |
| Dataset Created: CPRD (Objective 1-4) | +3 weeks (12 weeks) | 26.10.2020 |
| Analysis CPRD (Objective 1-4) | +5 weeks (17 weeks) | 30.11.2020 |
| Final Study Report Delivery | +8 weeks (25 weeks) | 29.01.2021 |

6.2.2 Procedures

6.2.3 Quality Control

All code for dataset generation, dataset preparation and analyses will be reviewed by a second researcher. All data will be reviewed for correctness and completeness, and the data will be cleaned appropriately. All code lists used for this study will be reviewed by a clinician or a pharmacologist.

6.3 Protection of Human Subjects

The Observational Study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, ICH GCPs, GPP and the applicable legislation on Non-Interventional Studies and/or Observational Studies.

The Investigator will perform the Observational Study in accordance with the regulations and guidelines governing medical practice and ethics in the country of the Observational Study and in accordance with currently acceptable techniques and know-how.

6.4 Communication Plan

6.4.1 Publication Plan

The results will be presented in at least in one national/international conference and a manuscript will be submitted to a journal.

6.4.2 Compliance with Study Registration and Results Posting Requirements

The study will be registered at ENCePP (<http://www.encepp.eu/>).

6.4.3 Compliance with Financial Disclosure Requirements

Any information that may be seen as a conflict of interest in terms of compensation or financial interests will be disclosed for each investigator.

7. LIST OF REFERENCES

1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;**388**:1545–602
2. British Thoracic Society/Scottish Intercollegiate Guidelines Network. *British Guideline on the Management of Asthma*. (Scottish Intercollegiate Guidelines Network, Edinburgh, 2016).
3. Royal College of Physicians. *Why Asthma Still Kills: the National Review of Asthma Deaths (NRAD) Confidential Enquiry Report*. (RCP, London, 2014)
4. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;**380**:651–9
5. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;**371**:1198–207
6. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015;**3**:355–66
7. Sweeney J, Patterson CC, Menzies-Gow A, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. *Thorax* 2016;**71**:339–46
8. Global Initiative For Asthma. (2020). Global Strategy for Asthma Management and Prevention. [online] Available at: <https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report-final-wms.pdf> [Accessed 29 April. 2020].
9. Rice JB, White AG, Scarpati LM, Wan G, Nelson WW. Long-Term Systemic Corticosteroid Exposure: A Systematic Literature Review. *Clin Ther*. 2017.
10. Al Efraij K, Johnson KM, Wiebe D, Sadatsafavi M, FitzGerald JM. A systematic review of the adverse events and economic impact associated with oral corticosteroids in asthma. *J Asthma*. 2018:1-13
11. Price DB, Trudo F, Voorham J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy*. 2018;**11**:193-204.
12. Chapman KR. Impact of 'mild' asthma on health outcomes: findings of a systematic search of the literature. *Respir Med*. 2005;**99**(11):1350-1362.

13. Bloom CI, Nissen F, Douglas IJ, Smeeth L, Cullinan P, Quint JK. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. *Thorax*. 2018;**73**(4):313-320.
14. Lefebvre P, Duh MS, Lafeuille MH, et al. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol*. 2015;**136**(6):1488-1495.
15. Covvey J.R., Johnston B.F., Wood F., et al. Is the BTS/SIGN guideline confusing? A retrospective database analysis of asthma therapy. *Prim Care Resp J*, 2013;**22**(3):390-295
16. Arellano FM., et al. Prescription patterns for asthma medications in children and adolescents with health care insurance in the United States. *Pediatr Allergy Immunol*. 2011;**22**:469–476.
17. Luskin AT., et. al. Health care resource use and costs associated with possible side effects of high oral corticosteroid use in asthma: a claims-based analysis. *Clinicoecon Outcomes Res*. 2016;**8**:641–648.
18. Broder MS., Chang EY., and Sapra S. Care of asthma patients in relation to guidelines. *Allergy Asthma Proc* 2010;**31**:452–460.
19. Bengtson LGS, et al. Inhaled corticosteroid-containing treatment escalation and outcomes for patients with asthma in a U.S. health care organization. *J Manag Care Spec Pharm*. 2017;**23**:1149–1159.
20. Lefebvre P., et al. Burden of systemic glucocorticoid-related complications in severe asthma. *Curr Med Res Opin*. 2017;**33**:57–65.
21. Moore WC., et al.; National Heart, Lung, Blood Institute's Severe Asthma Research Program. Safety of investigative bronchoscopy in the Severe Asthma Research Program. *J Allergy Clin Immunol*. 2011; **128**:328–336.
22. Sá-Sousa A., Almeida R., Vicente R. High oral corticosteroid exposure and overuse of short-acting beta-2-agonists were associated with insufficient prescribing of controller medication: a nationwide electronic prescribing and dispensing database analysis. *Clin Transl Allergy*. 2019;**9**:47
23. Zeiger R.S., Schatz M., Qiaowu L., Burden of Chronic Oral Corticosteroid Use by Adults with Persistent Asthma. *J Allergy Clin Immunol Pract*. 2017;**5**(4):1050-1060
24. Ekström M. Nwaru B.I., Hasvold P. et al. Oral corticosteroid use, morbidity and mortality in asthma: A nationwide prospective cohort in Sweden. *Allergy*. 2019;**74**:2181-2190
25. Bleecker E.R., Menzies-Gow A.N., Price D.B., et al. Systemic review of systemic corticosteroid use for asthma management. *Am J Respir Crit Care Med*. 2020;**201**(3) 276-293

26. Optimum Patient Care Research Database (OPCRD) <https://opcrd.co.uk/>
27. Kousoulis, AA., Rafi I., Lusignan S. The CPRD and the RCGP: building on research success by enhancing benefits for patients and practices. *British Journal of General Practice* 2015; 65 (631): 54-55
28. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, Wenzel SE, Wilson AM, Small MB, Gopalan G, Ashton VL. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *The Lancet Respiratory Medicine*. 2015 Nov 30;3(11):849-58
29. Israel E, Roche N, Price D, et al. Increased Dose of Inhaled Corticosteroid versus Add-On Long-acting b-Agonist for Step-Up Therapy in Asthma. *Ann Am Thorac Soc* 2015; 12, 6, 798–806
30. Roche N, Postma D, Price D, et al. Differential Effects of Inhaled Corticosteroids in Smokers/Ex-Smokers and Nonsmokers with Asthma. *Am J Resp Crit Care Med* 2015; 191, 8, 960-964
31. Suissa S, Kezough A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. *American Journal of Medicine*. 2010; 123:1001-1006
32. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. *Journal of Bone and Mineral Research*. 2000a Jun 1;15(6):993-1000
33. Torres A, Peetermans WE, Viegi G, et al. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax*. 2013; 68:1057-1065
34. ATC/DDD Index 2019 [Internet]. [cited 2020 April 16]. Available from: https://www.whocc.no/atc_ddd_index/
35. Cox DR. Regression models and life tables. *J R Stat Soc Ser B* 1972; 34:187–220
36. Brannsether B, Eide GE, Roelants M, et al. BMI and BMI SDS in childhood: annual increments and conditional change, *Annals of Human Biology*, 2017; 44:1, 28-33
37. Cole, T. J., M. C. Bellizzi, K. M. Flegal, and W. H. Dietz. 2000. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 320(7244): 1240–1243.

8. APPENDICES

8.1 BTS Treatment Steps

BTS steps are defined as 1=no regular preventer, 2=lowest ICS dose appropriate for age (or LTRA alone if <5 years), 3=add LABA (add LTRA if <5 years), 4=increase ICS dose to next level (medium in adults, low dose in children), may add in other therapy (adults: LTRA, theophylline, LAMA; children: LTRA), 5=increase ICS dose (high in adults, medium in children), add fourth drug (adults: LTRA, theophylline, beta agonist tablet, LAMA; children: theophylline), 6=same ICS dose and continuous or frequent use of oral steroids

8.2 GINA Treatment Steps

| | Step 1 | Step 2 | Step 3 | Step 4 | Step 5 |
|------------------------------------|---|---|---|--|---|
| PREFERRED CONTROLLER CHOICE | As needed Low dose ICS- formoterol | Daily low dose ICS or as needed low dose ICS- formoterol | Low dose ICS/LABA | Med dose ICS/LABA | High dose ICS/LABA Refer for add-on treatment e.g. tiotropium, anti- IgE, anti- IL5/5R, anti-IL4R |
| Other controller options | Low dose ICS taken with SABA | Leukotriene receptor antagonist (LTRA) or low dose ICS taken with SABA | Med dose ICS Low dose ICS+LTRA | High dose ICS, add-on tiotropium or add-on LTRA (or + theoph) | Add low dose OCS but consider AEs |
| PREFERRED RELIEVER | As needed low dose ICS- formoterol | | As needed low dose ICS-formoterol | | |
| Other Options | As needed SABA | | | | |

8.3 OCS Acute Dosing Instructions

| dose_id | text_dose |
|---------|--|
| 422 | 15 |
| 1062 | 20D |
| 1359 | 30D |
| 2476 | REDUCING |
| 2494 | SIX EVERY DAY |
| 5796 | SIX TO BE TAKEN DAILY |
| 20098 | 6 TABLETS DAILY FOR 10 DAYS |
| 20111 | TAKE 4 DAILY FOR 5 DAYS |
| 20117 | USE 6 TABLETS DAILY FOR 5 DAYS |
| 20118 | 6 ONCE DAILY30 |
| 20119 | SIX TABS DAILY FOR 5 DAYS |
| 20120 | 6tabs daily for 5 days |
| 20123 | TAKE FOUR TABLETS EACH MORNING (AS A SINGLE DOSE) FOR 3 DAYS. |
| 20132 | SIX TABLETS A DAY FOR 5 DAYS |
| 20136 | TAKE 8 TABLETS TOGETHER DAILY FOR 5 DAYS |
| 20140 | 6 TABS IN THE MORNING FOR 5 DAYS |
| 20147 | FOUR TABLETS DAILY FOR FIVE DAYS |
| 20148 | TAKE 6 TABLETS ONCE A DAY FOR 5 DAYS |
| 20161 | TAKE EIGHT TABLETS A DAY FOR FIVE DAYS |
| 20182 | TAKE 8 DAILY FOR 7 DAYS |
| 20196 | 4 a day for 3 days |
| 20198 | Take eight tablets in one dose for five days with food |
| 20200 | four tablets daily for three days |
| 20205 | 6 DAILY FOR SEVEN DAYS |
| 20206 | 6/DAY FOR 5 DAYS |
| 20209 | TAKE 6 A DAY FOR 7 DAYS |
| 20213 | six TABLETS DAILY FOR 3 DAYS |
| 20215 | 6daily for 5 days |
| 20216 | Take six tablets daily for five days |
| 20217 | TAKE 6 DAILY FOR 3 DAYS |
| 20220 | 8 daily for five days |
| 20227 | 8 TABLETS FOR 5 DAYS |
| 20228 | TAKE 8 TABS DAILY FOR 5 DAYS |
| 20229 | 4 DAILY FOR 1 WEEK |
| 20231 | TAKE 6 TABS DAILY FOR 5 DAYS |
| 20237 | eight Tabs Daily for 5 days This medicine can cause irritation of the stomach lining. Eating food before taking it will reduce this effect. If you experience severe indigestion symptoms contact your GP. |
| 20239 | take 4 daily for 3 days |
| 20242 | 6 daily for 5 days only |

20246 8 IN THE MORNING FOR ONE WEEK
20251 TAKE FOUR TABLETS EACH MORNING (AS A SINGLE DOSE) FOR 5 DAYS.
20257 3 TABLETS DAILY FOR 3 DAYS
20259 8D FOR 5D
20260 6 od for one week
20263 TAKE EIGHT DAILY FOR FIVE DAYS
20264 8 tabs altogether for 5 days
20265 8D
20269 TAKE 6 TABLETS FOR 5 DAYS
20274 6 TABLETS DAILY FOR 1 WEEK
20279 4 EVERY DAY FOR 5 DAYS
20283 take 6 tablets a day for 5 days
20284 6 TABS DAILY FOR 1 WEEK
20291 TAKE 8 TABLETS ONCE DAILY FOR 5 DAYS
20295 TAKE 6 PER DAY FOR 5 DAYS
20298 6 TABS ALTOGETHER EACH AM FOR 1 WEEK
20301 four tablets daily for 5 days
20312 8 tablets od for 5 days @NB -
20313 8 TABLETS EVERY DAY FOR 5 DAYS
20318 8 TABS IN THE MORNING FOR 5 DAYS
20319 8 TABLETS ONCE DAILY FOR 7 DAYS
20325 8 together once daily for 5 days
20327 8 ONCE DAILY FOR 1 WEEK
22094 6 EVERY DAY FOR 5 DAYS
22270 30MG EVERY DAY
22271 REDUCING DOSE
22451 eight tablets daily for five days
22458 6 per day for 5 days
22723 8 EVERY DAY FOR 5 DAYS
22724 6 A DAY FOR 5 DAYS
22825 8 TABLETS DAILY FOR 5 DAYS
23386 30mg od
23557 6 daily for 5 days
24893 4 DAILY FOR 5 DAYS
25649 8 od for 5 days
25651 6 EVERY DAY FOR 3 DAYS
25672 4 DAILY FOR 3 DAYS
25681 6 od for 5 days
25682 8 ONCE DAILY FOR 5 DAYS
25842 6 DAILY FOR 3 DAYS
26291 40MG DAILY FOR 5 DAYS

Observational Study Protocol
Study Code << D589BR00053 >>
Version 6.5
Date 01/28/22

| | |
|-------|--------------------------------------|
| 27993 | 30 MG DAILY FOR 5 DAYS |
| 27997 | 30 MG |
| 28161 | 8 TABLETS ONCE DAILY FOR 5 DAYS |
| 28162 | 30 MG (6 TABS) ONCE DAILY FOR 5 DAYS |
| 28550 | 6 ONCE DAILY FOR 1 WEEK |
| 28990 | 40 MG |
| 29865 | 30MGS DAILY |
| 30187 | 5 daily for 6 days |
| 30499 | 4 TABLETS DAILY FOR 5 DAYS |
| 30657 | SIX TABLETS DAILY FOR FIVE DAYS |
| 30845 | 6 TABLETS DAILY FOR 3 DAYS |
| 31102 | 6 tablets daily for 5 days |
| 31363 | eight tablets daily for 5 days |
| 32705 | 5 daily for 5 days |
| 33182 | take six daily for 5 days |
| 33882 | 6 tablets every day for 5 days |
| 34331 | 8 DAILY FOR 1 WEEK |
| 34431 | 8 DAILY FOR 5 DAYS |
| 34434 | 6 TABLETS ONCE A DAY FOR 5 DAYS |
| 34674 | take 6 daily for 5 days |
| 35425 | REDUCING REGIME |
| 39304 | 3 DAILY FOR 4 DAYS |
| 40529 | 8 TABLETS A DAY FOR 5 DAYS |
| 40604 | 6 EVERY DAY FOR 1 WEEK |
| 41142 | take 8 tablets daily for 5 days |
| 41190 | 6 TABLETS A DAY FOR 5 DAYS |
| 41274 | 6 daily for 1 week |
| 41608 | 60D |
| 41669 | 8 A DAY FOR 5 DAYS |
| 41714 | REDUCING DOSE AS DIRECTED |
| 42345 | SIX A DAY FOR 5 DAYS |
| 43629 | 4 a day for 5 days |
| 44189 | SIX TABLETS DAILY FOR 5 DAYS |
| 46636 | 20mg od |
| 46928 | 6 TABS DAILY FOR 5 DAYS |
| 47105 | REDUCING COURSE AS DIRECTED |
| 48505 | 40 mg daily |
| 48627 | TAKE 8 IN THE MORNING FOR 5 DAYS |
| 48869 | 30 MG DAILY |
| 49200 | 40 MG ONCE DAILY FOR 5 DAYS |
| 49470 | 40 MG ONCE DAILY |

Observational Study Protocol
Study Code << D589BR00053 >>
Version 6.5
Date 01/28/22

49562 6 a day for 7 days
49735 30 MG ONCE DAILY FOR 5 DAYS
49777 20 mg daily
51078 20 MG
51100 15 mg daily
51224 8 tabs daily for 5 days
51835 TAKE 6 IN THE MORNING FOR 5 DAYS
52325 6 ONCE DAILY FOR 5 DAYS
52511 60 MG DAILY
52946 8 DAILY FOR 7 DAYS
53177 4 AS DIRECTED
53449 6 DAILY FOR 5 DAYS THEN 3 DAILY FOR 5 DAYS
53770 25 mg daily
53855 EIGHT DAILY FOR FIVE DAYS
54046 8 tabs once daily for 5 days
54930 6 daily for 7 days
55516 20 MG ONCE DAILY
55609 6 ONCE DAILY FOR 3 DAYS
55870 six daily for five days
56199 6 TABLETS ONCE DAILY FOR 5 DAYS
56494 6 A DAY FOR 3 DAYS
57717 6 DAILY FOR 10 DAYS
58165 4 DAILY FOR 7 DAYS
58233 6 DAILY FOR 5 DAYS THEN STOP
58607 REDUCE AS DIRECTED
59820 3 ONCE DAILY FOR 5 DAYS
59892 6 DAILY FOR 2 WEEKS
60299 30 MG IN THE MORNING
61576 3 DAILY FOR 5 DAYS
61786 8 DAILY FOR 3 DAYS
62265 6 DAILY FOR 4 DAYS
62782 6 TABLETS FOR 5 DAYS
63743 6 TABS ONCE DAILY FOR 5 DAYS
64195 take 6 a day for 5 days
64196 40MG DAILY
65831 6 TABS DAILY FOR 7 DAYS
66397 take 6 tablets daily for 5 days
67041 2 DAILY FOR 3 DAYS
67553 4 daily for 5/7
67902 8 a day for 7 days
68067 6 daily for 5days

Observational Study Protocol
Study Code << D589BR00053 >>
Version 6.5
Date 01/28/22

| | |
|--------|-------------------------------------|
| 68368 | six daily for one week |
| 68621 | 3 DAILY FOR 3 DAYS |
| 69045 | 30MG DAILY |
| 72443 | 654321 |
| 72851 | Take six daily for five days |
| 73922 | REDUCING COURSE |
| 75245 | 4 ONCE DAILY FOR 5 DAYS |
| 75642 | 6 DAILY FOR 5 DAYS. |
| 76282 | 6 DAILY 5 DAYS |
| 76993 | TAKE 8 A DAY FOR 5 DAYS |
| 77505 | 6 DAILY FOR A WEEK |
| 77506 | 8 DAILY FOR 10 DAYS |
| 78674 | 6 TABLETS IN THE MORNING FOR 5 DAYS |
| 78676 | Take 8 daily for 5 days |
| 79335 | REDUCING AS DIRECTED |
| 79629 | 30 MG DAILY FOR 3 DAYS |
| 81076 | 15 MG ONCE DAILY |
| 81089 | 4 ONCE DAILY FOR 3 DAYS |
| 81223 | 20 mg daily for 3 days |
| 81448 | 6 ONCE DAILY FOR 7 DAYS |
| 85299 | 8 TABLET(S) DAILY FOR 5 DAYS |
| 85912 | 6 TABS DAILY FOR 3 DAYS |
| 87397 | 8 TABS EVERY DAY FOR 5 DAYS |
| 88697 | 6 daily for five days |
| 89592 | 30MG DAILY FOR 5 DAYS |
| 91933 | 30 MG ONCE DAILY |
| 92254 | 30 MG FOR 5 DAYS |
| 92278 | 6 IN THE MORNING FOR 5 DAYS |
| 92791 | 30 MG ONCE DAILY FOR 3 DAYS |
| 93137 | 8 ONCE DAILY FOR 7 DAYS |
| 93508 | 30 MG IN THE MORNING FOR 5 DAYS |
| 95254 | 8 IN THE MORNING FOR 5 DAYS |
| 100712 | 30 mg od |
| 101139 | 20MG DAILY |
| 102101 | 6 tablets daily after food |
| 102167 | SIX DAILY FOR 5 DAYS |
| 102168 | EIGHT DAILY FOR 5 DAYS |
| 102494 | 6 TABS A DAY FOR 5 DAYS |
| 103958 | 4 DAILY FOR 4 DAYS |
| 106889 | 4 TABS DAILY FOR 3 DAYS |
| 107192 | 6 tablets od for 5 days |

Observational Study Protocol
Study Code << D589BR00053 >>
Version 6.5
Date 01/28/22

| | |
|--------|--|
| 107677 | 6 IN THE MORNING FOR 7 DAYS |
| 107898 | 2 DAILY FOR 5 DAYS |
| 111315 | 8 daily 5 days |
| 112185 | SIX A DAY FOR FIVE DAYS |
| 114254 | 6,5,4,3,2,1 |
| 115664 | 4 TABS DAILY FOR 5 DAYS |
| 115678 | 4 TABLETS DAILY FOR 3 DAYS |
| 116332 | take 6 once daily for 5 days |
| 118251 | take 6 daily for 7 days |
| 118425 | 6 tabs od for 5 days |
| 118610 | TAKE 8 TABLETS DAILY FOR 7 DAYS |
| 118620 | TAKE SIX TABLETS DAILY FOR 5 DAYS |
| 119070 | TAKE 6 TABLETS ONCE DAILY FOR 5 DAYS |
| 123159 | 6 daily for 6 days |
| 123747 | 30mg |
| 125675 | 54321 |
| 125757 | 87654321 |
| 140941 | REDUCING DOSE AS ADVISED |
| 142922 | 20MG |
| 148005 | 15MG DAILY |
| 161250 | 40 MG DAILY (8 TABLETS) |
| 161689 | 30 MG DAILY (6 TABLETS) |
| 163781 | 25 MG ONCE DAILY |
| 171953 | 40 mgs daily |
| 172482 | 30 MGS DAILY AS ONE DOSE PC |
| 172484 | 40 MGS DAILY AS ONE DOSE |
| 172488 | 30 MGS DAILY |
| 172961 | ASD REDUCING DOSE |
| 175517 | 6 OD FOR 1 WEEK |
| 176279 | 8 IN THE MORNING FOR 7 DAYS |
| 176334 | 40 mg daily for 5 days |
| 176551 | 6 ONCE DAILY FOR 2 WEEKS |
| 176727 | 2 DAILY FOR SIX WEEKS AND THEN 1 DAILY |
| 176898 | 20 MGS DAILY |
| 181293 | 6 TABLET ONCE DAILY FOR 5 DAYS |
| 181548 | 30 mg/day |
| 182981 | 6 /day for 1 week |
| 189041 | 40mg od |
| 207464 | TAKE SIX TABLETS DAILY FOR 5 DAYS . TAKE AFTER FOOD |
| 207470 | TAKE SIX TABLETS DAILY FOR 5 DAYS THEN REDUCE BY ONE EACH DAY. TAKE AF |
| 207483 | TAKE SIX DAILY FOR 5 DAYS AND THEN REDUCE BY ONE EACH DAY. TAKE AFTER |

Observational Study Protocol
Study Code << D589BR00053 >>
Version 6.5
Date 01/28/22

| | |
|--------|--|
| 229892 | SIX DAILY FOR 10 DAYS |
| 244368 | 6 IN THE MORNING FOR 1 WEEK |
| 270105 | TAKE 8 TABLETS ONCE A DAY FOR 5 DAYS |
| 293572 | 8 TABLETS (40 MG) ONCE DAILY FOR 5 DAYS |
| 294428 | 20 MG DAILY FOR 5 DAYS |
| 294487 | 30 mg daily for 7 days |
| 298969 | SIX DAILY FOR SEVEN DAYS |
| 299702 | six tablets daily for seven days |
| 303431 | 30 mg om |
| 310363 | 6 FOR 5 DAYS |
| 319222 | 20 mg od |
| 320081 | 20MG EVERY DAY |
| 332415 | 6 ONCE DAILY FOR 10 DAYS |
| 333763 | 8 TABS ONCE DAILY FOR 7 DAYS |
| 341052 | 8 DAILY FOR 2 DAYS AND THEN 7 DAILY FOR 2 DAYS AND CONTINUE TO REDUCE DOSE BY ONE TABLET EVERY OTHER DAY |
| 341253 | 6 /day for 5 days |
| 344252 | 8 TABS ONCE DAILY REDUCING AS DIRECTED BY 5 MG (1 TAB) PER WEEK |
| 344770 | 30 MG ONCE DAILY FOR 7 DAYS |
| 345080 | 40 MG OM |
| 356760 | 8 TABLETS DAILY FOR 7 DAYS |
| 387887 | 8 PER DAY FOR 5 DAYS |
| 391280 | 40 |
| 393453 | 6 TABLETS DAILY FOR 5 DAYS THEN STOP |
| 394406 | AS DIRECTED REDUCING DOSE |
| 402313 | 8 TABLETS ONCE A DAY FOR 5 DAYS |
| 408137 | 40 MG PO ONCE DAILY FOR 4 DAYS |
| 413664 | 30 MG ONCE DAILY WITH FOOD |
| 415463 | 30 MG/DAILY |
| 427676 | 6 daily for one week |
| 430015 | ON REDUCING DOSE |
| 433858 | REDUCE DOSE AS DIRECTED |
| 435551 | 6 TABLETS DAILY FOR 7 DAYS |
| 435894 | TAKE 6 TABLETS DAILY FOR 7 DAYS |
| 436065 | 6 TABLETS DAILY FOR FIVE DAYS |
| 437363 | 2 DAILY FOR 5 DAYS THEN 1 DAILY |
| 437952 | 6 TABS EVERY MORNING FOR 5 DAYS |
| 448839 | 6 STAT REDUCE BY 1 DAILY |
| 455847 | 8 /DAY FOR 5 DAYS |
| 455965 | TAKE 8/DAY FOR 5 DAYS |
| 456127 | 6 /DAY FOR 5DAYS |
| 471629 | TAKE SIX A DAY FOR FIVE DAYS |

Observational Study Protocol
Study Code << D589BR00053 >>
Version 6.5
Date 01/28/22

480689 EIGHT DAILY FOR 7 DAYS
486771 40 mg od
487015 TAKE 6 TABLETS DAILY FOR 10 DAYS
492437 TAKE ONE DAILY AS DIRECTED
498626 REDUCING DOSE AS DISCUSSED
519390 8 TABLET DAILY FOR 5 DAYS
531388 8 TABLET ONCE DAILY FOR 5 DAYS
537677 30 mg od for 5 days
549330 4D
565974 8 TABS ONCE DAILY FOR 1 WEEK
688372 6 a day for three days use as directed
714377 1 daily reduce dosage when better
754620 6 daily for 5 days to keep a course at home
828600 TAKE EIGHT TABLETS DAILY FOR FIVE DAYS
841919 as per reducing dose
870038 8 TABS DAILY FOR 7 DAYS
887749 6 ONCE DAILY FOR SEVEN DAYS THEN 3 ONCE DAILY FOR SEVEN DAYS
891147 30 MG EVERY DAY
900884 6 EVERY DAY FOR 7 days
901164 2 Tabs Daily for 7 days
915958 6 ONCE DAILY FOR 1 WEEK;THAN REDUCE BY 1 PER DAY
958156 40MG EVERY DAY
973999 40 MGS ONCE DAILY
997332 SIX EVERY DAY FOR 5/7
997561 SIX EVERY DAY FOR 10/7
998508 SIX EVERY DAY FOR FIVE DAYS
1021203 TAKE 8 TABLETS DAILY FOR FIVE DAYS
1026028 TAKE 6 FOR 5 DAYS THEN STOP
1033003 REDUCING DOSE AS DIRECTED BY HOSPITAL
1043573 6 daily for 1wk
1065150 40 MG/DAILY
1082799 Take six daily for one week then take three daily for one week
1085894 8 TABLETS IN THE MORNING WITH FOOD FOR 5 DAYS
1100912 SIX AS DIRECTED
1137220 30 MG ONCE DAILY(6 TABS)
1188492 SIX DAILY FOR 7 DAYS
1212163 OVER 5 YEARS TAKE 6 DAILY FOR 3 DAYS
1228699 UNDER 5 YEARS TAKE 4 DAILY FOR 3 DAYS
1308303 80D
1365184 40 MG DAILY FOR 5 TO 7 DAYS
1365193 30 MG DAILY

Observational Study Protocol
Study Code << D589BR00053 >>
Version 6.5
Date 01/28/22

1365316 40 MG DAILY
1365353 20 MG DAILY
1365665 50 MG DAILY
1370098 30mg daily for 7 days
1394786 TAKE 6 EVERY DAY FOR 7 DAYS IN EVENT OF EXACERBATION OF COPD
1401170 between 30-60mg daily
1413578 15MGS ONE DAY 10MGS EVERY OTHER DAY DIE
1424026 TAKE AS DIRECTED IN THE EVENT OF ACUTE EXACERBATION OF ASTHMA
1502904 adjust dosage according to instructions from your Doctor
1519076 6 OD FOR 7 DAYS
1587491 TAKE EIGHT DAILY FOR 7 DAYS
1604258 6 DAILY FOR 5 DAYS AND THEN STOP
1678391 TAKE 6 TABLETS DAILY FOR 7 DAYS. THIS IS AN EMERGENCY COURSE OF STEROI
1777794 TWO TABLETS DAILY FOR FIVE DAYS
1862607 6 DAILY FOR WEEK
1865672 40 mgs od
2043097 EIGHT TABS DAILY FOR 5 DAYS
2044794 two tablets daily for 5 days
2048015 TAKE EIGHT TABLETS EACH MORNING (AS A SINGLE DOSE) FOR 5 DAYS
2048622 TAKE SIX TABLETS EACH MORNING (AS A SINGLE DOSE) FOR 7 DAYS.
2112703 6 TABS A DAY FOR 5 DAYS THEN REDUCE BY ONE A DAY TILL FINISHED
2181245 7654321
2296897 6 TABS ONCE DAILY FOR 7 DAYS
2420709 6 TABLETS DAILY USUALLY IN THE MORNING FOR 7 DAYS
2638584 8 OD FOR 1 WEEK THEN REDUCE BY 1 EVERY OTHER DAY
2665007 8 OD FOR 1 WEEK THEN REDUCE BY 1 EVERY OTHER DAY (TO HELP BREATHING).
2665487 8 OD FOR 1 WEEK THEN REDUCE BY 1 EVERY OTHER DAY (TO HELP BREATHING)
2835063 6 od for 1 week (RESCUE PACK FOR CHEST)
2835649 6 od for 1 week (RESCUE PACK)
2968652 30MG FOR 7 DAYS
3129995 6 ONCE DAILY 5 DAYS, 3 ONCE DAILY 5 DAYS
3133209 6 daily 5 days, 3 daily 5 days
3248057 8 TABLETS ONCE A DAY (AFTER BREAKFAST) FOR 5 DAYS
3248154 8 DAILY IN THE MORNING FOR 5 DAYS (AFTER FOOD)
3248744 6 TABLETS ONCE A DAY (AFTER BREAKFAST) FOR 5 DAYS
3248915 6 TABLETS ONCE A DAY (AFTER BREAKFAST) FOR 14 DAYS
3248972 6 TABLETS ONCE A DAY (AFTER BREAKFAST) FOR 10 DAYS
3253085 6 TABLETS ONCE A DAY (AFTER BREAKFAST) FOR 10-14 DAYS
3253186 eight Tabs Daily for 5 days This medicine can cause irritation of the
3289075 TAKE SIX TABLETS EACH MORNING (AS A SINGLE DOSE) FOR 3 DAYS.
3309756 6,5,4,3,2,1, AS DIRECTED

Observational Study Protocol
Study Code << D589BR00053 >>
Version 6.5
Date 01/28/22

3381661 6 EVERY DAY 1/52
3553156 6,5,4,3,2,1 AS DIRECTED
4058519 6 wk1; 4 wk 2 2 w 3 Daily 6 tablets week 1
4190352 EIGHT AS DIRECTED
4214636 6 TABLETS DAILY FOR 4 DAYS AND 4 TABLETS ON FINAL DAY
4300461 8 TABLET ONCE DAILY FOR 5 DAYS -PRN COURSE
4352687 4 FOR 3 DAYS THEN 2 FOR 3 DAYS THEN 1
4354127 standby script 6 daily
4378104 6 /6/5/5/4/4/3/3/2/2/1/1/day
4398838 6 EVERY DAY 1/52 THEN 3 EVERY DAY 1/52
4518850 8 TABLETS DAILY FOR 7 DAYS AND THEN REDUCING REGIME AND TO STOP AT END OF 2 ND WEEK
4565628 TWO TABLETS DAILY FOR FIVE DAYS then 1 daily
4568184 6 X 5MG TAB DAILY 5 DAYS
4828894 TAKE SIX 5MG TABLETS EVERY DAY FOR 7 DAYS (EMERGENCY STEROIDS FOR SHOR
4896695 6 A DAY 1 WEEK THEN 3 A DAY 1 WEEK
4907454 take six daily 1/52 then 3 daily 1/52
4954297 8 TABLETS DAILY FOR 5 DAYS, THEN REDUCE BY ONE TABLET A DAY.
5063265 6 FOR 5/7,4 FOR 3/7, THEN 2 FOR 3/7 THEN 1
5069936 take six daily until asthma controlled for 2 days, then gradually reduce to the lowest dose at which symptoms
are still controlled
5070376 4 FOR 5/7 THEN 2 FOR 5/7 THEN 1 FOR 5/7
5081038 as directed- reduce by 5 mgs every 4 days
5258282 8 EVERY MORNING FOR 7 DAYS THEN REDUCE AS DIRECTED
5259340 8,7,6,5,4,3,2,1
5358527 TAKE 8 A DAY FOR EXACERBATIONS
5359507 TAKE 6 A DAY FOR EXACERBATIONS
6974853 TAKE 8 TABLET(S) ONCE A DAY FOR 5 DAYS
6975069 TAKE 8 TABLET(S) ONCE A DAY FOR ONE WEEK THEN REDUCE BY ONE TABLET EACH DAY OVER
SEVEN DAYS
6978056 TAKE SIX A DAY FOR 10 DAYS THEN REDUCE BY ONE DAILY UNTIL FINISHED COURSE.
6979384 reduce to 7 tablets one day , then six tablets , then five, then four , then three, then two, then one tablet a
day , then stop.
6984170 EIGHT REDUCING TO ONE EVERY MORNING AFTER FOOD
6984189 SIX REDUCING TO ONE
6985211 EIGHT EVERY MORNING REDUCING TO ONE EVERY MORNING AFTER FOOD
6989310 SIX REDUCING TO ONE EVERY MORNING AFTER FOOD
7010416 6 DAILY THEN REDUCE TO 5;4;3;2;1
7010890 2 TABLETS DAILY WITH FOOD FOR 3 DAYS THEN ONE TABLET DAILY UNTIL COURSE COMPLETED
7057477 5 DAILY FOR 2 DAYS 4 DAILY FOR 2 DAYS 3 DAILY FOR 2 DAYS 2 DAILY FOR 2 DAYS 1 DAILY FOR 2
DAYS AND STOP
7077500 6 A DAY FOR 4/7 THEN 4 A DAY FOR 4/7 THEN 2 EVERY DAY FOR 4/7 THE ONE
7098860 6 a day 7 days then reduce by one every 3 days
7098861 take 4 a day for 2 days then reduce by one daily

Observational Study Protocol
Study Code << D589BR00053 >>
Version 6.5
Date 01/28/22

7099465 SIX DAILY FOR 5 DAYS THEN REDUCE BY ONE A DAY
7107642 8,7,6,5,4,3,2,1,
7122527 66554433
7134611 TAKE 8 A DAY FOR 5 DAYS THEN 6,4,2 THEN STOP
7135118 7.6.5.4.3..
7143328 SOLUBLE TABLETS 6 DAILY FOR 4 DAYS THEN REDUCE TO 3 DAILY
7143436 6 5 4 3 2 1.
7147449 8 DAILY TILL BETTER THEN 4 DAILY FOR SAME NO OF DAYS KEEP THE REST FOR A FURTHER
ATTACK
7152705 8 daily till better then 4 daily for the same no of days
7155047 8,8,7,6,5,4,3,21 THEN STOP
7172754 TAKE 30MGS ONCE A DAY FOR 5 DAYS AND 15MGS A DAY FOR THE FOLLOWING 15 DAYS
7182773 6 DAILY TIMES 4 THEN 4 DAILY TIMES 4 THEN 2 DAILY
7184120 5;4;3;2 & 1 TABLETS TO BE TAKEN ON CONSECUTIVE DAYS
7184122 6;5;4;3;2;1 TABLETS ON CONSECUTIVE DAYS
7188810 DECREASING
7194097 6ODCCREDUCE
7194235 6ODREDUCING
7194632 6ODCC REDUC
7222881 reduce to 7 daily for 1 week then reduce by 1 tablet each week
7229471 8 TABLETS A DAY FOR 2 DAYS, 6 TABLETS FOR 2 DAYS , 4 ADAY FOR TWO DAYS
7231588 4 TABS DAILY FOR 7 DAYS THEN 2 DAILY FOR 2 DAYS THEN 1 DAILY FOR 2 DAYS THEN STOP
7231589 6 TABS DAILY FOR 7 DAYS THEN 4 DAILY FOR 4 DAYS THEN 2 DAILY FOR 4DAYS THEN STOP
7276080 TAKE 8 TABS STRAIGHT AWAY THEN REDUCE BY ONE TABLET EACH DAY TO STOP.
7286283 4 ONCE DAILY FOR 2 DAYS; 3 ONCE DAILY FOR 2 DAYS; 2 ONCE DAILY FOR 2 DAYS; 1 ONCE DAILY
FOR 2 DAYS
7292220 6 TABS DAILY FOR 5 DAYS THEN REDUCE BY ONE TABLET(S) DAILY
7318532 40 MG ONCE DAILY FOR 5 D
7325439 6 a day; reduce by 1 each day
7328746 30 MG IN THE MORNING FOR 5 DAYS THEN REDUCE GRADUALLY
7328979 REDUCE BY 5 MG EV 2 DAYS UNTIL STOPPED
7443438 TAKE 4 TODAY THEN 3 2 AND 1
7490074 8 Tabs each morning for seven days
7503111 then 4 daily for 5 days

8.4 Asthma Read Codes

| read_code | read_term |
|-----------|------------------------------|
| 173A. | Exercise-induced asthma |
| H3120 | Chronic asthmatic bronchitis |
| H33.. | Asthma |

| | |
|-------|--|
| | (Hay fever with asthma) or (extrinsic asthma without status asthmaticus) |
| H330. | |
| H3300 | Extrinsic asthma without status asthmaticus |
| H3301 | Extrinsic asthma with: [asthma attack] or [status asthmaticus] |
| H330z | Extrinsic asthma NOS |
| H331. | Intrinsic asthma |
| H3310 | Intrinsic asthma without status asthmaticus |
| H3311 | Intrinsic asthma with: [asthma attack] or [status asthmaticus] |
| H331z | Intrinsic asthma NOS |
| H332. | Mixed asthma |
| H334. | Brittle asthma |
| H335. | Chronic asthma with fixed airflow obstruction |
| H33z. | Asthma unspecified |
| H33z0 | (Severe asthma attack) or (status asthmaticus NOS) |
| H33z1 | Asthma attack |
| H33z2 | Late-onset asthma |
| H33zz | Asthma NOS |
| H3B.. | Asthma-chronic obstructive pulmonary disease overlap syndrome |
| 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 |
| Xa0IZ | Asthmatic bronchitis |

| | |
|-------|---|
| Xa9zf | Acute asthma |
| XaLPE | Nocturnal asthma |
| Xaa7B | Chronic asthma with fixed airflow obstruction |
| Xac33 | Asthma-chronic obstructive pulmonary disease overlap syndrome |
| Xafdj | Acute severe exacerbation of asthma |
| Xafdy | Moderate acute exacerbation of asthma |
| Xafdz | Life threatening acute exacerbation of asthma |

8.5 SABA Read Codes

| read_code | MX_PRODUCT_NAME |
|-----------|---|
| c12w. | SALBUTAMOL inh 100micrograms/inhalation |
| c131. | ASMAVEN inh 100micrograms |
| c133. | SALBULIN inh |
| c134. | VENTOLIN inh 100micrograms/inhalation |
| c136. | VENTOLIN rcap 200micrograms |
| c137. | VENTOLIN rcap 400micrograms |
| c13C. | SALBUTAMOL disc 200micrograms |
| c13D. | SALBUTAMOL disc 400micrograms |
| c13E. | VENTODISKS disc 400micrograms/blister |
| c13F. | VENTODISKS disc 200micrograms/blister |
| c13G. | VENTODISKS disc 400micrograms/blister |
| c13H. | SALAMOL inh 100micrograms/actuation |
| c13I. | AIROMIR cfc free inh 100micrograms/inhalation |
| c13J. | VENTOLIN inh 100micrograms/inhalation |
| c13K. | SALAMOL EASI-BREATHE breath act inh 100micrograms/actuation |
| c13L. | VENTOLIN ACCUHALER 200micrograms/actuation |
| c13M. | VENTOLIN ACCUHALER 200micrograms/actuation |
| c13N. | SALBUTAMOL vortex inh 100micrograms/inhalation |
| c13P. | SALBUTAMOL spacehaler 100micrograms/inhalation |
| c13Q. | SALBUTAMOL CYCLOCAPS inh caps 200micrograms [APS] |
| c13R. | SALBUTAMOL breath act pwdr inh 200micrograms/actuation |
| c13S. | SALBUTAMOL breath act pwdr inh 95micrograms |
| c13T. | VENTOLIN inh 100micrograms/inhalation |
| c13U. | SALBUTAMOL breath act inh 100micrograms/actuation |
| c13V. | SALBUTAMOL inh 100micrograms/inhalation |
| c13Y. | SALAMOL inh 100micrograms/actuation |
| c13c. | AEROLIN AUTOHALER breath act inh 100micrograms/actuation |
| c13d. | VENTODISKS disc 200micrograms/blister |
| c13e. | VENTODISKS disc 400micrograms/blister |
| c13f. | VENTODISKS disc 200micrograms/blister |
| c13g. | VENTODISKS disc 400micrograms/blister |

- c13h. SALBUVENT inh 100micrograms/actuation
- c13l. AEROLIN AUTOHALER breath act inh 100micrograms/actuation
- c13n. AEROLIN AUTOHALER breath act inh 100micrograms/actuation
- c13p. MAXIVENT inh 100micrograms/inhalation
- c13q. SALBUTAMOL inh caps 200micrograms
- c13r. SALBUTAMOL inh caps 400micrograms
- c13v. SALBUTAMOL inh 100micrograms/inhalation
- c13x. SALBUTAMOL inh caps 200micrograms
- c13y. SALBUTAMOL inh caps 400micrograms
- c144. BRICANYL inh
- c145. BRICANYL refill canister
- c146. BRICANYL spacer inh
- c14f. BRICANYL TURBOHALER 500micrograms
- c14g. BRICANYL TURBOHALER 500micrograms
- c14j. BRICANYL TURBOHALER 500micrograms
- c14t. TERBUTALINE inh 250micrograms/actuation
- c14u. TERBUTALINE inh 250micrograms/actuation
- c14v. TERBUTALINE inh 250micrograms/actuation
- c151. BEROTEC inh 200micrograms/actuation
- c153. BEROTEC inh 100micrograms/actuation
- c154. FENOTEROL inh 100micrograms/actuation
- c15y. FENOTEROL inh 200micrograms/actuation
- c173. BRONCHODIL inh 500micrograms/dose
- c17y. REPROTEROL inh 500micrograms/dose
- c181. PULMADIL inh
- c182. PULMADIL inh
- c183. PULMADIL AUTO inh
- c18z. RIMITEROL inh
- c1E1. SALAMOL EASI-BREATHE breath act inh 100micrograms/actuation
- c1E2. PULVINAL SALBUTAMOL breath act pwdr inh 200micrograms/actuation
- c1E3. VENTODISKS disc 200micrograms/blister
- c1E4. VENTODISKS disc 400micrograms/blister
- c1E5. VENTODISKS disc 200micrograms/blister
- c1E6. VENTODISKS disc 400micrograms/blister
- c1E7. EASYHALER SALBUTAMOL breath act pwdr inh 100micrograms/actuation
- c1E8. EASYHALER SALBUTAMOL breath act pwdr inh 200micrograms/actuation
- c1E9. SALBULIN inh
- c1EA. SALBUTAMOL breath act pwdr inh 100micrograms/actuation
- c1EC. SALBUTAMOL disc 400micrograms
- c51A. DUOVENT inh 40micrograms + 100micrograms/actuation
FENOTEROL + IPRATROPIUM BROMIDE breath act inh 100micrograms +
40micrograms/actuation
- c51B.

c51C. IPRATROPIUM BROMIDE + SALBUTAMOL inh 20mcg + 100mcg
c51D. COMBIVENT inh 20mcg + 100mcg
c51i. DUOVENT inh 40micrograms + 100micrograms/actuation
c51x. DUOVENT AUTOHALER breath act inh
c621. VENTIDE inh
c622. VENTOLIN rcap 200micrograms
c623. VENTIDE paed rcap
c722. AEROCROM inh
c72y. SODIUM CROMOGLICATE + SALBUTAMOL inh & spacer
c72z. SODIUM CROMOGLICATE + SALBUTAMOL inh
i966. VENTOLIN inh 100micrograms/inhalation
x00Af SALBUTAMOL inh 100micrograms/inhalation
x02Xr COMBIVENT inh 20mcg + 100mcg
x02ql SALAMOL inh 100micrograms/actuation
x02uD VENTOLIN ACCUHALER 200micrograms/actuation

8.6 SAMA Read codes

read_code MX_PRODUCT_NAME
c311. ATROVENT inh 20micrograms/actuation
c312. ATROVENT UDVs neb soln 500micrograms/2ml
c313. ATROVENT FORTE inh 40micrograms/actuation
c314. ATROVENT UDVs neb soln 0.25mg/ml
c315. ATROVENT AUTOHALER breath act inh 20micrograms/actuation
c316. STERI-NEB IPRATROPIUM unit dose neb soln 250micrograms/ml
c317. STERI-NEB IPRATROPIUM unit dose neb soln 250micrograms/ml
c318. ATROVENT AEROCAPS 40mcg
c319. ATROVENT AEROHALER 40mcg
c31A. IPRATROPIUM BROMIDE inh caps 40mcg
c31B. IPRATROPIUM BROMIDE caps + inh 40mcg
c31C. RESPONTIN NEBULES 250micrograms/ml
c31D. RESPONTIN NEBULES 250micrograms/ml
c31F. TROPIOVENT STERIPOULE unit dose neb soln 250micrograms/ml
c31G. ATROVENT cfc free inh 20micrograms/actuation
c31t. IPRATROPIUM BROMIDE cfc free inh 20micrograms/actuation
c31u. IPRATROPIUM BROMIDE inh 20micrograms/dose
c31v. IPRATROPIUM BROMIDE unit dose neb soln 250micrograms/ml
c31w. IPRATROPIUM BROMIDE unit dose neb soln 250micrograms/ml
c31x. IPRATROPIUM BROMIDE inh 20micrograms/dose
c31y. STERI-NEB IPRATROPIUM unit dose neb soln 250micrograms/ml
c31z. IPRATROPIUM BROMIDE inh 40micrograms/metered inhalation
c51A. DUOVENT inh 40micrograms + 100micrograms/actuation

| | |
|-------|---|
| | FENOTEROL + IPRATROPIUM BROMIDE breath act inh 100micrograms + |
| c51B. | 40micrograms/actuation |
| c51C. | IPRATROPIUM BROMIDE + SALBUTAMOL inh 20mcg + 100mcg |
| c51D. | COMBIVENT inh 20mcg + 100mcg |
| c51E. | COMBIVENT UDV's neb soln 2.5ml |
| | IPRATROPIUM BROMIDE + SALBUTAMOL unit dose neb soln 500micrograms + |
| c51F. | 2.5mg/2.5ml |
| | SALBUTAMOL + IPRATROPIUM BROMIDE unit dose neb soln 2.5mg + |
| c51H. | 500micrograms/2.5ml |
| c51i. | DUOVENT inh 40micrograms + 100micrograms/actuation |
| c51v. | DUOVENT UDV's neb soln |
| | IPRATROPIUM BROMIDE + SALBUTAMOL unit dose neb soln 500micrograms + |
| c51w. | 2.5mg/2.5ml |
| c51x. | DUOVENT AUTOHALER breath act inh |
| c531. | IPRAMOL STERI-NEB unit dose neb soln 500micrograms + 2.5mg/2.5ml |
| x02Uk | ATROVENT AEROCAPS 40mcg |
| x02Xr | COMBIVENT inh 20mcg + 100mcg |

8.7 ICS Read Codes

| read_code | MX_PRODUCT_NAME |
|-----------|--|
| c611. | BECLOFORTE inh 250micrograms/actuation |
| c612. | BECOTIDE 50 inh 50micrograms/actuation |
| c613. | BECOTIDE rcap 100micrograms |
| c614. | BECOTIDE rcap 200micrograms |
| c617. | BECOTIDE 100 inh 100micrograms/actuation |
| c619. | BECODISKS disc 100micrograms |
| c61A. | BECODISKS disc 200micrograms |
| c61B. | BECOTIDE rcap 400micrograms |
| c61C. | BECODISKS disc 100micrograms |
| c61D. | BECODISKS disc 200micrograms |
| c61E. | BECLOMETASONE breath act inh 250micrograms/actuation |
| c61F. | BECLOMETASONE breath act inh 100micrograms/actuation |
| c61G. | FILAIR inh 50micrograms/actuation |
| c61H. | FILAIR inh 100micrograms/actuation |
| c61J. | FILAIR FORTE inh 250micrograms/actuation |
| c61K. | BECLAZONE inh 50micrograms/actuation |
| c61L. | BECLAZONE inh 100micrograms/actuation |
| c61M. | BECLAZONE inh 250micrograms/actuation |
| c61N. | BECLOFORTE disks (refill pack) 400micrograms/actuation |
| c61O. | BECLOMETASONE breath act inh 100micrograms/actuation |
| c61P. | BECLOMETASONE disc 100micrograms |

c61Q. BECLOFORTE INTEGRA inh/compt spacer 250micrograms/actuation
c61R. BECLOFORTE INTEGRA inh/compt spacer 250micrograms/actuation
c61S. BECLOMETASONE inh/compt spacer 250micrograms/actuation
c61T. BECLOMETHASONE breath act inh 250micrograms/actuation [APS]
c61V. BECLOMETASONE vortex inh 50micrograms/actuation
c61W. BECLOMETASONE inh caps 100micrograms
c61X. BECLOMETASONE inh 100micrograms/actuation
c61Y. BDP spacehaler 100micrograms/actuation
c61Z. BECLOMETASONE vortex inh 250micrograms/actuation
c61a. BECODISKS disc 200micrograms
c61b. BECOTIDE rcap 400micrograms
c61c. BECODISKS disc 100micrograms
c61d. BECODISKS disc 200micrograms
c61e. BECODISKS disc 400micrograms
c61f. BECODISKS disc 400micrograms
c61g. FILAIR inh 50micrograms/actuation
c61h. FILAIR inh 100micrograms/actuation
c61i. BECOTIDE 200 inh 200micrograms/actuation
c61j. AEROBEC AUTOHALER 50micrograms/actuation
c61k. AEROBEC forte AUTOHALER 250micrograms/actuation
c61l. AEROBEC AUTOHALER 100micrograms/actuation
c61m. BECLOFORTE DISKHALER 400micrograms/actuation
c61n. BECLOFORTE disks (refill pack) 400micrograms/actuation
c61p. BECLOMETASONE disc 100micrograms
c61q. BECLOMETASONE disc 200micrograms
c61r. BECLOMETASONE inh 100micrograms/actuation
c61s. BECLOMETASONE disc 200micrograms
c61t. BECLOMETASONE inh 250micrograms/actuation
c61u. BECLOMETASONE inh 200micrograms/actuation
c61v. BECOTIDE 50 inh 50micrograms/actuation
c61w. BECLOMETASONE inh caps 100micrograms
c61x. BECLOMETASONE inh caps 200micrograms
c61z. BECOTIDE 100 inh 100micrograms/actuation
c621. VENTIDE inh
c641. PULMICORT inh 200micrograms
c643. PULMICORT refill canister 200micrograms
c644. PULMICORT LS inh 50micrograms
c645. PULMICORT LS refill canister 50micrograms
c647. PULMICORT inh 200micrograms
c648. PULMICORT TURBOHALER breath act pwdr inh 200micrograms/actuation
c649. PULMICORT TURBOHALER breath act pwdr inh 400micrograms/actuation
c64A. BUDESONIDE inh 200micrograms/actuation

- c64B. BUDESONIDE inh 50micrograms/actuation
- c64C. PULMICORT inh 200micrograms
- c64D. PULMICORT LS inh 50micrograms
- c64E. PULMICORT inh 200micrograms
- c64F. BUDESONIDE dry pdr inh cart ref 200micrograms
- c64G. NOVOLIZER BUDESONIDE inh pdr (refill) 200micrograms
- c64H. EASYHALER BUDESONIDE breath act pwdr inh 100micrograms/actuation
- c64I. EASYHALER BUDESONIDE breath act pwdr inh 200micrograms/actuation
- c64J. EASYHALER BUDESONIDE breath act pwdr inh 400micrograms/actuation
- c64K. BUDESONIDE inh 100micrograms/actuation
- c64L. BUDESONIDE inh 100micrograms/actuation
- c64M. PULMICORT inh 200micrograms
- c64N. BUDESONIDE inh 200micrograms/actuation
- c64c. PULMICORT TURBOHALER breath act pwdr inh 100micrograms/actuation
- c64d. BUDESONIDE breath act pwdr inh 100micrograms/actuation
- c64e. PULMICORT inh 200micrograms
- c64g. BUDESONIDE breath act pwdr inh 200micrograms/actuation
- c64h. BUDESONIDE breath act pwdr inh 400micrograms/actuation
- c64m. BUDESONIDE inh caps 200micrograms
- c64n. BUDESONIDE inh caps 400micrograms
- c64o. BUDESONIDE inh 200micrograms/actuation
- c64p. NOVOLIZER BUDESONIDE inh pdr + device 200micrograms
- c64u. BUDESONIDE dry pdr inh cart+dev 200micrograms
- c64v. BUDESONIDE inh 200micrograms/actuation
- c64x. BUDESONIDE inh 200micrograms/actuation
- c64y. BUDESONIDE inh 50micrograms/actuation
- c64z. BUDESONIDE inh 200micrograms/actuation
- c651. FLIXOTIDE disc 50micrograms
- c652. FLIXOTIDE disc 100micrograms
- c653. FLIXOTIDE disc 250micrograms
- c654. FLUTICASONE disc 500micrograms
- c655. FLUTICASONE disc 100micrograms
- c656. FLUTICASONE disc 250micrograms
- c657. FLIXOTIDE disc 50micrograms
- c658. FLIXOTIDE disc 100micrograms
- c65A. FLUTICASONE disc 50micrograms
- c65B. FLIXOTIDE disc 100micrograms
- c65C. FLIXOTIDE disc 250micrograms
- c65D. FLIXOTIDE inh 25micrograms/actuation
- c65E. FLIXOTIDE inh 50micrograms/actuation
- c65F. FLIXOTIDE inh 125micrograms/actuation
- c65G. FLUTICASONE inh 25micrograms/actuation

- c65H. FLUTICASONES inh 50micrograms/actuation
- c65I. FLUTICASONES inh 50micrograms/actuation
- c65J. FLUTICASONES inh 250micrograms/actuation
- c65K. FLIXOTIDE inh 250micrograms/actuation
- c65L. FLIXOTIDE disc 500micrograms
- c65M. FLIXOTIDE disc 500micrograms
- c65N. FLUTICASONES disc 500micrograms
- c65O. FLUTICASONES disc 500micrograms
- c65P. FLUTICASONES breath act pwr inh 50micrograms/inhalation
- c65Q. FLUTICASONES breath act pwr inh 100micrograms/inhalation
- c65R. FLIXOTIDE ACCUHALER 250micrograms/inhalation
- c65S. FLUTICASONES breath act pwr inh 500micrograms/inhalation
- c65T. FLIXOTIDE ACCUHALER 50micrograms/inhalation
- c65U. FLIXOTIDE ACCUHALER 100micrograms/inhalation
- c65V. FLIXOTIDE ACCUHALER 250micrograms/inhalation
- c65W. FLIXOTIDE ACCUHALER 500micrograms/inhalation
- c65b. FLUTICASONES cfc free inh 125micrograms/actuation
- c65c. FLUTICASONES cfc free inh 250micrograms/actuation
- c65d. FLIXOTIDE EVOHALER 125micrograms/actuation
- c65e. FLIXOTIDE EVOHALER 250micrograms/actuation
- c65f. FLUTICASONES cfc free inh 50micrograms/actuation
- c65g. FLUTICASONES inh 25micrograms/actuation
- c661. ASMABEC spacehaler 250micrograms/actuation
- c662. BECOTIDE EASI-BREATHE breath act inh 50micrograms/actuation
- c663. BECOTIDE EASI-BREATHE breath act inh 100micrograms/actuation
- c664. BECLOFORTE EASI-BREATHE breath act inh 250micrograms/actuation
- c665. QVAR cfc free inh 50micrograms/actuation
- c666. QVAR cfc free inh 100micrograms/actuation
- c667. QVAR AUTOHALER cfc/free b/act inh 50micrograms/actuation
- c668. QVAR AUTOHALER cfc/free b/act inh 100micrograms/actuation
- c669. BECLAZONE inh 200micrograms/actuation
- c66A. BECLOMETASONE breath act inh 50micrograms/actuation
- c66B. BECLOMETASONE breath act pwr inh 100micrograms/actuation
- c66C. BECLOMETASONE breath act inh 250micrograms/actuation
- c66D. ASMABEC CLICKHALER dry pdr inh 50micrograms
- c66E. ASMABEC CLICKHALER dry pdr inh 100micrograms
- c66F. BECLOMETASONE breath act pwr inh 250micrograms/actuation
- c66G. BECLOMETASONE breath act pwr inh 400micrograms/actuation
- c66H. BECLOMETASONE breath act pwr inh 200micrograms/actuation
- c66I. PULVINAL BECLOMETASONE DIPROPIONATE breath act pwr inh 100micrograms/actuation

| | |
|-------|--|
| c66J. | PULVINAL BECLOMETASONE DIPROPIONATE breath act pwdr inh 200micrograms/actuation |
| c66K. | PULVINAL BECLOMETASONE DIPROPIONATE breath act pwdr inh 400micrograms/actuation |
| c66L. | BECLOMETASONE CYCLOCAPS inh caps 100micrograms [APS] |
| c66M. | BECLOMETASONE CYCLOCAPS inh caps 200micrograms [APS] |
| c66N. | BECLOMETASONE CYCLOCAPS inh caps 400micrograms [APS] |
| c66P. | BECODISKS disc 100micrograms |
| c66Q. | BECODISKS disc 200micrograms |
| c66R. | BECODISKS disc 400micrograms |
| c66S. | BECODISKS disc 100micrograms |
| c66T. | BECOTIDE 200 inh 200micrograms/actuation |
| c66U. | BECODISKS disc 400micrograms |
| c66V. | BECLOMETASONE EXTRAFINE PARTICLE cfc free inh 50micrograms/actuation |
| c66W. | BECLOMETASONE EXTRAFINE PARTICLE cfc free inh 100micrograms/actuation |
| c66X. | BECLOMETASONE breath act inh 50micrograms/actuation |
| c66Y. | BECLOMETASONE breath act inh 100micrograms/actuation |
| c66Z. | QVAR EASI-BREATHE cfc/free b/act inh 50micrograms/actuation |
| c66a. | QVAR EASI-BREATHE cfc/free b/act inh 100micrograms/actuation |
| c66b. | EASYHALER BECLOMETASONE breath act pwdr inh 200micrograms/actuation |
| c66c. | CLENIL MODULITE cfc free inh 50micrograms/actuation |
| c66d. | CLENIL MODULITE cfc free inh 100micrograms/actuation |
| c66e. | CLENIL MODULITE cfc free inh 200micrograms/actuation |
| c66f. | CLENIL MODULITE cfc free inh 250micrograms/actuation |
| c66g. | BECLOMETASONE cfc free inh 200micrograms/actuation |
| c66h. | BECLOMETASONE cfc free inh 250micrograms/actuation |
| c681. | MOMETASONE FUROATE dry pdr inh 200micrograms/actuation |
| c682. | MOMETASONE FUROATE dry pdr inh 400micrograms/actuation |
| c683. | ASMANEX TWISTHALER dry pdr inh 200micrograms/actuation |
| c684. | ASMANEX TWISTHALER dry pdr inh 400micrograms/actuation |
| c691. | ALVESCO cfc free inh 160micrograms/actuation |
| c692. | ALVESCO cfc free inh 80micrograms/actuation |
| c69y. | CICLESONIDE cfc free inh 80micrograms/actuation |
| c69z. | CICLESONIDE cfc free inh 160micrograms/actuation |
| p436. | BECLOFORTE VM pack 250micrograms/actuation |
| x00Hz | BECODISKS disc 200micrograms |
| x00I0 | BECODISKS disc 400micrograms |
| x00QU | PULMICORT inh 200micrograms |
| x00gE | PULMICORT TURBOHALER breath act pwdr inh 100micrograms/actuation |
| x00gF | PULMICORT TURBOHALER breath act pwdr inh 200micrograms/actuation |
| x00gG | PULMICORT TURBOHALER breath act pwdr inh 400micrograms/actuation |
| x01MQ | BECLOMETASONE inh 100micrograms/actuation |

x02Mk BUDESONIDE inh 200micrograms/actuation
x02ct FLIXOTIDE ACCUHALER 100micrograms/inhalation
x03d9 PULMICORT inh 200micrograms

8.8 LABA & ICS/LABA Read codes

| read_code | MX_PRODUCT_NAME |
|-----------|--|
| c19.. | SALMETEROL inh 25micrograms/actuation |
| c191. | SALMETEROL inh 25micrograms/actuation |
| c192. | SEREVENT inh 25micrograms/actuation |
| c193. | SEREVENT DISKHALER 50micrograms |
| c194. | SEREVENT DISKHALER 50micrograms |
| c195. | SALMETEROL disc 50micrograms |
| c196. | SALMETEROL disc 50micrograms |
| c197. | SALMETEROL disc 50micrograms |
| c198. | SEREVENT ACCUHALER 50micrograms/actuation |
| c199. | SEREVENT inh 25micrograms/actuation |
| c19A. | SALMETEROL inh 25micrograms/actuation |
| c19B. | SALMETEROL inh 25micrograms/actuation |
| c19z. | SALMETEROL disc 50micrograms |
| c1C1. | FORMOTEROL FUMARATE inh caps 12mcg |
| c1C2. | FORADIL inh caps 12mcg |
| c1C3. | FORMOTEROL FUMARATE breath act inh 6 micrograms/actuation |
| c1C4. | FORMOTEROL FUMARATE breath act inh 12micrograms/actuation |
| c1C5. | OXIS 6 TURBOHALER 6 micrograms/actuation |
| c1C6. | OXIS 12 TURBOHALER 12micrograms/actuation |
| c1C7. | ATIMOS MODULITE cfc free inh 12micrograms/actuation |
| c1C8. | FORMOTEROL FUMARATE breath act inh 12micrograms/actuation |
| c1Cz. | FORMOTEROL FUMARATE breath act inh 12micrograms/actuation |
| c1D1. | SERETIDE 100 ACCUHALER |
| c1D2. | SERETIDE 250 ACCUHALER |
| c1D3. | SERETIDE 500 ACCUHALER |
| c1D4. | SERETIDE 50 EVOHALER 25micrograms + 50micrograms/actuation |
| c1D5. | SERETIDE 125 EVOHALER 25micrograms + 125micrograms/actuation |
| c1D6. | SERETIDE 250 EVOHALER 25micrograms + 250micrograms/actuation |
| c1D7. | SIRDUPLA 25micrograms/125micrograms inhaler |
| c1D8. | SIRDUPLA 25micrograms/250micrograms inhaler |
| c1D9. | AIRFLUSAL FORSPIRO 50micrograms/500micrograms pdr inhaler |
| c1Du. | FLUTICASONE + SALMETEROL cfc free inh 50micrograms + 25micrograms/actuation |
| c1Dv. | FLUTICASONE + SALMETEROL cfc free inh 125micrograms + 25micrograms/actuation |
| c1Dw. | FLUTICASONE + SALMETEROL cfc free inh 250micrograms + 25micrograms/actuation |
| c1Dx. | FLUTICASONE + SALMETEROL dry pdr inh 100micrograms + 50micrograms/inhalation |

| | |
|-------|---|
| c1Dy. | FLUTICASONE + SALMETEROL dry pdr inh 250micrograms + 50micrograms/inhalation |
| c1Dz. | FLUTICASONE + SALMETEROL dry pdr inh 500micrograms + 50micrograms/inhalation |
| c1b1. | ONBREZ BREEZHALER capsules for inhalation + inhaler 150micrograms [NOVARTIS] |
| c1b2. | ONBREZ BREEZHALER capsules for inhalation + inhaler 150micrograms [NOVARTIS] |
| c1b3. | ONBREZ BREEZHALER capsules for inhalation + inhaler 300micrograms [NOVARTIS] |
| c1b4. | ONBREZ BREEZHALER capsules for inhalation + inhaler 300micrograms [NOVARTIS] |
| c1c1. | Flutiform Cfc-free inhaler 50 micrograms + 5 micrograms/dose 120 doses |
| c1c2. | Flutiform Cfc-free inhaler 125 micrograms + 5 micrograms/dose 120 doses |
| c1c3. | Flutiform Cfc-free inhaler 250 micrograms + 10 micrograms/dose 120 doses |
| c1cx. | Flutiform Cfc-free inhaler 250 micrograms + 10 micrograms/dose 120 doses |
| c1cy. | Flutiform Cfc-free inhaler 125 micrograms + 5 micrograms/dose 120 doses |
| c1cz. | Flutiform Cfc-free inhaler 50 micrograms + 5 micrograms/dose 120 doses |
| c1d1. | STRIVERDI RESPIMAT 2.5micrograms inhaler |
| c1d2. | OLODATEROL 2.5micrograms inhaler |
| c671. | SYMBICORT TURBOHALER 100micrograms + 6micrograms/actuation |
| c672. | SYMBICORT TURBOHALER 200micrograms + 6micrograms/actuation |
| c673. | SYMBICORT TURBOHALER 400micrograms + 12micrograms/actuation |
| c674. | DUORESP SPIROMAX 160mcg/4.5mcg breath-act dry powder inhaler |
| c675. | DUORESP SPIROMAX 320mcg/9mcg breath-act dry powder inhaler |
| c67x. | BUDESONIDE + FORMOTEROL breath act pwdr inh 400micrograms + 12micrograms/actuation |
| c67y. | BUDESONIDE + FORMOTEROL breath act pwdr inh 200micrograms + 6micrograms/actuation |
| c67z. | SYMBICORT TURBOHALER 100micrograms + 6micrograms/actuation |
| c6A1. | FOSTAIR cfc free inh 100micrograms + 6micrograms/actuation |
| c6A2. | FOSTAIR NEXTHALER 100micrograms + 6micrograms powder inhaler |
| c6A3. | FOSTAIR 200micrograms/6micrograms inhaler |
| c6A4. | FOSTAIR NEXTHALER 200micrograms/6micrograms powder inhaler |
| c6Aw. | BECLOMET DIPROP+FORMOTERL FUMARATE DIHYD 200mcg/6mcg pdr inh |
| c6Ax. | BECLOMET DIPROP+FORMOTERL FUMARATE DIHYD 200mcg/6mcg inhaler |
| c6Ay. | BECLOMET DIPROP+FORMOTERL FUMARATE DIHYD 100mcg/6mcg pdr inh |
| c6Az. | BECLOMETASONE + FORMOTEROL 100 micrograms + 6 micrograms/dose |
| c6B1. | RELVAR ELLIPTA 184micrograms/22micrograms inhaler |
| c6B2. | FLUTICASONE FUROATE+VILANTEROL 184mcg/22mcg dry pdr inhaler |
| c6B3. | RELVAR ELLIPTA 92micrograms/22micrograms inhaler |
| c6B4. | FLUTICASONE FUROATE+VILANTEROL 92mcg/22mcg dry pdr inhaler |
| x02qr | SEREVENT ACCUHALER 50micrograms/actuation |
| x04xm | SERETIDE 100 ACCUHALER |
| x0594 | SERETIDE 125 EVOHALER 25micrograms + 125micrograms/actuation |
| x05J2 | SYMBICORT TURBOHALER 100micrograms + 6micrograms/actuation |

8.9 LAMA Read codes

| read_code | MX_PRODUCT_NAME |
|-----------|---|
| c33.. | TIOTROPIUM inh caps 18 micrograms |
| c331. | TIOTROPIUM inh pdr cap (refill) 18 micrograms |
| c332. | TIOTROPIUM inh caps 18 micrograms |
| | Spiriva Respimat Solution For Inhalation 2.5 micrograms/puff 60 |
| c333. | puffs |
| | Spiriva Respimat Solution For Inhalation 2.5 micrograms/puff 60 |
| c33x. | puffs |
| c33y. | SPIRIVA inh pdr caps+dev 18 micrograms |
| c33z. | SPIRIVA inh caps 18 micrograms |
| c341. | EKLIRA GENUAIR inhalation powder 322micrograms |
| c342. | Acridinium Bromide Dry Powder Inhaler 375 micrograms/dose |
| c351. | Incruse Ellipta 55micrograms/dose dry powder inhaler |
| c352. | UMECLIDIINIUM 55micrograms/dose dry powder inhaler |
| o323. | SEEBRI BREEZHALER 44micrograms inhalation capsules |
| o324. | GLYCOPYRRONIUM 44micrograms inhalation capsules |
| x05gG | SPIRIVA inh pdr cap (refill) 18 micrograms |

8.10 LABA/LAMA Read codes

| read_code | read_term |
|-----------|--|
| c1e.. | INDACATEROL+GLYCOPYRRONIUM |
| c1e1. | ULTIBRO BREEZHALER 85mcg/43mcg inh powder capsules+inhaler |
| | INDACATEROL+GLYCOPYRRONIUM 85mcg/43mcg inh powder |
| c1e2. | caps+inh |
| c51I. | ANORO ELLIPTA 55micrograms/22micrograms dry powder inhaler |
| c51J. | UMECLIDIINIUM+VILANTEROL 55mcg/22mcg dry powder inhaler |
| c51K. | DUAKLIR GENUAIR 340micrograms/12micrograms powder inhaler |
| | ACLIDIINIUM+FORMOTEROL FUMARATE DIHYD 340mcg/12mcg |
| c51L. | pdr inh |
| c51M. | SPIOLTO RESPIMAT 2.5micrograms/2.5micrograms inhaler |
| | TIOTROPIUM+OLODATEROL 2.5micrograms/2.5micrograms |
| c51N. | inhaler |

8.11 LTRA Read codes

| read_code | MX_PRODUCT_NAME |
|-----------|--|
| cA11. | MONTELUKAST (AS SODIUM SALT) tabs 10mg |
| cA12. | SINGULAIR paed chewable tab 5mg |
| cA13. | SINGULAIR tabs 10mg |
| cA14. | SINGULAIR paed chewable tab 5mg |

cA15. SINGULAIR paed chewable tab 4mg
cA16. SINGULAIR paed grans 4mg/sachet
MONTELUKAST (AS SODIUM SALT) grans
cA1y. 4mg/sachet
MONTELUKAST (AS SODIUM SALT) chewable tab
cA1z. 4mg
cA21. ZAFIRLUKAST tabs 20mg
cA22. ACCOLATE tabs 20mg
x04cV SINGULAIR paed chewable tab 4mg

8.12 Theophylline Read codes

| read_code | MX_PRODUCT_NAME |
|-----------|---|
| c411. | AMINOPHYLLINE tabs 100mg |
| c412. | AMINOPHYLLINE inj 250mg/10ml |
| c413. | AMINOPHYLLINE inj 250mg/ml |
| c419. | THEODROX tabs |
| c41B. | NORPHYLLIN SR tablets 225mg |
| c41a. | PHYLLOCONTIN CONTINUS tabs 225mg PHYLLOCONTIN CONTINUS forte tabs 350mg |
| c41b. | PHYLLOCONTIN CONTINUS paed tab 100mg |
| c41c. | AMINOPHYLLINE SR tablets 225mg |
| c41d. | [IVAX] AMINOPHYLLINE HYDRATE mr tab 350mg |
| c41f. | 350mg |
| c41g. | AMINOPHYLLINE mr tab 100mg |
| c41h. | AMNIVENT sr tab 225mg AMINOPHYLLINE inj 25mg/ml |
| c41k. | [CELLTECH] AMINOPHYLLINE HYDRATE mr tab 225mg |
| c41m. | 225mg |
| c421. | CHOLEDYL tabs 100mg |
| c422. | CHOLEDYL tabs 200mg |
| c423. | CHOLEDYL syrup 62.5mg/5ml |
| c42w. | CHOLINE THEOPHYLLINATE tabs 100mg |
| c42x. | CHOLINE THEOPHYLLINATE tabs 200mg |
| c431. | BIOPHYLLINE syrup 125mg/5ml |
| c432. | NUELIN tabs 125mg |
| c433. | NUELIN liq 60mg/5ml |
| c434. | LASMA tabs 300mg |
| c435. | NUELIN SA tabs 175mg |

c436. NUELIN SA-250 tabs
c437. PRO-VENT caps 300mg
c438. SLO-PHYLLIN caps 60mg
c439. SLO-PHYLLIN caps 125mg
c43a. SLO-PHYLLIN caps 250mg
c43b. THEO-DUR tabs 200mg
c43c. THEO-DUR tabs 300mg
c43e. UNIPHYLLIN CONTINUS tabs 400mg
c43f. UNIPHYLLIN CONTINUS tabs 200mg
c43h. UNIPHYLLIN CONTINUS tabs 300mg
c43m. THEOPHYLLINE syrp 125mg/5ml
c43n. THEOPHYLLINE tabs 125mg
c43o. THEOPHYLLINE liq 60mg/5ml
c43p. THEOPHYLLINE mr tab 175mg
c43q. THEOPHYLLINE mr tab 250mg
c43r. THEOPHYLLINE mr tab 300mg
c43s. THEOPHYLLINE mr cap 60mg
c43t. THEOPHYLLINE mr cap 125mg
c43u. THEOPHYLLINE mr cap 250mg
c43v. THEOPHYLLINE mr tab 200mg
c43w. THEOPHYLLINE mr tab 300mg
c43x. THEOPHYLLINE mr tab 350mg
c43y. THEOPHYLLINE mr tab 400mg
c43z. THEOPHYLLINE mr tab 200mg
c51t. FRANOL tabs
c51u. FRANOL PLUS tabs
x02IT NUELIN tabs 125mg
x02tm UNIPHYLLIN CONTINUS tabs 200mg

8.13 ICS/LABA/LAMA Snowmed codes

| snomed | nm |
|-------------------|---|
| | Trimbow 87micrograms/dose / 5micrograms/dose / 9micrograms/dose |
| 34681611000001100 | inhaler |
| | Generic Trimbow 87micrograms/dose / 5micrograms/dose / |
| 34683311000001106 | 9micrograms/dose inhaler |
| | Trelegy Ellipta 92micrograms/dose / 55micrograms/dose / |
| 34952211000001104 | 22micrograms/dose dry powder inhaler |
| | Generic Trelegy Ellipta 92micrograms/dose / 55micrograms/dose / |
| 34955111000001103 | 22micrograms/dose dry powder inhaler |

8.14 Oral Steroids Read codes

| read_code | read_term |
|-----------|--------------------------------------|
| fe3.. | DEXAMETHASONE [ENDOCRINE] |
| fe31. | DEXAMETHASONE 500micrograms tablets |
| fe32. | DEXAMETHASONE 2mg tablets |
| fe33. | DECADRON 500micrograms tablets |
| fe36. | *ORADEXON 500microgram tablets |
| fe37. | *ORADEXON 2mg tablets |
| fe3A. | DEXSOL 2mg/5mL oral solution |
| fe3B. | DEXAMETHASONE 10mg/5mL oral solution |
| fe3C. | MARTAPAN 2mg/5mL oral solution |
| | DEXAMETHASONE 500micrograms/5mL |
| fe3r. | solution |
| | DEXAMETHASONE 2mg/5mL sugar free |
| fe3s. | solution |
| fe3u. | DEXAMETHASONE 2mg/5mL liquid |
| fe4.. | HYDROCORTISONE |
| fe41. | HYDROCORTISONE 10mg tablets |
| fe42. | HYDROCORTISONE 20mg tablets |
| fe43. | *HYDROCORTISTAB 20mg tablets |
| fe44. | *HYDROCORTONE 10mg tablets |
| fe45. | *HYDROCORTONE 20mg tablets |
| fe4e. | PLENADREN 5mg m/r tablets |
| fe4f. | HYDROCORTISONE 5mg m/r tablets |
| fe4g. | PLENADREN 20mg m/r tablets |
| fe4h. | HYDROCORTISONE 20mg m/r tablets |
| fe5.. | METHYLPREDNISOLONE [ENDOCRINE] |
| fe51. | MEDRONE 2mg tablets |
| fe52. | MEDRONE 4mg tablets |
| fe53. | MEDRONE 16mg tablets |
| fe5f. | MEDRONE 100mg tablets |
| fe5m. | METHYLPREDNISOLONE 100mg tablets |
| fe5n. | METHYLPREDNISOLONE 2mg tablets |
| fe5o. | METHYLPREDNISOLONE 4mg tablets |
| fe5p. | METHYLPREDNISOLONE 16mg tablets |
| fe6.. | PREDNISOLONE [ENDOCRINE] |
| fe61. | PREDNISOLONE 1mg tablets |
| fe62. | PREDNISOLONE 5mg tablets |
| fe64. | *DELTA-PHORICOL 5mg tablets |
| fe65. | DELTACORTRIL ENTERIC 2.5mg tablets |
| fe66. | DELTACORTRIL ENTERIC 5mg tablets |
| fe67. | *DELTALONE 1mg tablets |

| | |
|-------|---|
| fe68. | *DELTALONE 5mg tablets |
| fe69. | *DELTASTAB 1mg tablets |
| fe6a. | *DELTASTAB 5mg tablets |
| fe6c. | *PRECORTISYL 1mg tablets |
| fe6d. | *PRECORTISYL 5mg tablets |
| fe6e. | PRECORTISYL FORTE 25mg tablets |
| fe6f. | *PREDNESOL 5mg tablets |
| fe6g. | *SINTISONE 5mg tablets |
| fe6h. | PREDNISOLONE 2.5mg e/c tablets |
| fe6i. | PREDNISOLONE 5mg e/c tablets |
| fe6j. | PREDNISOLONE 5mg soluble tablets |
| fe6k. | PREDNISOLONE 50mg tablets |
| fe6l. | DILACORT 5mg gastro-resistant tablets |
| fe6m. | DILACORT 2.5mg gastro-resistant tablets |
| fe6t. | PREDNISOLONE 10mg tablets |
| fe6v. | *PREDNISOLONE 2.5mg tablets |
| fe6w. | *PREDNISOLONE 2.5mg tablets |
| fe6z. | PREDNISOLONE 25mg tablets |
| fe7.. | PREDNISONONE |
| fe71. | *PREDNISONONE 1mg tablets |
| fe72. | *PREDNISONONE 5mg tablets |
| fe73. | *DECORTISYL 5mg tablets |
| fe74. | *ECONOSONE 1mg tablets |
| fe75. | *ECONOSONE 5mg tablets |
| fe76. | Prednisone 20mg tablet |
| fe77. | LODOTRA 2mg m/r tablets |
| fe78. | LODOTRA 5mg m/r tablets |
| fe79. | LODOTRA 1mg m/r tablets |
| fe7x. | PREDNISONONE 5mg m/r tablets |
| fe7y. | PREDNISONONE 2mg m/r tablets |
| fe7z. | PREDNISONONE 1mg m/r tablets |
| x00yP | Oral prednisolone |
| x01Mh | Oral dexamethasone |
| x01Na | Oral hydrocortisone |
| x01Nb | Oral methylprednisolone |

8.15 Ankylosing spondylitis Read codes

| Code | Term |
|-------|---|
| 388p. | BASDAI - Bath ankylosing spondylitis disease activity index |
| F5520 | Malleus ankylosis |
| F5521 | Ossicle ankylosis (excluding malleus) |

J0460 Stiff temporomandibular joint
J0460 Temporomandibular joint ankylosis
N0450 Juvenile ankylosing spondylitis
N085. Ankylosis of joint
N0851 Joint ankylosis of the shoulder region
N0853 Joint ankylosis of the forearm
N0854 Joint ankylosis of the hand
N0855 Hip joint ankylosis
N0855 Joint ankylosis of the pelvic region and thigh
N0856 Knee joint ankylosis
N0856 Joint ankylosis of the lower leg
N0857 Joint ankylosis of the ankle and foot
N0857 Ankle joint ankylosis
N0858 Joint ankylosis of other specified site
N0859 Ankylosis of multiple joints
N085C Ankylosis of the elbow joint
N085F Ankylosis of the wrist joint
N085G Ankylosis of the 1st CMC joint
N085K Ankylosis of PIP joint
N085L Ankylosis of DIP joint
N085M Ankylosis of the hip joint
N085P Ankylosis of the knee joint
N085Q Ankylosis of the ankle joint
N085R Ankylosis of the subtalar joint
N085S Ankylosis of other tarsal joint
N085U Ankylosis of toe joint
N085z Ankylosis of joint NOS
N10.. Inflammatory spondylopathies
N100. Ankylosing spondylitis
N100. Marie - Strumpell spondylitis
N10y. Other inflammatory spondylopathies
N10y0 Inflammatory spondylopathies in diseases EC
N10yz Other inflammatory spondylopathies NOS
N10z. Spondylitis NOS
N117. Diffuse idiopathic skeletal hyperostosis
N117. Forestier's disease
N117. Ankylosing vertebral hyperostosis
N1460 Lumbosacral ankylosis
N1461 Sacroiliac ankylosis
N1462 Sacral ankylosis NOS
N148. Ankylosis/instability of cervical, thoracic or lumbar spine
N1480 Atlanto-occipital ankylosis

| | |
|-------|----------------------------|
| N1481 | Atlanto-axial ankylosis |
| N1482 | Cervical spine ankylosis |
| N1483 | Cervico-thoracic ankylosis |
| N1484 | Thoracic spine ankylosis |
| N1485 | Thoraco-lumbar ankylosis |
| N1486 | Lumbar spine ankylosis |
| N14z. | Ankylosis of spine NOS |
| N14z. | Spinal disorder NOS |
| N14z. | Back disorders NOS |

8.16 Sjogren's syndrome Read codes

| Code | Term |
|-------|-------------------------------------|
| C37z. | Disorder of metabolism NOS |
| C37z. | Marinesco-Sjogren syndrome |
| H57y3 | Lung disease with Sjogren's disease |
| N002. | Sicca (Sjogren's) syndrome |
| N002. | Keratoconjunctivitis sicca |
| PH12. | Ichthyosiform erythroderma |
| PH12. | Sjogren - Larsson syndrome |

8.17 Systemic lupus erythematosus Read codes

| Code | Term |
|-------|--|
| F3710 | Polyneuropathy in disseminated lupus erythematosus |
| F4D33 | Eyelid discoid lupus erythematosus |
| H57y4 | Lung disease with systemic lupus erythematosus |
| K01x4 | Nephrotic syndrome in systemic lupus erythematosus |
| K01x4 | Lupus nephritis |
| M154. | Lupus erythematosus |
| M1540 | Lupus erythematosus chronicus |
| M1541 | Discoid lupus erythematosus |
| M1542 | Lupus erythematosus migrans |
| M1543 | Lupus erythematosus nodularis |
| M1544 | Lupus erythematosus profundus |
| M1545 | Lupus erythematosus tumidus |
| M1547 | Subacute cutaneous lupus erythematosus |
| M154z | Lupus erythematosus NOS |
| Myu78 | [X]Other local lupus erythematosus |
| N000. | Systemic lupus erythematosus |
| N000z | Systemic lupus erythematosus NOS |
| Nyu43 | [X]Other forms of systemic lupus erythematosus |

8.18 Ulcerative colitis Read codes

| Code | Term |
|-------|--|
| J401z | Crohn's colitis |
| J401z | Crohn's disease of the large bowel NOS |
| J402. | Regional ileocolitis |
| J41.. | Ulcerative colitis and/or proctitis |
| J41.. | Idiopathic proctocolitis |
| J41.. | Mucous colitis and/or proctitis |
| J410. | Ulcerative proctocolitis |
| J4100 | Ulcerative ileocolitis |
| J4101 | Ulcerative colitis |
| J4102 | Ulcerative rectosigmoiditis |
| J4103 | Ulcerative proctitis |
| J4104 | Exacerbation of ulcerative colitis |
| J410z | Ulcerative proctocolitis NOS |
| J411. | Ulcerative (chronic) enterocolitis |
| J412. | Ulcerative (chronic) ileocolitis |
| J413. | Ulcerative pancolitis |
| J41y. | Other idiopathic proctocolitis |
| J41y0 | Pseudopolyposis of colon |
| J41y0 | Inflammatory polyps of colon |
| J41y1 | Toxic megacolon |
| J41yz | Other idiopathic proctocolitis NOS |
| J41z. | Idiopathic proctocolitis NOS |
| J43.. | Other non-infective inflammatory gastroenteritis and colitis |
| J43.. | Enterocolitis |
| J43.. | Gastroenteritis |
| J4303 | Radiation colitis |
| J431. | Toxic gastroenteritis |
| J4310 | Toxic gastritis |
| J4312 | Toxic enterocolitis |
| J4313 | Pseudomembranous colitis |
| J4313 | Toxic colitis |
| J431z | Toxic gastroenteritis NOS |
| J4323 | Allergic colitis |
| J4333 | Dietetic colitis |
| J436. | Microscopic colitis |
| J4360 | Collagenous colitis |
| J4361 | Lymphocytic colitis |
| J437. | Colitis |

| | |
|-------|--|
| J438. | Left sided colitis |
| J4z3. | Non-infective colitis NOS |
| J4z5. | Exacerbation of non-infective colitis |
| J4z6. | Indeterminate colitis |
| J521. | Pseudomembranous colitis |
| J521. | Spastic colon |
| J521. | Irritable bowel syndrome |
| J521. | Irritable colon - Irritable bowel syndrome |
| J5210 | Irritable bowel syndrome with diarrhoea |
| Jyu41 | [X]Other ulcerative colitis |
| N0310 | Arthropathy in ulcerative colitis |
| N0454 | Juvenile arthritis in ulcerative colitis |

8.19 Polymyalgia rheumatica

| | |
|-------|--|
| N20.. | Polymyalgia |
| N20.. | Polymyalgia rheumatica |
| N200. | Giant cell arteritis with polymyalgia rheumatica |

8.20 Psoriatic arthritis Read codes

| Code | Term |
|-------|---|
| 38Va. | Psoriatic Arthritis Impact of Disease 9 questionnaire |
| M160. | Psoriatic arthropathy |
| M160. | Psoriatic arthropathy |
| M1600 | Psoriasis spondylitica |
| N0452 | Juvenile arthritis in psoriasis |
| X701u | |
| X701v | |
| X701w | |
| X7026 | |
| X7027 | |
| XaeFq | |

8.21 Multiple sclerosis Read codes

| Code | Term |
|-------|---------------------------------------|
| 666A. | Multiple sclerosis review |
| F20.. | Disseminated sclerosis |
| F20.. | Multiple sclerosis |
| F200. | Multiple sclerosis of the brain stem |
| F201. | Multiple sclerosis of the spinal cord |

| | |
|-------|--|
| F202. | Generalised multiple sclerosis |
| F203. | Exacerbation of multiple sclerosis |
| F204. | Benign multiple sclerosis |
| F206. | Primary progressive multiple sclerosis |
| F207. | Relapsing and remitting multiple sclerosis |
| F208. | Secondary progressive multiple sclerosis |
| F20z. | Multiple sclerosis NOS |

8.22 Crohn's disease Read codes

| Code | Term |
|-------|--|
| J08z9 | Orofacial Crohn's disease |
| J40.. | Regional enteritis - Crohn's disease |
| J40.. | Granulomatous enteritis |
| J40.. | Crohn's disease |
| J400. | Regional enteritis of the small bowel |
| J4000 | Regional enteritis of the duodenum |
| J4001 | Regional enteritis of the jejunum |
| J4002 | Crohn's disease of the terminal ileum |
| J4003 | Crohn's disease of the ileum unspecified |
| J4004 | Crohn's disease of the ileum NOS |
| J4005 | Exacerbation of Crohn's disease of small intestine |
| J400z | Crohn's disease of the small bowel NOS |
| J401. | Regional enteritis of the large bowel |
| J4010 | Regional enteritis of the colon |
| J4011 | Regional enteritis of the rectum |
| J4012 | Exacerbation of Crohn's disease of large intestine |
| J401z | Crohn's colitis |
| J401z | Crohn's disease of the large bowel NOS |
| J402. | Regional ileocolitis |
| J40z. | Regional enteritis NOS |
| J40z. | Crohn's disease NOS |
| J4z1. | Non-infective jejunitis NOS |
| J4z2. | Non-infective ileitis NOS |
| J4z3. | Non-infective colitis NOS |
| J4z4. | Non-infective sigmoiditis NOS |
| J4z5. | Exacerbation of non-infective colitis |
| J4zz. | Non-infective gastroenteritis NOS |
| J4zz. | Diarrhoea - presumed non-infectious |
| Jyu40 | [X]Other Crohn's disease |
| N0311 | Arthropathy in Crohn's disease |
| N0453 | Juvenile arthritis in Crohn's disease |

8.23 Cancer of respiratory system Read codes

| Code | Term |
|-------|--|
| B2... | Malignant neoplasm of respiratory tract and intrathoracic organs |
| B22.. | Malignant neoplasm of trachea, bronchus and lung |
| B220. | Malignant neoplasm of trachea |
| B2200 | Malignant neoplasm of cartilage of trachea |
| B2201 | Malignant neoplasm of mucosa of trachea |
| B220z | Malignant neoplasm of trachea NOS |
| B221. | Malignant neoplasm of main bronchus |
| B2210 | Malignant neoplasm of carina of bronchus |
| B2211 | Malignant neoplasm of hilus of lung |
| B221z | Malignant neoplasm of main bronchus NOS |
| B222. | Malignant neoplasm of upper lobe, bronchus or lung |
| B2220 | Malignant neoplasm of upper lobe bronchus |
| B2221 | Malignant neoplasm of upper lobe of lung |
| B222z | Malignant neoplasm of upper lobe, bronchus or lung NOS |
| B223. | Malignant neoplasm of middle lobe, bronchus or lung |
| | Malignant neoplasm of middle lobe |
| B2230 | bronchus |
| B2231 | Malignant neoplasm of middle lobe of lung |
| B223z | Malignant neoplasm of middle lobe, bronchus or lung NOS |
| B224. | Malignant neoplasm of lower lobe, bronchus or lung |
| B2240 | Malignant neoplasm of lower lobe bronchus |
| B2241 | Malignant neoplasm of lower lobe of lung |
| | Malignant neoplasm of lower lobe, bronchus or lung |
| B224z | NOS |
| B225. | Malignant neoplasm of overlapping lesion of bronchus and lung |
| B226. | Mesothelioma |
| B22y. | Malignant neoplasm of other sites of bronchus or lung |
| B22z. | Malignant neoplasm of bronchus or lung NOS |
| B23.. | Malignant neoplasm of pleura |
| B230. | Malignant neoplasm of parietal pleura |
| B231. | Malignant neoplasm of visceral pleura |
| B232. | Mesothelioma of pleura |
| B23y. | Malignant neoplasm of other specified pleura |
| B23z. | Malignant neoplasm of pleura NOS |
| B24.. | Malignant neoplasm of thymus, heart and mediastinum |
| | Malignant neoplasm of anterior |
| B242. | mediastinum |
| B243. | Malignant neoplasm of posterior mediastinum |

- B24X. Malignant neoplasm of mediastinum, part unspecified
- B24y. Malignant neoplasm of other site of heart, thymus and mediastinum
- B24z. Malignant neoplasm of heart, thymus and mediastinum NOS
- B25.. Malignant neoplasm, overlapping lesion of heart, mediastinum and pleura
Malignant neoplasm, overlapping lesion of respiratory and intrathoracic organs
- B26.. Malignant neoplasm of other and ill-defined sites within the respiratory and intrathoracic organs
- B2z.. Malignant neoplasm of other and ill-defined sites within the respiratory and intrathoracic organs
- B2z0. Malignant neoplasm of upper respiratory tract, part unspecified
- B2zy. Malignant neoplasm of other site of respiratory tract
- B2zz. Malignant neoplasm of respiratory tract NOS
- B57.. Secondary malignant neoplasm of respiratory and digestive systems
- B570. Secondary malignant neoplasm of lung
- B571. Secondary malignant neoplasm of mediastinum
- B572. Secondary malignant neoplasm of pleura
- B573. Secondary malignant neoplasm of other respiratory organs
- B57z. Secondary malignant neoplasm of respiratory or digestive system NOS
- B81.. Carcinoma in situ of respiratory system
- B811. Carcinoma in situ of trachea
- B812. Carcinoma in situ of bronchus and lung
- B8120 Carcinoma in situ of carina of bronchus
- B8121 Carcinoma in situ of main bronchus
- B8122 Carcinoma in situ of upper lobe bronchus and lung
- B8123 Carcinoma in situ of middle lobe bronchus and lung
Carcinoma in situ of lower lobe bronchus and lung
- B8124 lung
- B812z Carcinoma in situ of bronchus or lung NOS
- B81y. Carcinoma in situ of other specified parts of respiratory system
- B81y0 Carcinoma in situ of pleura
- Xa0KF Tumour of lung
- Xa0KG Malignant tumour of lung
- XaFr7 Local recurrence of malignant tumour of lung
- X78QF Malignant tumour of lung parenchyma
- X78QG Adenocarcinoma of lung
- XaBAp Bronchioloalveolar adenocarcinoma of lung
- X78QI Carcinoid tumour of lung
- X78QJ Carcinoma of lung parenchyma
- X78QK Large cell carcinoma of lung
- X78QL Clear cell carcinoma of lung
- X78QM Giant cell carcinoma of lung
- X78QN Small cell carcinoma of lung
- X78QO Oat cell carcinoma of lung

X78QP Squamous cell carcinoma of lung
X78QQ Epithelioid haemangioendothelioma of lung
X78QR Lymphomatoid granulomatosis of lung
Xa3A5 Metastasis to lung of unknown primary
X2032 Pulmonary tumour embolism
X78kX Secondary lymphangitic carcinoma
X78kY Lymphangitis carcinomatosa
X78QT Pancoast tumour
XE1yN Ca middle lobe bronchus/lung
XE1yP Ca lower lobe bronchus/lung
Byu20 [X]Malignant neoplasm of bronchus or lung, unspecified
XE1vb Malignant neoplasm of upper lobe, bronchus or lung
XE1yL Ca upper lobe bronchus/lung
Malignant neoplasm of bronchus or lung
XE1vc NOS
Xa98a Bronchial adenoma
X78QD Papilloma of bronchus
X78QW Histiocytoma of lung
X78QX Adenoma of lung
X78Q6 Tumour of bronchus
X78Q7 Malignant tumour of bronchus
X78Q8 Squamous cell carcinoma of bronchus
Squamous cell carcinoma of bronchus in left lower
XaEJe lobe
XaEJf Squamous cell carcinoma of bronchus in left upper lobe
XaEJg Squamous cell carcinoma of bronchus in right lower lobe
XaEJh Squamous cell carcinoma of bronchus in right middle lobe
Squamous cell carcinoma of bronchus in right upper
XaEJi lobe
X77nT Carcinoid bronchial adenoma
X78QS Non-small cell lung cancer
X78kV Metastasis to bronchus
Xa3A4 Metastasis to bronchus of unknown primary
XE1yJ Ca main bronchus
X78QA Carcinoma in situ of bronchus
X78QE Tumour of lung parenchyma
X78QU Carcinoma in situ of lung parenchyma
X78QY Intrapulmonary teratoma
X78QZ Hamartoma of lung
X78Py Tumour of lower respiratory tract

8.24 Rheumatoid arthritis Read Codes

| Read Code | Read Term |
|-----------|---|
| N040. | Rheumatoid arthritis |
| X701h | Seropositive rheumatoid arthritis |
| XaBMO | Seropositive erosive rheumatoid arthritis |
| Nyu11 | [X]Other seropositive rheumatoid arthritis |
| Nyu1G | [X]Seropositive rheumatoid arthritis, unspecified |
| X701i | Seronegative rheumatoid arthritis |
| N041. | Felty's syndrome |
| X701j | Rheumatoid arthritis with organ / system involvement |
| N0421 | Rheumatoid lung |
| X701k | Fibrosing alveolitis associated with rheumatoid arthritis |
| X701l | Rheumatoid vasculitis |
| X705t | Nailfold rheumatoid vasculitis |
| X705u | Systemic rheumatoid vasculitis |
| X705v | Necrotising rheumatoid vasculitis |
| G5yA. | Rheumatoid carditis |
| N042z | Rheumatoid arthropathy with visceral or systemic involvement NOS |
| Nyu10 | [X]Rheumatoid arthritis with involvement of other organs or systems |
| X701m | Rheumatoid arthritis with multisystem involvement |
| N0408 | Rheumatoid arthritis of metacarpophalangeal joint |
| N040B | Rheumatoid arthritis of hip |
| N040D | Rheumatoid arthritis of knee |
| N040C | Rheumatoid arthritis of sacroiliac joint |
| N040M | Rheumatoid arthritis of interphalangeal joint of toe |
| N040L | Rheumatoid arthritis of lesser metatarsophalangeal joint |
| N040G | Rheumatoid arthritis of subtalar joint |
| N040A | Rheumatoid arthritis of distal interphalangeal joint of finger |
| N0407 | Rheumatoid arthritis of wrist |
| N0402 | Rheumatoid arthritis of shoulder |
| Xa3gL | Rheumatoid arthritis - multiple joint |
| N0409 | Rheumatoid arthritis of proximal interphalangeal joint of finger |
| N040F | Rheumatoid arthritis of ankle |
| N0400 | Rheumatoid arthritis of cervical spine |
| N040E | Rheumatoid arthritis of tibiofibular joint |
| N040K | Rheumatoid arthritis of first metatarsophalangeal joint |
| N0401 | Other rheumatoid arthritis of spine |
| N0406 | Rheumatoid arthritis of distal radioulnar joint |
| N040H | Rheumatoid arthritis of talonavicular joint |
| N040J | Rheumatoid arthritis of other tarsal joint |
| N040T | Flare of rheumatoid arthritis |
| Xa3gM | Rheumatoid arthritis - hand joint |

| | |
|-------|---|
| Xa3gN | Rheumatoid arthritis - ankle/foot |
| Xa3gO | Rheumatoid arthritis - other joint |
| Xa3gP | Rheumatoid arthritis NOS |
| N0402 | Rheumatoid arthritis of shoulder |
| N0403 | Rheumatoid arthritis of sternoclavicular joint |
| N0404 | Rheumatoid arthritis of acromioclavicular joint |
| N0403 | Rheumatoid arthritis of sternoclavicular joint |
| N0405 | Rheumatoid arthritis of elbow |
| N0406 | Rheumatoid arthritis of distal radio-ulnar joint |
| N0407 | Rheumatoid arthritis of wrist |
| N040C | Rheumatoid arthritis of sacro-iliac joint |
| N040E | Rheumatoid arthritis of tibio-fibular joint |
| N040K | Rheumatoid arthritis of 1st metatarsophalangeal joint |
| N040N | Rheumatoid vasculitis |
| N040P | Seronegative rheumatoid arthritis |
| N040Q | Rheumatoid bursitis |
| N040R | Rheumatoid nodule |
| N040S | Rheumatoid arthritis - multiple joint |
| N0455 | Juvenile rheumatoid arthritis |

8.25 Temporal arteritis Read codes

| | |
|-------|--|
| G755. | Giant cell arteritis |
| G7550 | Cranial arteritis |
| G7551 | Temporal arteritis |
| G7552 | Horton's disease |
| G755z | Giant cell arteritis NOS |
| N200. | Giant cell arteritis with polymyalgia rheumatica |
| Nyu41 | [X]Other giant cell arteritis |

8.26 Height, weight, BMI Read Codes

| Read code | Read term |
|-----------|-----------|
| 229.. | Height |
| 22A.. | Weight |
| 22K.. | BMI |

8.27 Blood Eosinophil Count Read codes

| Read code | Read term |
|-----------|-------------------------|
| 42K.. | Eosinophil count |
| 42K1. | Eosinophil count normal |

| Read code | Read term |
|-----------|--------------------------------|
| 42K2. | Eosinopenia |
| 42K3. | Eosinophil count raised |
| 42KZ. | Eosinophil count NOS |
| 42b9. | Percentage eosinophils |
| 4E32. | Sputum: eosinophilia |
| D403 | Hereditary eosinophilia |
| D403. | Eosinophilia |
| D4033 | Allergic eosinophilia |
| D4034 | Secondary eosinophilia NOS |
| D403z | Eosinophilia NOS |
| H583. | Pulmonary eosinophilia |
| H5831 | Tropical eosinophilia |
| H583z | Pulmonary eosinophilia NOS |
| J08z | Oral mucosa eosinoph.granuloma |
| X0011 | Eosinophil non-allergic rhinit |
| X102G | Asthmatic pulm eosinophilia |
| X102H | Cryptogenic pulm eosinophilia |
| X3009 | Eosinophilic oesophagitis |
| X80VM | Eosinophil |
| Xa0kb | Tropical pulm eosinophilia |
| Y02Rr | Eosinophil non-allergic rhinit |
| Y108t | Eosinophilic pneumonia |
| Y108u | EP - Eosinophilic pneumonia |
| Y108v | Pulm infiltrate + eosinophilia |
| Y108w | PIE - Pul infil + eosinophilia |
| Y108z | Acute eosinophilic pneumonia |
| Y1090 | Simple pulmonary eosinophilia |
| Y1094 | Asthmatic pulm eosinophilia |
| Y1095 | Cryptogenic pulm eosinophilia |
| Y1096 | Chronic eosinophilic pneumonia |
| Y1097 | Crypt eosinophilic pneumonia |
| Y1098 | Chronic pulmonary eosinophilia |
| Y1099 | Tropical pulm eosinophilia |
| Y20fq | Eosinophilic disorder |
| Y3017 | Eosinophilic oesophagitis |
| Y80ID | Eosinophil |
| Ya14p | EP-Acute eosinophil pneumonia |
| Yaeib | Percentage eosinophil count |
| YakcK | Eosinophil count - observation |

8.28 Spirometry measurement Read codes

| Read code | Read term |
|-----------|--|
| 3396. | Forced vital capacity - FVC |
| 33960 | FVC - forced vital capacity normal |
| 33961 | FVC - forced vital capacity abnormal |
| 3397. | Forced expiratory volume - FEV |
| 3398. | FEV1/FVC ratio normal |
| 3399. | FEV1/FVC ratio abnormal |
| 339a. | FEV1 before bronchodilation |
| 339b. | FEV1 after bronchodilation |
| 339e. | FEV1 pre steroids |
| 339f. | FEV1 post steroids |
| 339h. | FVC after bronchodilation |
| 339j. | FEV1/FVC ratio pre steroids |
| 339k. | FEV1/FVC ratio post steroids |
| 339l. | FEV1/FVC ratio before bronchodilator |
| 339M. | FEV1/FVC ratio |
| 339m. | FEV1/FVC ratio after bronchodilator |
| 339O. | Forced expired volume in 1 second |
| 339O1 | Forced expired volume in one second/vital capacity ratio |
| 339P. | Expected FEV1 |
| 339R. | FEV1/FVC percent |
| 339s. | Forced vital capacity before bronchodilation |
| 339S. | Percent predicted FEV1 |
| 339S0 | Percentage predicted FEV1 after bronchodilation |
| 339T. | FEV1/FVC > 70% of predicted |
| 339U. | FEV1/FVC < 70% of predicted |
| X77Qu | Forced expired volume in 1 second |
| X77Ra | Forced expired volume in one sec/forced vital capacity ratio |
| XaCJK | Expected FEV1 |
| XaEFy | FEV1/FVC percent |
| XaEFz | Percent predicted FEV1 |
| XalxQ | FEV1 before bronchodilation |
| XalxR | FEV1 after bronchodilation |
| XalxU | FEV1 pre steroids |
| XalxV | FEV1 post steroids |
| XaJ3K | FVC after bronchodilation |
| XaJ9B | FEV1/FVC ratio pre steroids |
| XaJ9C | FEV1/FVC ratio post steroids |
| XaJ9D | FEV1/FVC ratio before bronchodilator |
| XaJ9E | FEV1/FVC ratio after bronchodilator |
| XaPpl | Forced vital capacity before bronchodilation |
| XaVx3 | Percentage predicted FEV1 after bronchodilation |

8.29 Peak Expiratory Flow Read codes

| Read code | Read term |
|-----------|--------------------------------|
| 339.. | Respiratory flow rates |
| 3391 | Resp. flow rate measured |
| 3392 | Resp. flow rate not measured |
| 3393 | Resp. flow rate normal |
| 3394 | Resp. flow rate abnormal |
| 3395 | Peak exp. flow rate: PEFR/PFR |
| 339A. | PFR - before bronchodilation |
| 339B. | PFR - after bronchodilation |
| 339C. | PFR - expected |
| 339D. | PFR - best ever |
| 339E. | PFR >80% of predicted |
| 339F. | PFR 60-80% of predicted |
| 339G. | PFR <60% of predicted |
| 339H. | Predicted peak flow |
| 339I. | Expected peak flow rate x 50% |
| 339J. | Optimal peak flow rate |
| 339K. | Expected peak flow rate x 30% |
| 339L. | Expected peak flow rate x 80% |
| 339V. | Recorded/predicted PEFR ratio |
| 339W. | Worst peak flow rate |
| 339X. | Percentage of best ever PEFR |
| 339Y. | Percentage of PEFR variability |
| 339Z. | Respiratory flow rates NOS |
| 339c. | PEFR pre steroids |
| 339d. | PEFR post steroids |
| 339g. | Serial peak expirat flow rate |
| 339n. | Serial PEFR abnormal |
| 339o. | PEFR using EN 13826 device |
| 339p. | Predict PEFR using EN13826 std |
| 339u. | Peak inspiratory flow rate |
| 745C0 | Measure peak expirat flow rate |

Observational Study Protocol
Study Code << D589BR00053 >>
Version 6.5
Date 01/28/22

9. ATTACHMENTS

10. SIGNATURES

Authoring Instructions

- o *The following signature pages for an Observational Study protocol may be required and further details on who is required to sign can be found in the SOP 8-P102-CV-C Design, Execution, and Reporting of AstraZeneca Sponsored Observational Studies:*
 - o *Global Medical Affairs Lead or Global Clinical Lead/Delegate for global studies*
 - o *MC Medical Director/Delegate for local studies*
 - o *Global Epidemiologist /Local Study Leader*
 - o *Optional signature from Biostatistician or Delivery Director*
 - o *Always print the names and addresses.*

ASTRAZENECA SIGNATURE(S)

<<Study Description>>

<<*This Observational Study Protocol* >> <<*has/have*>> *been subjected to an internal AstraZeneca review*>>

I agree to the terms of this Study protocol.

AstraZeneca representative

<<*Name, title*>>

Date
(Day Month Year)

<<*Email address and telephone number*>>

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.