Study Report

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 OPCRD and CPRD databases

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Countries of study	United Kingdom
Data source	Combined data from the OPCRD and the CPRD
Author	Observational and Pragmatic Research Institute

LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse events
BTS	British Thoracic Society
CPRD	Clinical Practice Research Datalink
GINA	Global Initiative for Asthma
GP	General practice
HES	Hospital Episode Statistics
HR	Hazard ratio
HRU	Healthcare resources utilization
ICD	International Classification of Diseases
ICS	Inhaled corticosteroid
OCS	Oral corticosteroid
OPCRD	Optimum Patient Care Research Database

1 Executive Summary

1.1 Introduction

Asthma is a major public health problem, and medications are suboptimally used. Despite an expanding arsenal of newer treatment regimens, oral corticosteroids (OCS) are still widely used in patients with asthma both as maintenance and intermittent therapy, despite long-term OCS use having been shown to increase the risks of numerous adverse events.

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 thus received intermittent rather than long-term OCS. It is unclear to what extent intermittent use of OCS will increase the risk of adverse outcomes. Also, little is known about the healthcare resource utilisation and costs associated with intermittent OCS use.

1.2 Study aims and objectives

This study aims to investigate the hypothesis that patients with more frequent intermittent OCS prescribing patterns suffer an increase in adverse events and increased healthcare costs. There were four objectives in this study: first, 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; second, to assess the association between patterns of intermittent OCS use and OCS-related adverse outcomes in patients with asthma; third, to describe the impact of different patterns of intermittent OCS use on the frequency of healthcare resource utilisation in patients with asthma; and fourth, to describe the adverse events for patients with an average annual OCS dose of 250-499mg, 500-999mg, or =>1g of OCS during the follow up.

1.3 Methods

A historical cohort combining data from the Optimum Patient Care Research Database (OPCRD) and the Clinical Practice Research Datalink (CPRD) to include patients with active asthma, registered at GP practices in the UK, was used. Intermittent OCS users were defined as 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, and non-users were defined as patients who have never received an OCS prescription. Intermittent OCS

prescriptions were identified using a stepwise OPRI algorithm which uses information associated to the OCS prescriptions and recommendations by the NICE guideline to distinguish between acute/intermittent prescriptions and maintenance ones. Only patients with a minimum 1-year baseline period and aged 4 years old or above at index date were included. Patients who have ever had a diagnosis for a chronic condition treated with OCS, or with a chronic adverse event outcome prior to the index date were excluded. The index date for the OCS arm was the first recorded prescription of an OCS corticosteroid, while that of the non-OCS arm was the nearest GP visit to the index date for the matched OCS arm patient. Patients within the two arms were matched on gender. The duration of the study was from the time of the patient's first OCS with concurrent asthma event until death or the end-of-records, whichever occurs first.

The primary outcome was a diagnostic (or, where appropriate, medication) 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. In the adolescent population, growth suppression and behavioural disorders were also investigated.

CPRD HES linked data was used to describe hospital admissions, A&E attendances, and Outpatient visits. All HRU events and asthma specific events and costs were described for eight HRU categories: physician office visits, outpatient visits, hospital attendances (both including and excluding day cases), length of stay for hospital attendance (both overall and ≥1 overnight), and day cases. The number and costs of prescriptions were also evaluated.

Risks of adverse events were compared between OCS users and non-users using multivariable Cox proportional hazards model, with adjustments for the variables identified as confounders in the post-matching baseline analysis. The cumulative dose and average daily exposure of OCS were modelled as time-varying exposures.

1.4 Results

In total, 2,130,881 patients on OCS were identified. After applying the exclusion criteria, 476,167 patients on intermittent OCS and 476,167 matched controls were included in the analysis. The mean age was 38.1 years, and 44% were females. Most patients had mild to moderate asthma at baseline: prior to receiving the initial dose of OCS, the majority of patients were receiving GINA step 1 or 2 treatments (119,687 (25.1%) and 152,156 (32.0%),

respectively), while 65,625 (13.8%) had no prior asthma medications; only 50,944 (10.7%) patients were on GINA step 4 or 5 treatment.

The OCS users were initially categorized into five categories by intermittent OCS use patterns: one-off, sporadic, infrequent, moderately frequent, and frequent. To allow for easier interpretation, these were further categorized into three categories : one-off (initial one-off group; patients who had only one OCS prescription; 198,420 patients; 41.7%), less frequent (initial sporadic, infrequent, or moderately frequent groups; patients who had more than one prescription, and all with ≥90 days of gap; 127,419 patients; 26.8%), and frequent (patients who had more than one prescription, and all with <90 days of gap; 150,326 patients; 31.6%). Patients with more frequent bursts of OCS were older, and females received more OCS regardless of OCS frequency. Meanwhile, patients who had one-off OCS use were least likely to be obese, but most likely. Whilst those with more frequent OCS prescriptions had poorer asthmatic control by RCP readings, no relationship was observed between maximum eosinophil reading and OCS use pattern categories. There were also no relationships between prior asthma treatment and OCS use pattern categories.

Overall, OCS users had higher risks of any adverse event than non-OCS users, with frequent OCS users having the highest risk (hazard ratio (HR) 1.44, 95% confidence interval [1.43, 1.45]), followed by less frequent (HR 1.38 [1.36, 1.38]) and one-off (HR 1.2 [1.19, 1.21]) users. These trends were generally also observed for individual adverse events. Subgroup analysis stratifying by age groups, baseline GINA step, baseline ICS prescriptions, and baseline SABA prescriptions showed that there were no effect modification of OCS use with the risks of adverse events by the above subgroup variables . Further analysis showed that higher cumulative dose, but not annualised OCS dose, was associated with higher risks of adverse events.

The above translated to higher healthcare costs incurred by OCSs users than non-users (£8935 for OCS users vs £4635 for OCS non-users, p<0.0001). The mean episodes and annualized rates across follow-up of general practitioner consultations, accident and emergency attendances, outpatient attendances, length of stay, and prescriptions were significantly higher in OCS users, generally regardless of the causes underlying the events or prescriptions.

1.5 Conclusion

This study devised a classification algorithm which systematically classified patterns of intermittent OCS use. Intermittent OCS use was associated with increased risks of adverse events, with frequent users having the highest risks. Furthermore, OCS users incurred higher healthcare costs than non-users.

2 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. Patients often receive large numbers of short-acting beta-agonists (SABA) prescriptions, despite United Kingdom (UK) asthma guidelines stating that at least three times of SABA use 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 SABA per month should trigger an asthma review. Nonetheless, underuse of Inhaled Corticosteroids (ICS) is common, with an estimated 14% of patients who had asthma death not having been prescribed maintenance ICS at the time of their death.[3] Underuse of ICS has contributed to asthma deaths and worse asthmatic control.[3] New treatment regimens, e.g. biologics therapies, for patients with asthma are being recommended for the severe asthma population. The biologics 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]

Amidst the suboptimal use of existing treatments and increasingly 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, such as the British Thoracic Society/ Scottish Intercollegiate Guidelines Network (BTS/SIGN) guideline and the Global Initiative for Asthma (GINA) guideline, 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 β2 agonist therapy. The 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.[2] GINA recommends 40-50mg prednisolone, daily for 5-7 days and a maintenance dose of ≤7.5mg.[8]

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) 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), which found 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]

The limited understanding of the association of intermittent OCS use with adverse events was also due to the wide variety of measures used in the literature to classify OCS use. These measures focused on aggregate measures over time periods rather than prescription patterns, such as the number of days of continuous OCS prescription,[16–19] continuous periods covered with OCS,[20] average number of days covered over a time period,[21] prescribing instruction including titration patterns,[15] and the cumulative and average daily dosage over time periods.[22–24] However, cumulative exposure to intermittent OCS may not be an ideal measure because of possible variations among patients with regard to factors

such as disease duration and severity.[25] In contrast to cumulative dosage, prescription patterns paint a more granular picture of patients' requirement for intermittent OCS and thus disease status, as well as allowing exploration of the progression of intermittent OCS use over time.

3 Study Aims, Objectives, and Feasibility Analysis

3.1 Study Aim

This study aimed to investigate the hypothesis that patients with more frequent OCS prescribing patterns suffer an increased risk in adverse events and increased healthcare utilization and costs.

3.2 Study Objectives

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.

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

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

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.

4 Materials and Methods

4.1 Study Design

4.1.1 Patient population and data source

This was 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 GOLD 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 was 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.[28] The CPRD records were linked to Hospital Episode Statistics (HES), which records all healthcare utilization in 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 was 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 has approval from Independent Scientific Advisory Committee (ISAC; approval number 20_000071).

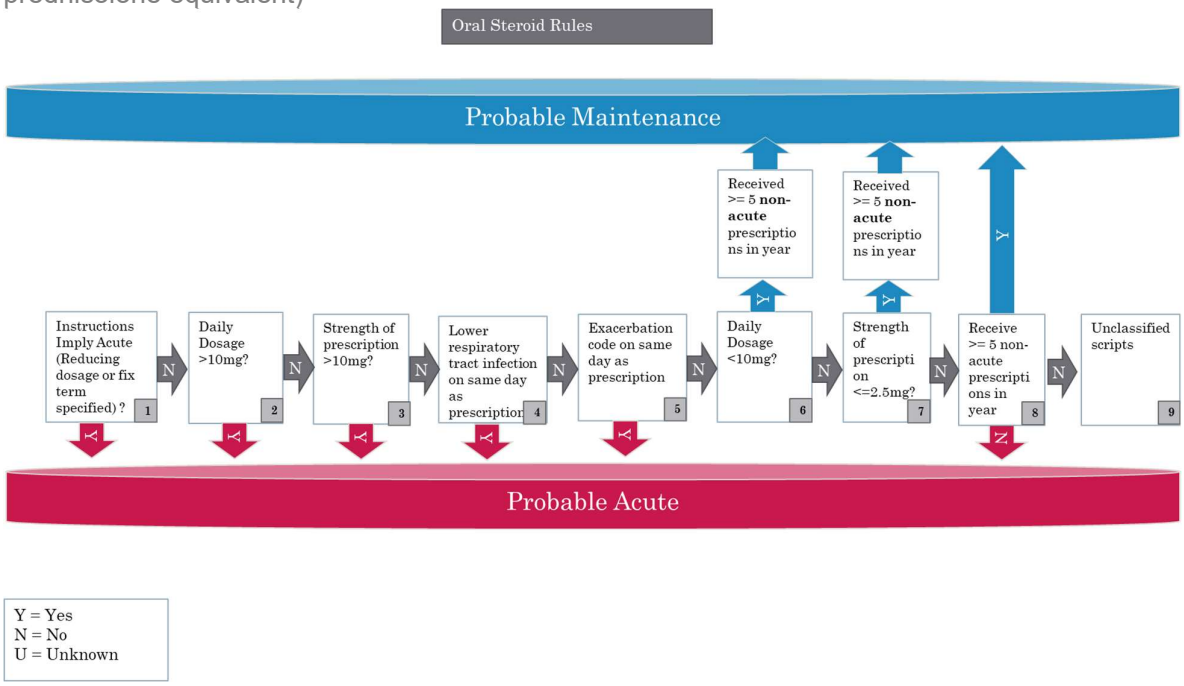
The OPCRD and CPRD datasets were constructed separately and patients with duplicate data were excluded before pooling for analyses. These two databases have been combined in multiple prior and current studies conducted by OPRI.[29–31] CPRD GOLD, which was the database to which access has been requested, contains data from practices using Vision software only; OPCRD contains data from a range of software providers including EMIS, iSoft, Microtest, SystemOne and Vision. For this study, we took a conservative approach and dropped 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 constituted about 12% of the OPCRD database so this was not anticipated to have a significant impact on final patient numbers. The most recent extraction of EMR data from OPCRD and CPRD with

linked HES data (up to March 2019 at the time of protocol finalization) from general practices for patients diagnosed with asthma was used.

4.2 Objective 1 study design and feasibility analysis

Patients' OCS prescriptions were classified as acute using an existing OPRI OCS algorithm (Figure 1). The OPRI OCS algorithm uses information associated to the OCS prescriptions and recommendations by the NICE guideline[32] to determine whether they were likely an acute/intermittent or a maintenance script. This was done in a stepwise approach using the most definitive information first, e.g. the dosing instructions. For prescriptions that did not enable a decision using the dosing instructions, the next most definitive information was used, this being the daily dose. Expert respiratory clinicians were involved in the development of this algorithm. This approach has been used in previous OPRI studies to determine intermittent/maintenance OCS prescribing. A paper by Heatley *et al* describing and validating the algorithm has been submitted to an international peer-reviewed journal to be considered for publication.

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

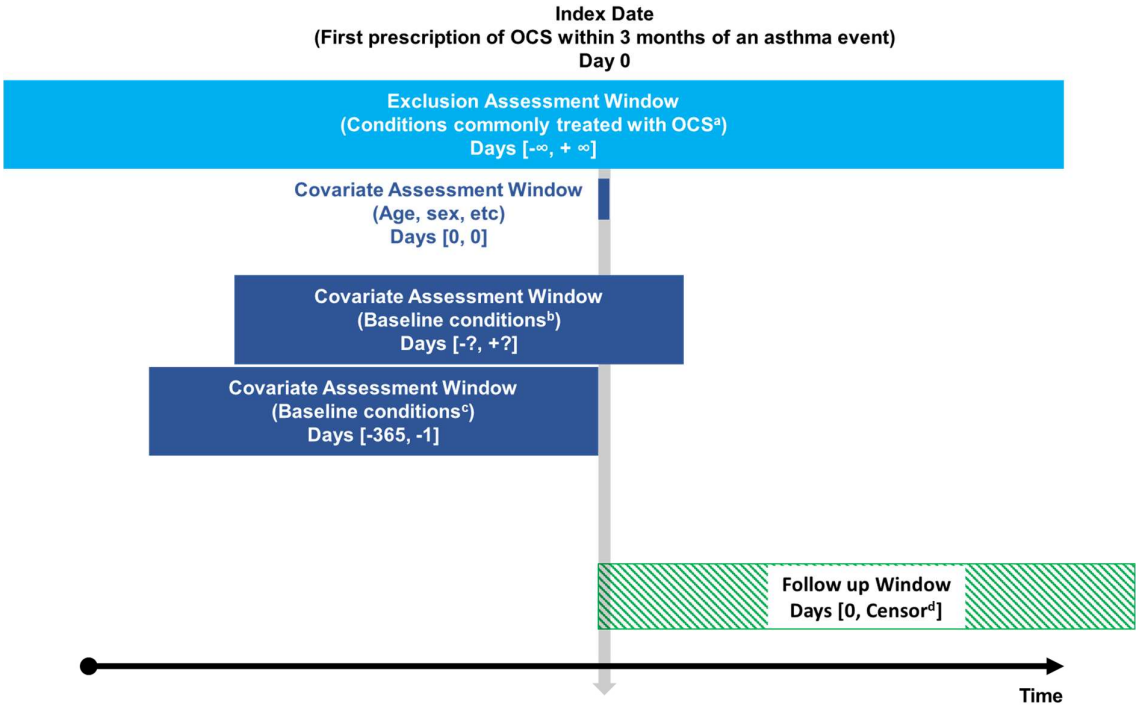


Patients' index date was determined as their first OCS prescription with a concurrent (+/- 3 month i.e. 6-month interval) asthma event (**Error! Reference source not found.**). Patients

were categorised according to their OCS patterns and by demographic, clinical, and therapy indicators indicated below. Patients were first categorised into six OCS use patterns:

- One-off, defined as only having a single OCS prescription ever;
- Sporadic, defined as all the between-prescription gaps ≥ 365 days;
- Infrequent, defined as all the between-prescription gaps ≥182 days and <365 days;
- Moderately frequent, defined as all the between-prescription gaps ≥90 days and <182 days;
- Frequent, defined by all the between-prescription gaps <90 days; and
- Mixed, defined by a mixture of prescription gaps.

Figure 2 General study design



a. 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
b. Baseline conditions included e.g. most recent Height & Body Mass Index etc
c. Asthma Severity (GINA [2019] treatment step), BEC, Lung Function
d. 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

Initial feasibility analyses undertaken within OPCRD described the proportion of patients with the above OCS use patterns, in order to better understand the OCS patterns that should be considered for use in this analysis. Most patients were found to have either one-off OCS prescriptions or mixed patterns (Table 1).

Table 1 OCS Prescribing patterns for patients in OPCRD

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%

For clearer and easier interpretation and to facilitate clinical translation of results, these patterns were subsequently simplified into three OCS use patterns, with patients having any frequent prescription pattern within mixed patterns classified as frequent, and those having more than one OCS prescription but not fulfilling the frequent prescription pattern classified as less frequent:

- One-off, defined as only having a single OCS prescription ever;
- Less frequent, defined as having multiple prescriptions with between-prescription gap(s) of ≥90 days; and
- Frequent, defined as having multiple prescriptions with between-prescription gap(s) of <90 days.

Baseline patient characteristics described as part of Objective 1 were summarized in Table 2.

Table 2 Fixed variables measured at baseline

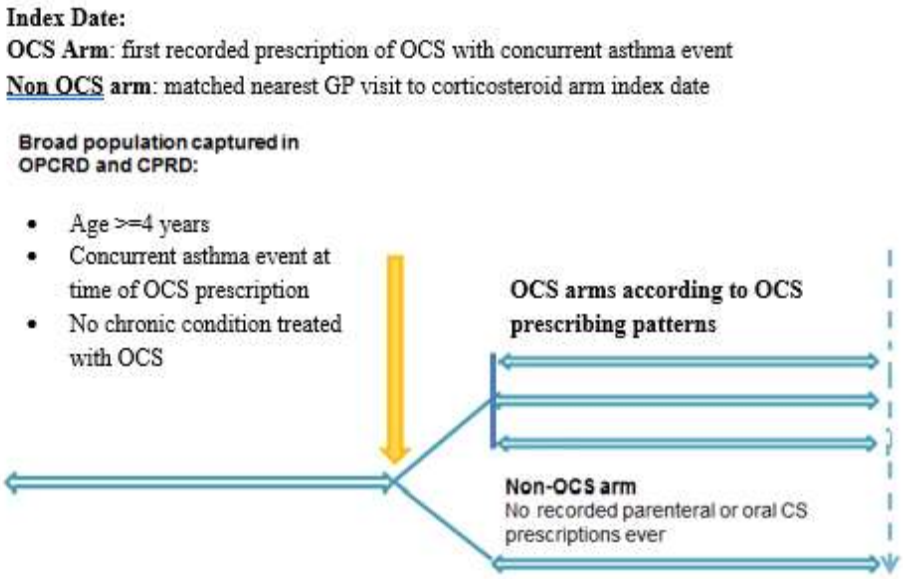
Age	Age in years on index date.
Gender	Female or Male
Height	Measurement in metres (m) on reading closest to index date, in adulthood
Body Mass Index (BMI)	Defined as the ratio of weight (kg) to squared height (m^2) closest to the index date. Categorised as: Adolescent (<18 years old)[33] Calculated using UK reference population. Standardised BMI z-score based upon gender, weight, height and age Adult (18 years old and over) • Underweight <18.5 • Normal w eight 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 and expressed in years
Asthma Control using RCP3 questionnaire	RCP questions recorded as part of an asthma review. Categorised as: • Controlled

	• Not controlled
GINA treatment steps	Patients categorised by GINA Treatment Steps
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 x 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 by 0, 1-2, 3-11, 12+, and 0,1-2,3+
Number of ICS-containing prescriptions	Total number of ICS-containing prescriptions/inhalers/dose in baseline year (i.e. the year prior to the index date. Categories included 0, 1-6, 7-12, and 13 or more prescriptions

4.3 Objective 2 study design

For objective 2, a matched historical cohort study was performed using patient data from both OPCRD and CPRD UK. The duration of the study was from the time of the patient's first OCS with concurrent asthma event until the end-of-records. This objective compared patients exposed to intermittent oral corticosteroids (OCS arm) and patients without any exposure to oral corticosteroids (non-OCS arm) (Figure 3).

Figure 3 Objective 2 study design



The index date for the OCS arm was the first recorded prescription of an OCS corticosteroid with a concurrent (within 3 months) asthma event defined as an asthma QOF diagnosis or asthma QOF prescription, while that of the non-OCS arm was the nearest GP visit to the index date for the matched OCS arm patient. Patients within the two arms were matched on age and gender but not asthma diagnosis; that is, the non-OCS arm included patients who did not have asthma. A 3-month window around the initial OCS date was included to help ensure that the OCS prescription related to an asthma clinical event. Data was right censored at the end of data availability.

Primary outcome was a diagnostic Read code for the following conditions: type 2 diabetes mellitus, osteoporosis/osteoporotic fractures, hypertension, glaucoma, sleep apnoea, weight gain (defined as an increase in Body Mass Index (BMI) by at least 1 kg/m2 compared to index date) and depression/anxiety, pneumonia, cataracts, sleep disorders, cardiovascular disease, chronic kidney disease, dyslipidaemia and peptic ulcer disease, and, in the paediatric population, also growth suppression and behavioural disorders. These were defined as follows:

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 ≥ 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 was still considered to 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, for children, more than 1% centile band.[34]

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 (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. Paediatric 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)

Subgroup analyses were performed with stratification for age groups (4-<12 years old, 12-<18 years old, 18-<65 yeas old, and 65 years old or above), GINA treatment steps 1-5 (one category each, plus no treatment), SABA prescriptions (0, 1-2, 3-12, and 13 or more prescriptions), and ICS prescriptions (0, 1-6, 7-12, and 13 or more prescriptions) at baseline.

4.3.1 Objective 3 study design

CPRD HES-linked data was used to describe hospital admissions, A&E attendances, and Outpatient visits. All-cause HRU events and asthma specific events were described for eight HRU categories described further below which were then further described as respiratory or non-respiratory, and according to specific causes. The HRU outcomes and associated costs were calculated as annualised HRU and annualised costs for and compared between each OCS use pattern, as well as OCS non-users. Regression analyses are performed to investigate associations between OCS use patterns and HRU. Prices assigned to primary

care consultation costs were 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 were based on the national average hospital costs as found in PSSRU document. Prices assigned to drugs were 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) were used to fill any gaps.

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
    c. Cause-specific outpatient HRU as defined by main specialty description
        i. Cardiovascular: Cardiology, Cardiothoracic Surgery, Elderly Medicine, General Internal Medicine, or Neurology as main specialty
        ii. Cataract / glaucoma: Medical Ophthalmology or Ophthalmology as main specialty
        iii. Hypertension: Cardiology, Clinical Pharmacology, or General Internal Medicine as main specialty
        iv. Osteoporosis: Elderly Medicine, Rheumatology, or Trauma and Orthopaedic as main specialty
        v. Peptic ulcer: Gastroenterology, or General Internal Medicine as main specialty
        vi. Pneumonia: General Internal Medicine, or Respiratory Medicine as main specialty
        vii. Anxiety and depression: Adult Mental Health, Child and Adolescent Psychiatry, Forensic Psychiatry, Medical Psychotherapy, or Old Age Psychiatry as main specialty
        viii. Renal: Renal Medicine as main specialty
        ix. T2DM: Endocrinology, General Internal Medicine, Ophthalmology, or Renal Medicine as main specialty

3. A&E attendances (CPRD-HES only):
    a. All-cause,

b. Respiratory-related (HES variables DIAG2 = 25 (Respiratory conditions) or DIAG = 'AST%' or DIAG2 = 'J4%')
c. Cause-specific A&E HRU as defined by AE codes
    i. Cataract / glaucoma: AE code for “ophthalmological conditions”
    ii. Peptic ulcer: AE code for “gastrointestinal conditions”
    iii. Cardiovascular: AE code for “cardiac conditions” or “cerebro-vascular conditions” or “other vascular conditions”
    iv. Anxiety / depression: AE code for “psychiatric conditions”
    v. T2DM: AE code for “diabetes and other endocrinological conditions”
    vi. Missing: AE code for “diagnosis not classifiable” or “missing”
    vii. Other causes: any other AE code

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

9. Cause-specific inpatient HRU costs, defined by ICD-10 codes of primary diagnoses:
    a. T2DM: E11
    b. Hypertension: I10
    c. Cardiovascular: I21-I22, I50, I70, I73.9, I42, I48, I63.9, I64, I69.4
    d. Osteoporosis / osteoporotic fractures: M80-M85
    e. Sleep disorders: G47 excluding G47.3
    f. Sleep apnoea: G47.3
    g. Peptic ulcer: K25-K27
    h. Cataract: H25-H28
    i. Glaucoma: H40-H42
    j. Depression / anxiety: F20.4 F25.1, F32, F33, F40, F41
    k. Pneumonia: J12-J18
    l. Chronic kidney disease: N17, N18.3, N18.4, N18.5, N19

4.3.2 Objective 4 study design

The unadjusted incidence rates 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 patient-year), were compared using the incidence rate difference and the incidence rate ratio (IRR) with 95% CIs. Each patient was followed until the first occurrence of the outcome of interest and was censored at death or the end of available records.

4.4 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.
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

4.5 Exclusion criteria

1. Patients with a diagnosis, ever, for a chronic condition treated with OCS: Ankylosing spondylitis, Sjogren's syndrome, Systemic lupus erythematosus, Temporal arteritis, Ulcerative colitis, Psoriatic arthritis, Multiple sclerosis, Polymyalgia rheumatica, Crohn's disease
2. Patients with a chronic AE outcome prior to the index date were excluded from the analysis. This will ensure that the first chronic condition was the post index date incident event.

5 Study Variables

5.1 Exposures

Exposure was defined as a prescription of oral corticosteroids, which was prescribed for the treatment of asthma (defined by use of asthma medication(s), 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 3. Doses were converted into prednisolone equivalents using the defined daily dose (DDD) obtained from the ATC/DDD classification system.[35]

Table 3 Oral corticosteroid drug codes and conversion factors

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

Drug name	Prednisolone equivalent conversion factor	ATC code systemic use	DDD
Triamcinolone	1.33	H02AB08	7.5

OCS use patterns were described and analysed using the three-tier pattern categorization (one-off, less frequent, and frequent) as described in section 4.1.2 above.

5.2 Other Variables and Covariates

Baseline variables that were included were summarized in Table 2 above. Time-varying covariates measured during follow-up were summarized in Table 4 below.

Table 4 Variable 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 treatment step	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))

6 Statistical Analysis

6.1 General Calculation of Epidemiological Measure(s) of Interest

The distributions of values at each decision step of the OPRI OCS algorithm (Figure 1) were displayed as a histogram. Experts reviewed these histograms and determined whether the existing decision points were the most appropriate. Summary statistics were provided for the prescriptions decisions.

Use pattern analysis were 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 was descriptive in nature, providing the absolute and relative number of subjects, mean, median, standard deviation, and interquartile range for continuous variables for the baseline variables, and n and % for categorical variables.

Analyses were 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:

- ≥4 – 11 years,
- ≥12 – 17 years
- ≥18 - 64 years
- ≥65+ years

6.2 Objective-specific analysis

6.2.1 Objective 2

The risk of developing an adverse outcome was analysed using survival analysis methods. Patients with prior diagnosis of an adverse outcome, and which was classed as chronic, were excluded from the corresponding analysis in order to specifically assess incident-only adverse outcomes, meaning that the sample size for analysis of individual adverse outcomes or a set of any adverse outcomes differed from one to another. Kaplan-Meier curves were used to describe the overall risk profile of each adverse outcome. To assess the association between intermittent OCS (vs non-OCS) prescription and risk of adverse outcomes, a multivariable Cox proportional hazard model was used to calculate HR and 95% CI for each adverse outcome. The Cox models were adjusted for age, sex, BMI, smoking status and time-varying OCS prescriptions, defined a priori. The multivariable analysis was further stratified by age, GINA 2020 treatment step and prescriptions for ICS and SABA in the 12 months pre index.

6.2.2 Sample size calculation

Diabetes: approximately 950 events were needed to detect a 34% risk increase of diabetes

onset for OCS patients,[36] 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 meant 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 were needed to detect a 33% risk increase of fracture at any site for OCS patients,[37] 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 meant following up approximately 12,500 patients over a period of 5 years or 31,000 patients over 2 years.

Pneumonia: approximately 140 events were needed to detect a 2.17-fold increase in pneumonia risk for OCS patients[38] 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 meant following up approximately 6,000 patients over a period of 5 years or 15,000 patients over 2 years.

6.2.3 Objective 3

Outcomes were described as mean numbers ± 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 was described as mean ± standard deviation (SD), as median numbers with interquartile range (IQR), and as categorical variables (0, 1, 2-7, 8-14, ≥14 days).

Annualised HRU was calculated as:

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

Annualised cost was calculated as:

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

HRU and associated costs were assessed annually, and annual averages for the follow-up period were calculated. Annualized HRU and healthcare costs were reported for each OCS

pattern. Healthcare costs of patients within each category of intermittent OCS prescription patterns (one-off, less frequent, and frequent) were compared against OCS non-users using a log-gamma generalized linear model, with incidence rate ratios (IRRs) and corresponding 95% confidence intervals (CIs) as summary statistics. Both unadjusted IRRs and IRRs adjusted for gender, age, smoking status, BMI, and GINA treatment step were estimated.

6.2.4 Objective 4

A patient's cumulative OCS dose was calculated at as the sum of all prednisolone-equivalent doses (g) prescribed from index date up until the outcome event. In case of time-varying exposure, this was assessed at the occurrence of each new prescription. In case of assessment at the end of follow-up, this was assessed at the moment of the onset of the condition of interest, or the end of follow-up. The unadjusted and adjusted (with adjustment for age, gender, smoking status, and BMI) incidence rates of each adverse outcome for each OCS use pattern category (>0-<0.5g, 0.5-<1.0g, 1.0-<2.5g, 2.5-<5g, 5-<10g, or =>10g) were compared using incidence rate ratio (IRR) with Wald-type 95% CI, with the OCS non-user group as reference. Each patient was followed until the first occurrence of the outcome of interest and was censored at death or the end of available records.

6.3 Missing data analysis

Missing data for BMI, smoking status and PEF % predicted was imputed using multiple imputation techniques. Missing dosing instructions for OCS and other medication groups were imputed using modal daily doses at patient-drug level and drug level, respectively.

The rules for missing value imputation were summarized in Table 5.

Table 5 Rules for missing value imputation

Missing value	Rule(s)
Date (days & months)	- Impute 15th of the month for missing days - Impute July 1st for missing days and months
Strength from generic active ingredient read codes	- 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)	- 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

6.4 Software

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

6.5 Ethical approval and registrations

The current study protocol was approved by Anonymized Data Ethics and Protocol Transparency Committee (ADEPT-1120), performed in compliance with Good Clinical Practice and Good Pharmacoepidemiology Practice and registered with the European Union Electronic Register of Post-Authorization studies (EUPAS37065) and the Independent Scientific Advisory Committee (ISAC_ 20_000071).

7 Results

7.1 Overall Patient Population/Study cohort

In total, 2,130,881 patients on OCS were identified from CPRD and OPCRD. After applying the exclusion criteria, 476,167 patients on intermittent OCS were included in the analysis (Table 6). Supplemental Figure 4 shows the distribution of OCS cases excluded due to prior adverse events. A control cohort of 476,167 patients was identified by 1:1 matching to the above patients. The median follow-up duration for the OCS cohort was 8.2 years (IQR 4.2-13.7 years), while that for the non-OCS cohort was 9.1 years (IQR 4.7-14.7 years).

Table 6 Number of patients excluded for each exclusion criteria

	Patients		
	Excluded	**%**	**Remaining**
All OCS Patients (CPRD and OPCRD)			2,130,881
Excluded due to chronic condition treated with OCS	325,202	15.3%	1,805,679
Excluded due to OCS Rx not within 90 days of an asthma event	475,341	26.3%	1,330,338
Excluded after Rx cleaning (doses, strengths, quanity) *	234,164	17.6%	1,096,174
Excluded patents <4 yo	88,776	8.1%	1,007,398
Excluded due to less than 12 month before or after initial OCS	171,255	17.0%	836,143
Exclude patens wit no asthma diagnosis ever	200,712	24.0%	635,431
Excluded due to maintenance OCS RX	64,425	10.1%	571,006
Excluded due to missing demographc data (gender, dob)	770	0.1%	570,236
Excluded due to matching CPRD and OPCRD patients	94,069	16.5%	476,167

7.2 Data availability for important study variables

Age, sex, and asthma medication prescription records were available for all included subjects. Maximum eosinophil level was available in 99,606 (20.9%) patients, RCP reading was available in 271,409 (57.0%) patients, and percentage of predicted PEF was available in 174,939 (36.7%) patients.

7.3 Demographic and Clinical Characteristics

The mean age at initial OCS showed a bimodal distribution (Supplemental Figure 2) with a mean of 38.1 years (range, 4-108 years); 55.7% were female. There were no significant differences in age and sex distributions between the OCS cohort and the control cohort (Table 8 and Table 9). Patients with more frequent OCS use were older. Also, both cohorts had more females than males; the difference widened with more frequent OCS use.

Table 7 All Patients (OPCRD and CPRD) demographic and clinical characteristics at baseline

	Non-OCS (never users) n=476,167†	Any OCS n=476,167 (100%)	One-off OCS n=198,422 (41.7%)	Less frequent OCS* n=127,419 (26.8%)	Frequent OCS# n=150,326 (31.6%)
Age, mean, years (SD)	38.1 (22.4)	38.1 (22.4)	35.6 (22.3)	36.9 (22.1)	42.4 (22.2)
Age category, n (%)					
4–<12 years	76,859 (16.1)	77.131 (16.2)	35,478 (17.9)	22,568 (17.7)	19,085 (12.7)
12–<18 years	36,329 (7.6)	36,262 (7.6)	19,336 (9.7)	9,518 (7.5)	7,408 (4.9)
18–<65 years	292,846 (61.5)	292,778 (61.5)	118,163 (59.6)	78,572 (61.7)	96,043 (63.9)
≥65 years	70,133 (14.7)	69,996 (14.7)	25,445 (12.8)	16,761 (13.2)	27,790 (18.5)
Female, %	55.7	55.7	51.8	56.3	60.2
Follow-up, median, years (IQR)	9.0 (4.7, 14.7)	8.3 (4.2, 13.7)	6.4 (3.1, 11.5)	9.8 (5.6, 14.9)	9.6 (5.1, 15.2)
Time in database pre-index, median, years (IQR)	16.8 (7.8, 30.4)	17.0 (7.5, 31.1)	15.1 (6.9, 28.3)	16.2 (7.2, 30.1)	20.6 (9.1, 34.9)
BMI					
Underweight, n (%)	23,904 (5.0)	35,998 (7.6)	15,159 (7.6)	10,257 (8.0)	10,553 (7.0)
Normal, n (%)	144,517 (30.4)	138,469 (29.1)	56,728 (28.6)	37,665 (29.6)	44,061 (29.3)
Overweight, n (%)	102,328 (21.5)	109,042 (22.9)	42,521 (21.4)	28,899 (22.7)	37,612 (25.0)
Obese, n (%)	66,473 (14.0)	100,995 (21.2)	36,410 (18.3)	26,529 (20.8)	38,048 (25.3)
Unknown, n (%)	138,946 (29.2)	91,710 (19.3)	47,601 (24.0)	24,057 (18.9)	20,038 (13.3)
Mean (SD)	25.8 (5.9)	26.6 (7.0)	26.2 (6.8)	26.5 (6.9)	27.2 (7.1)
Smoking status, n (%‡)					
Never	135,708 (28.5)	141,231 (29.7)	60,921 (30.7)	37,512 (29.4)	42,813 (28.5)
Current	117,089 (24.6)	131,851 (27.7)	53,508 (27.0)	34,951 (27.4)	43,384 (28.9)
Ex	67,711 (14.2)	84,377 (17.7)	33,951 (17.1)	21,075 (16.5)	29,375 (19.5)
Unknown	155,659 (32.7)	118,708 (24.9)	50,042 (25.2)	33,881 (26.6)	34,754 (23.1)
SABA prescriptions; n (%)					
0	470,929 (98.9)	113,262 (23.8)	44,766 (22.6)	30,987 (24.3)	37,507 (25.0)
1–2	3,524 (0.7)	213,594 (44.9)	96,751 (48.8)	55,660 (43.7)	61,183 (40.7)
3–11	1,476 (0.3)	133,255 (28.0)	51,519 (26.0)	36,602 (28.7)	45,134 (30.0)
≥12	238 (0.0)	16,056 (3.4)	5,384 (2.7)	4,170 (3.3)	6,502 (4.3)
ICS prescriptions; n (%)					
0	472,462 (99.2)	191,141 (40.1)	80,403 (40.5)	50,177 (39.4)	60,560 (40.3)
1–3	2,354 (0.5)	183,159 (38.5)	79,561 (40.1)	50,015 (39.2)	53,583 (35.6)
4–6	747 (0.2)	59,230 (12.4)	22,712 (11.4)	16,260 (12.8)	20,258 (13.5)
7–9	310 (0.1)	23,952 (5.0)	8,874 (4.5)	6,315 (4.9)	8,763 (5.8)
10–12	179 (0.0)	11,968 (2.5)	4,393 (2.2)	3,043 (2.4)	4,532 (3.0)
≥13	115 (0.0)	6,718 (1.4)	2,479 (1.2)	1,609 (1.3)	2,630 (1.7)

BMI, body mass index; **ICS**, inhaled corticosteroid; **OCS**, oral corticosteroid; **SABA**, short-acting β_2 agonist.
†Non-OCS patients were matched with all patients receiving OCS prescriptions according to 1:1 ratio; *Patients who received all OCS prescriptions with a gap of ≥90 days; #Patients who received at least some OCS prescriptions with a gap of <90 days, allowing for other prescription gaps to be ≥90 days; ‡Only the percentages of patient with known smoking status were calculated.

Table 8 CPRD Patients demographic and clinical characteristics at baseline

	OCS-naïve n=149,191†		Any OCS n=149,191 (100%)		One-off OCS n=74,999 (50.3%)		Less frequent OCS‡ n=40,890 (27.4%)		Frequent OCS§ n=33,302 (22.3%)	
Age, mean, years (SD)	38.7	(22.4)	38.7	(22.4)	35.9	(22.7)	38.6	(23.1)	45.2	(23.3)
Female, %	52.6		52.6		50.7		54.1	0	55.1	0
Follow-up, median years (IQR)	20.9	(13.5-29.8)	19.1	(11.6-28.0)	17.8	(10.4-26.2)	20.9	(13.4-29.6)	20.2	(12.3-29.8)
GINA step, n (%)										
0	143,524	96.2	24,111	16.16	9,482	12.65	7,894	19.31	6,737	20.21
1	4,997	3.35	35,761	23.97	19,612	26.15	8,877	21.71	7,276	21.85
2	208	0.14	41,504	27.82	21,682	28.91	11,469	28.05	8,348	25.07
3	462	0.31	35,015	23.47	18,164	24.22	9,269	22.67	7,579	22.76
4	0	0	11,562	7.75	5,557	7.41	3,083	7.54	2,920	8.77
5	0	0	1,238	0.83	502	0.67	298	0.73	442	1.33
BMI										
Underweight, n (%)	1,852	1.24	1,851	1.24	909	1.2	469	1.14	481	1.45
Normal, n (%)	32,359	21.69	29,554	19.81	14,902	19.87	7,993	19.55	6,657	19.99
Overweight, n (%)	25,108	16.83	28,212	18.91	13,589	18.12	7,613	18.62	7,006	21.04
Obese, n (%)	15,292	10.25	23,945	16.05	11,122	14.83	6,566	16.06	6,254	18.78
Unknown, n (%)	74,580	49.99	65,629	43.99	34,477	45.97	18,249	44.63	12,904	38.75
Mean (SD)	26.326	(5.4)	27.62	(6.2)	27.42	(6.1)	27.63	(6.2)	27.99	(6.4}
Smoking status, n (%Δ)										
Never	42,715	46.7	45,922	41.5	24,137	43.8	12,293	41.4	9,510	37.0
Current	31,867	34.9	41,102	37.2	19,439	35.3	11,465	38.6	10,193	39.6
Ex	16,858	18.4	23,527	21.3	11,549	21.0	5,961	20.1	6,007	23.4
Unknown	57,751	38.71	38,640	25.9	19,874	26.5	11,171	27.32	7,592	22.8
SABA fills; n (%)										
0	143,986	96.51	45,848	30.73	19,134	25.51	14,571	35.63	12,139	36.45
1–2	3,505	2.35	59,437	39.84	33,614	44.82	14,712	35.98	11,112	33.37
3–11	1,476	0.99	38,670	25.92	19,934	26.58	10,197	24.94	8,538	25.64
≥12	223	0.15	5,236	3.51	2,317	3.09	1,410	3.45	1,511	4.54
ICS fills; n (%)										
0	145,522	97.54	61,006	40.89	29,566	39.42	17,069	41.74	14,385	43.19
1–3	2,329	1.56	53,651	35.96	29,109	38.81	14,374	35.15	10,175	30.55
4–6	747	0.5	18,934	12.69	9,196	12.26	5,260	12.86	4,487	13.47
7–9	315	0.21	8,505	5.7	3,931	5.24	2,344	5.73	2,233	6.7
10–12	181	0.12	4,343	2.91	1,974	2.63	1,167	2.85	1,200	3.6
≥13	121	0.08	2,747	1.84	1,239	1.65	680	1.66	831	2.49

BMI, body mass index; **GINA**, Global Initiative for Asthma; **ICS**, inhaled corticosteroid; **IQR**, interquartile range; **SABA**, short-acting β_2-agonist; **SD**, standard deviation.

[a]The doses of systemic corticosteroids contributing to OCS exposure were converted to prednisolone equivalents using the DDD obtained from the ATC/DDD classification system;[13] [b] GINA treatment step is based on GINA 2020 guidelines; treatment step 0 refers to patients with no prescribed asthma medication, [c] Number of fills in the 12 months prior to the index date.

Table 8 Comparison of mean age by the frequency of OCS prescription

			OCS Sequence Categories		
	No OCS	OCS	One Off	Less Frequent	Frequent
Mean	38.12	38.08	35.55	36.89	42.44
Min	4	4	4	4	4
Max	108	108	108	106	105
n		476,167	198,420	127,419	150,326

Table 9 Comparison of OCS prescriptions by sex

			OCS Sequence Categories		
Gender	**No OCS**	**OCS**	**One Off**	**Less Frequent**	**Frequent**
Female	55.7%	55.7%	51.8%	56.3%	60.2%
Male	44.3%	44.3%	48.2%	43.7%	39.8%

Additionally, the distribution of body mass index categories, smoking status, and height among all patients were summarized in Supplemental Tables 1-3, respectively. These distributions were similar between the OCS and control cohorts.

Prior to receiving the initial dose of OCS, the majority of patients were receiving GINA step 1 or 2 treatments (119,687 (25.1%) and 152,156 (32.0%), respectively; Table 10), while 65,625 (13.8%) had no prior asthma medications. These contrasted the 50,944 (10.7%) patients who were on GINA step 4 or 5 treatment. This reflected that the patients in the OCS cohort mostly had mild to moderate asthma. Meanwhile, the vast majority of patients in the control cohort had no prior asthma medication (464,859 (95%)), and none had step 4 or 5 medications.

Table 10 Respiratory regimen by GINA steps prior to the initial dose of OCS

					OCS Sequence Categories													
GINA Classification	**No OCS**		**OCS**		**One Off**	**↓%**	**→%**	**[95% CI]**		**Less Frec**	**↓%**	**→%**	**[95% CI]**		**Frequent**	**↓%**	**→%**	**[95% CI]**	
No Athma Medication	464,857	98%	65,624	13.8%	25,034	12.6%	38%	12.5%	12.8%	17,704	13.9%	27%	13.7%	14.1%	22,886	15.2%	35%	15.0%	15.4%
Step 1 (ICS PRN/SABA alone)	9,979	2%	119,687	25.1%	53,602	27.0%	45%	0.268	0.272	30,971	24.3%	26%	24.1%	24.5%	35,114	23.4%	29%	23.1%	23.6%
Step 2 (Daily Low Dose ICS)	403	0%	152,156	32.0%	64,768	32.6%	43%	32.4%	32.8%	42,330	33.2%	28%	33.0%	33.5%	45,058	30.0%	30%	29.7%	30.2%
Step 3 (Low ICS/LABA or Med ICS)	926	0%	87,754	18.4%	36,481	18.4%	42%	18.2%	18.6%	23,417	18.4%	27%	18.2%	18.6%	27,856	18.5%	32%	18.3%	18.7%
Step 4 (Med ICS/LABA or High ICS)	0	0%	41,519	8.7%	15,669	7.9%	38%	7.8%	8.0%	10,767	8.5%	26%	8.3%	8.6%	15,083	10.0%	36%	9.9%	10.2%
Step 5 (High ICS/LABA +)	0	0%	9,425	2.0%	2,866	1.4%	30%	1.4%	1.5%	2,230	1.8%	24%	1.7%	1.8%	4,329	2.9%	46%	2.8%	3.0%
Total	476,165		476,165		198,420					127,419					150,326				

The types of asthma medication taken by patients in the OCS cohort were explored in more detail. In total, 213,594 (44.9%) patients had received 1-2 SABA prescriptions prior to the initial dose of OCS, with 113,262 (23.8%) never having received any prior SABA prescription.

(Table 11). Similarly, most patients (242,388 (50.9%)) have received only 1-6 ICS prescriptions prior to the initial dose of OCS, and 191,141 (40.1%) have never received any prior ICS prescriptions (Table 12).

Table 11 Number of SABA prescriptions prior to initial dose of OCS

			OCS Sequence Categories								
SABA Categories	**OCS**		**One Off**	**↓ %**	**→%**	**Less Frequent**	**↓ %**	**→%**	**Frequent**	**↓ %**	**→%**
No SABA	113,262	23.8%	44,768	22.6%	40%	30,987	24.3%	27%	37,507	25.0%	33%
1 - < 3	213,594	44.9%	96,751	48.8%	45%	55,660	43.7%	26%	61,183	40.7%	29%
3 - < 12	133,255	28.0%	51,519	26.0%	39%	36,602	28.7%	27%	45,134	30.0%	34%
12 - < 90	16,056	3.4%	5,384	2.7%	34%	4,170	3.3%	26%	6,502	4.3%	40%
Total	476,167		198,422			127,419			150,326		

Table 12 Number of ICS prescriptions prior to initial dose of OCS

			OCS Sequence Categories								
ICS Categories	**OCS**		**One Off**	**↓ %**	**→%**	**Less Frequent**	**↓ %**	**→%**	**Frequent**	**↓ %**	**→%**
0	191,141	40.1%	80,403	40.5%	42%	50,177	39.4%	26%	60,560	40.3%	32%
1 - < 7	242,388	50.9%	102,271	51.5%	42%	66,275	52.0%	27%	73,841	49.1%	30%
7 - < 13	35,920	7.5%	13,267	6.7%	37%	9,358	7.3%	26%	13,295	8.8%	37%
13 - < 25	6,553	1.4%	2,463	1.2%	38%	1,572	1.2%	24%	2,545	1.7%	39%
25 - < 105	165	0.0%	43	0.0%	26%	37	0.0%	22%	85	0.1%	52%
	476,167		198,447			127,419			150,326		

The maximum eosinophil levels, RCP readings, and percentage predicted PEF of patients in the OCS cohort are summarized in Supplemental Tables 4, 5 and 6, respectively. An estimated 66.0% of patients taking intermittent OCS had poor asthmatic control by RCP reading, while most patients had 50-80% (40.0%) or 80-100% (52.3%) predicted PEF prior to initial dose of OCS.

7.4 Objective-specific outcomes

7.4.1 Objective 1

7.4.1.1 General observations in the overall population

Although the most common OCS use pattern category throughout the study period was an one off prescription, observed in 198,422 (41.7%) patients, 150,326 (31.6%) patients were observed to have frequent OCS prescriptions. The remaining patients (127,419 (26.8%)) had less frequent (≥90-day gaps) OCS prescriptions.

Some important observations between baseline patient characteristics and OCS use pattern categories were made:

- Patients with more frequent bursts of OCS were older (Table 8), and a higher proportion of patients having more frequent OCS use patterns were females (Table 9).
- More of the patients who had more frequent OCS use patterns were obese (Supplemental Table 1), while more of those who received more frequent OCS prescriptions never smoked (Supplemental Table 2).
- Those who had more frequent OCS use patterns had poorer asthmatic control by RCP readings (Supplemental Table 5).
- Maximum eosinophil reading did not differ between OCS use pattern categories (Supplemental Table 4).
- Prior asthma treatment did not differ between OCS use pattern categories, including the respiratory regimen by GINA steps (Table 10), and the numbers of SABA (Table 11) and ICS (Table 12) prescriptions.

Despite the lack of differences in prior asthma treatment between OCS use pattern categories, more frequent OCS prescriptions were strongly associated with higher median per-prescription OCS dose (150mg for patients in the “one off” category, 420 mg for those in the “less frequent” category, and 940 mg for those in the “frequent” category).

7.4.1.2 Stratification by SABA use categories

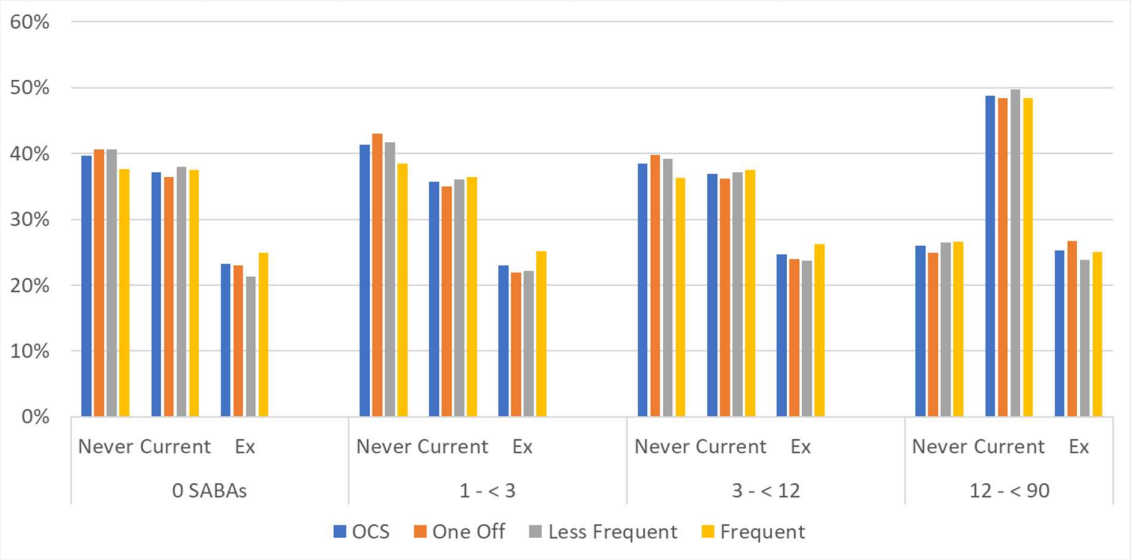
There were no differences in age, sex, and body mass index distributions between SABA use categories (Supplemental Tables 7, 8 and 9, respectively). The follow-up time after the first OCS prescription (Table 13) was the longest in those who had never had any prior SABA prescription (median 9.1 years, IQR 2.3-15.1 years), and shortest in those in the most frequent prior SABA use category (median 7.5 years, IQR 3.8-13.4 years). This trend was consistent across OCS use pattern categories, although the differences diminished with more frequent OCS use.

Table 13 Follow-up time after the first OCS prescription

			OCS Sequence Categories					
SABA Categories	OCS	IQRs	One Off	IQRs	Less Frequent	IQRs	Frequent	IQRs
0 SABAs	9.1	(2.3 - 15.1)	7.2	(3.4 - 13.1)	10.8	(6.1 - 16.4)	10.0	(5.2 - 16.0)
1 - < 3	8.1	(4.3 - 13.3)	6.4	(3.2 - 11.3)	9.6	(5.7 - 14.6)	9.4	(5.1 - 14.8)
3 - < 12	7.9	(4.0 - 13.3)	5.8	(2.8 - 10.6)	9.3	(5.3 - 14.4)	9.5	(5.0 - 14.9)
12 - < 90	7.5	(3.8 - 13.4)	5.1	(2.5 - 9.7)	8.6	(4.9 - 14.1)	9.2	(4.6 - 15.7)

While there were no differences in the smoking status of patients who have had 0-11 prior SABA prescriptions, there were significantly more current smokers among those who have had at least 12 prior SABA prescriptions (Figure 4; Supplemental Table 10). These trends were consistent across OCS use pattern categories, with the differences again diminishing in more frequent OCS users.

Figure 4 Smoking status of patients stratified by SABA use categories



Furthermore, patients with higher SABA use categories had higher GINA treatment steps (

Figure 5; Supplemental Table 11) and more prior ICS prescriptions (Figure 6; Supplemental Table 12). These trends were also consistent across OCS use pattern categories.

Figure 5 Prior GINA treatment steps of patients stratified by SABA use categories

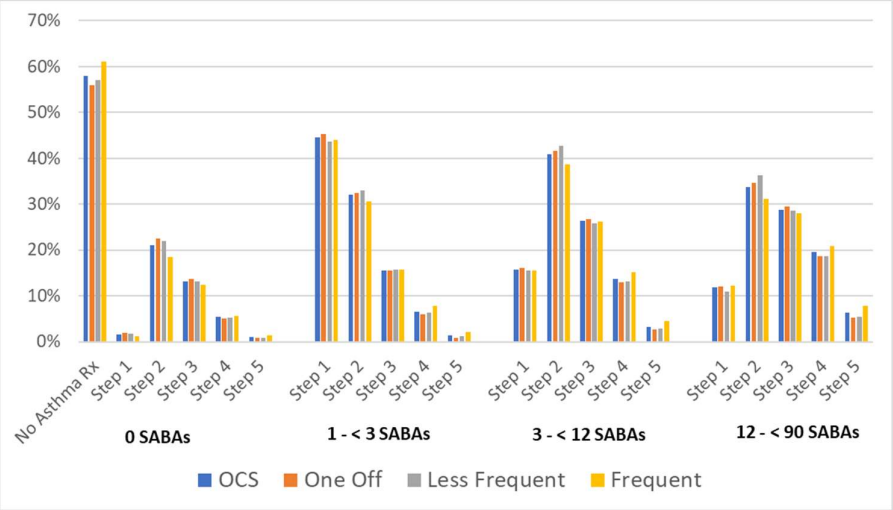
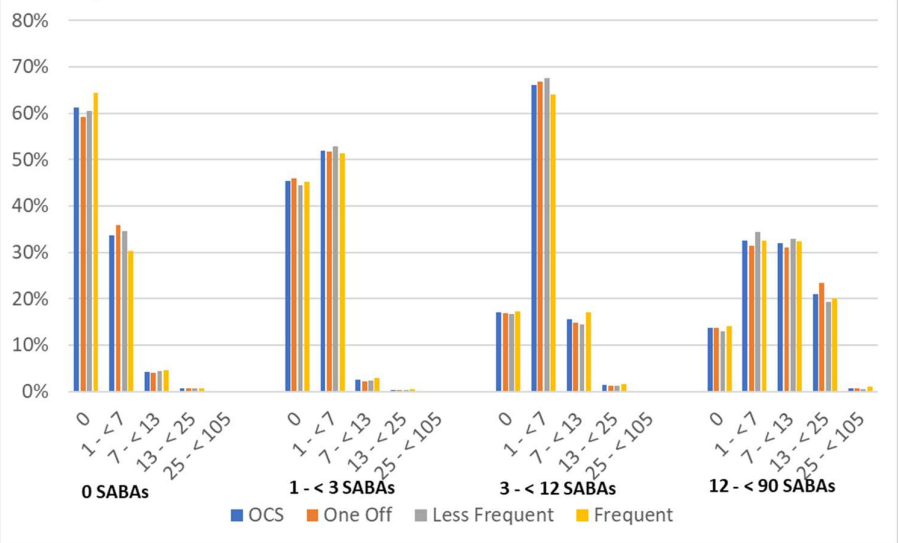


Figure 6 Prior ICS prescriptions of patients stratified by SABA use categories (number of inhalers)



7.4.1.3 Stratification by ICS use categories

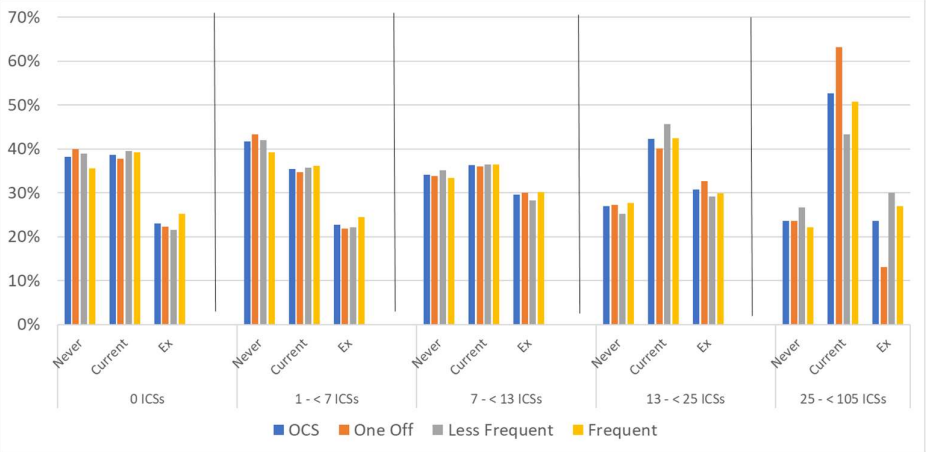
There were no differences in sex distributions between ICS use categories (Supplemental Table 13). Patients who had 13-24 prior ICS prescriptions were the oldest with a median age of 57 years (IQR 39-70), while those with 1-6 prescriptions were the youngest with median age 35 years (IQR 17-52); this is shown in Table 14. The distribution of body mass index categories was not substantially different across ICS use categories, which was consistent across OCS use pattern categories (Supplemental Table 14).

Table 14 Age of patients stratified by ICS use categories (median and interquartile ranges)

Median Age (IQRs) at initial OCS Prescription								
	OCS Sequence Categories							
# of ICSs	OCS		One Off		Less Frequent		Frequent	
0	37	(18-55)	33	(15-50)	36	(17-53)	44	(27-60)
1 - < 7	35	(17-52)	32	(15-49)	35	(16-51)	41	(24-57)
7 - < 13	51	(33-67)	51	(31-68)	49	(30-66)	53	(36-68)
13 - < 25	57	(39-70)	57	(39-72)	55	(38-69)	57	(41-70)
25 - < 105	44	(29-63)	43	(31-62)	52	(32-66)	44	(28-62)

While fewest of those who had no or 1-6 prior ICS prescriptions were ex-smokers, the highest proportion of those who had at least 13 prior ICS prescriptions were current smokers, with the difference between smoker groups being more prominent in those with the highest number of prior ICS prescriptions (Figure 7; Supplemental Table 15).

Figure 7 Smoking statuses of patients stratified by ICS use categories



Importantly, we observed no clear relationship between ICS use categories and OCS use pattern categories (Table 15 and Figure 8). Those with more prior ICS prescriptions were more likely to have reached higher GINA treatment steps (Figure 9; Supplemental Table 16) with more prior SABA prescriptions (Figure 10; Supplemental Table 17).

Table 15 OCS use pattern of patients stratified by ICS use categories

			OCS Sequence Categories								
# of ICSs	OCS		One Off			Less Frequent			Frequent		
	n	%	n	↓ %	→%	n	↓ %	→%	n	↓ %	→%
0	191,140	40.1%	80,403	40.5%	42%	50,177	39.4%	26%	60,560	40.3%	32%
1 - < 7	242,387	50.9%	102,271	51.5%	42%	66,275	52.0%	27%	73,841	49.1%	30%
7 - < 13	35,920	7.5%	13,267	6.7%	37%	9,358	7.3%	26%	13,295	8.8%	37%
13 - < 25	6,553	1.4%	2,436	1.2%	37%	1,572	1.2%	24%	2,545	1.7%	39%
25 - < 105	165	0.0%	43	0.0%	26%	37	0.0%	22%	85	0.1%	52%
Total	476,165		198,420			127,419			150,326		

Figure 8 OCS use pattern of patients stratified by ICS use categories

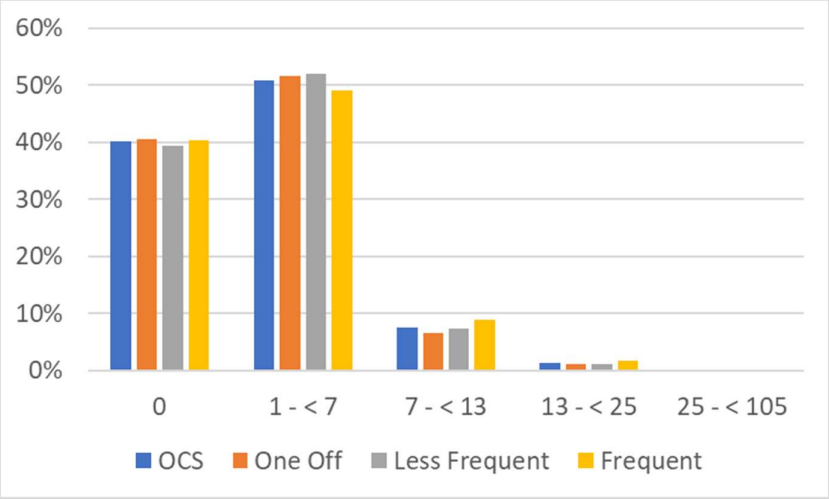


Figure 9 Prior GINA treatment steps of patients stratified by ICS use categories

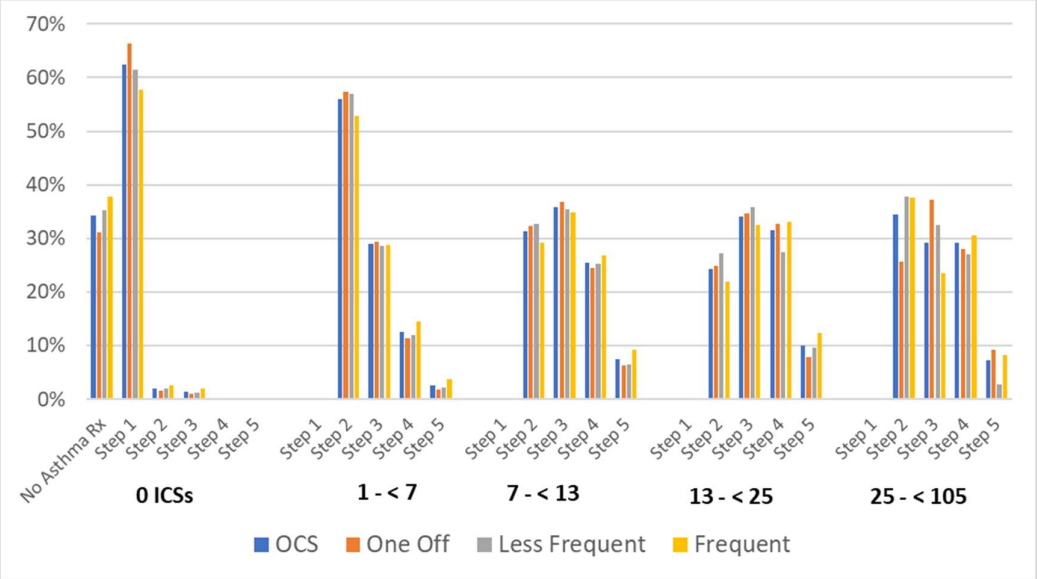
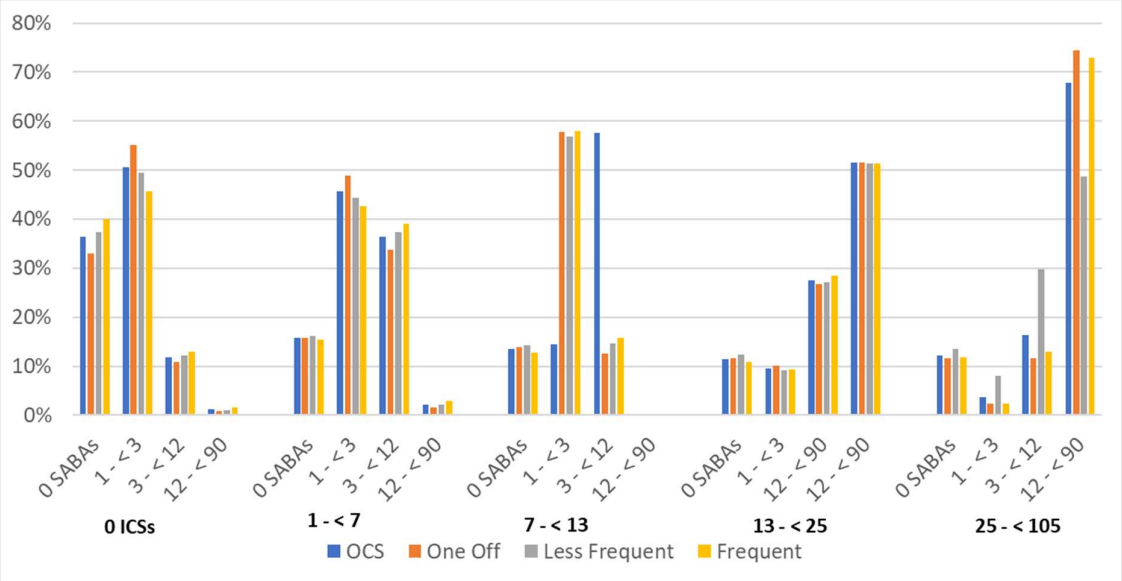


Figure 10 Prior SABA use categories of patients stratified by ICS use categories



7.4.1.4 Stratification by age categories

Distribution of age categories did not differ between OCS use pattern categories (Table 16).

Table 16 OCS use pattern categories of patients stratified by age categories.

			OCS Sequence Categories								
Age Categories	**OCS**		**One Off**	**↓ %**	**→%**	**Less Frequent**	**↓ %**	**→%**	**Frequent**	**↓ %**	**→%**
3 - <12	77,131	16.2%	35,478	17.9%	46.0%	22,568	17.7%	29.3%	19,085	12.7%	24.7%
12 - <18	36,262	7.6%	19,336	9.7%	53.3%	9,518	7.5%	26.2%	7,408	4.9%	20.4%
18 - <65	292,778	61.5%	118,163	59.6%	40.4%	78,572	61.7%	26.8%	96,043	63.9%	32.8%
65 - <110	69,996	14.7%	25,445	12.8%	36.4%	16,761	13.2%	23.9%	27,790	18.5%	39.7%
Total	**476,167**		**198,422**			**127,419**			**150,326**		

More of the older patients were females, regardless of OCS sequence categories (Supplementary Table 18). Fewer of the older patients were underweight (1.7% of those aged at least 65 years old vs 57.8% of those aged 3-12 years old) and more were obese (30.0% of those aged at least 65 years old vs 3.1% of those aged 3-12 years old; Figure 11), which was consistent across OCS use pattern categories (Supplemental Table 19). Less of those aged <18 years have ever smoked, and more of those aged at least 65 years were ex-smokers (Figure 12; Supplemental Table 20).

Figure 11 Body mass index categories of patients stratified by age categories

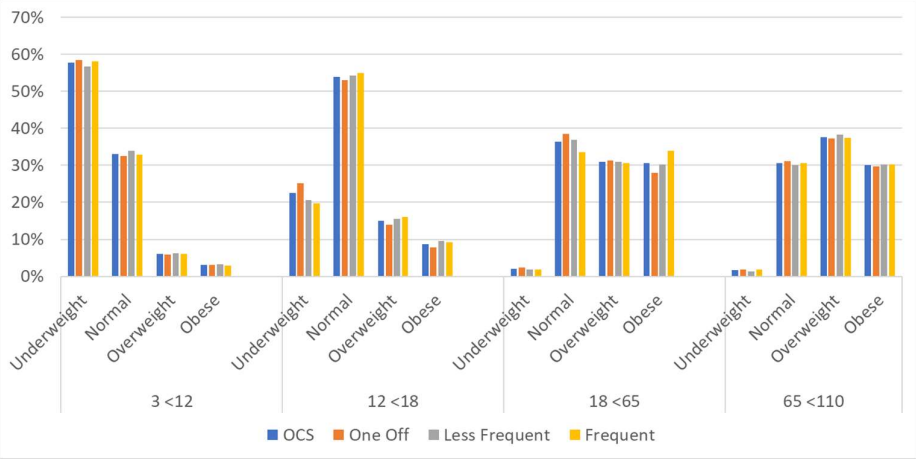
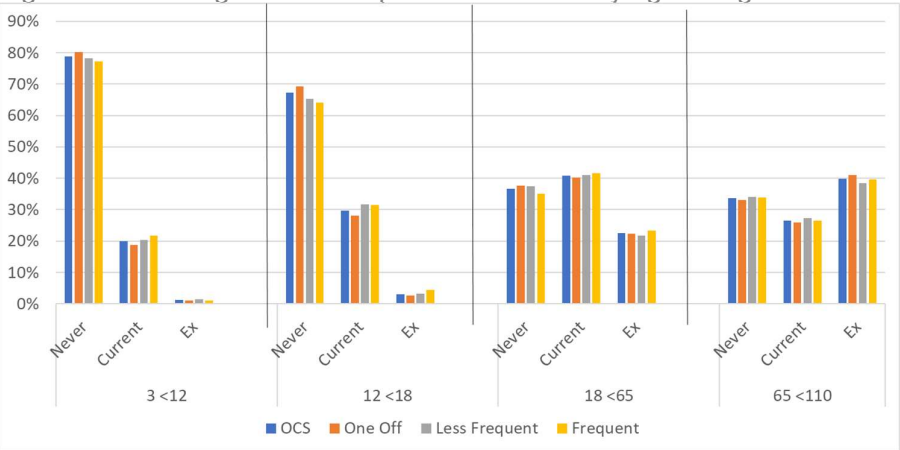


Figure 12 Smoking statuses of patients stratified by age categories



GINA step 2 (Figure 13; Supplemental Table 21), 1-6 prior ICS prescriptions (Figure 14; Supplemental Table 22), and 1-2 prior SABA prescriptions (Figure 15; Supplemental Table 23) were the most common prior treatments across all age groups, with the differences in prior treatments diminishing with aging.

Figure 13 Prior GINA treatment step of patients stratified by age categories

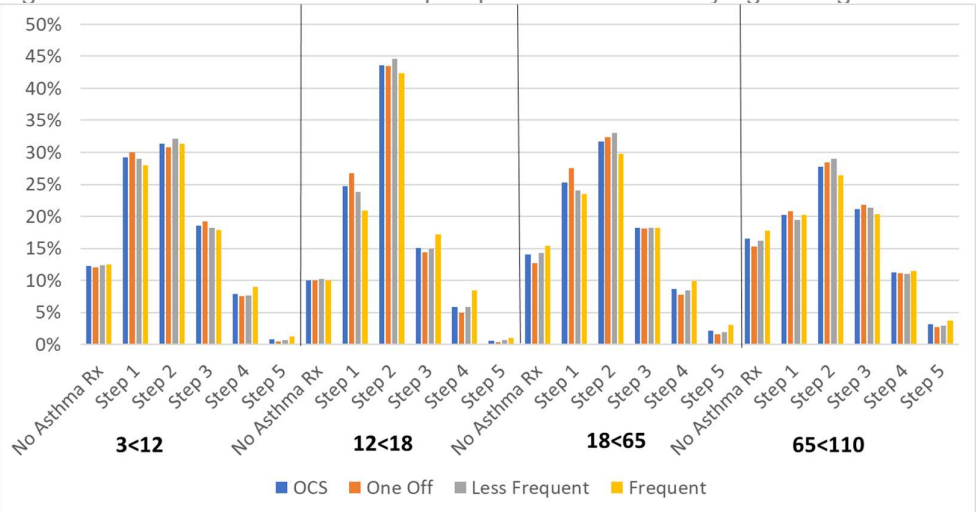


Figure 14 Prior ICS use categories of patients stratified by age categories

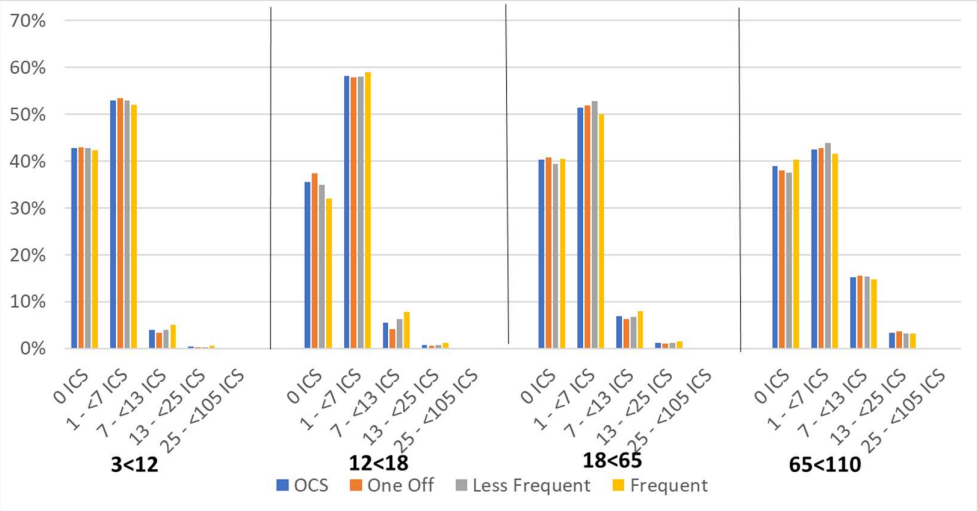
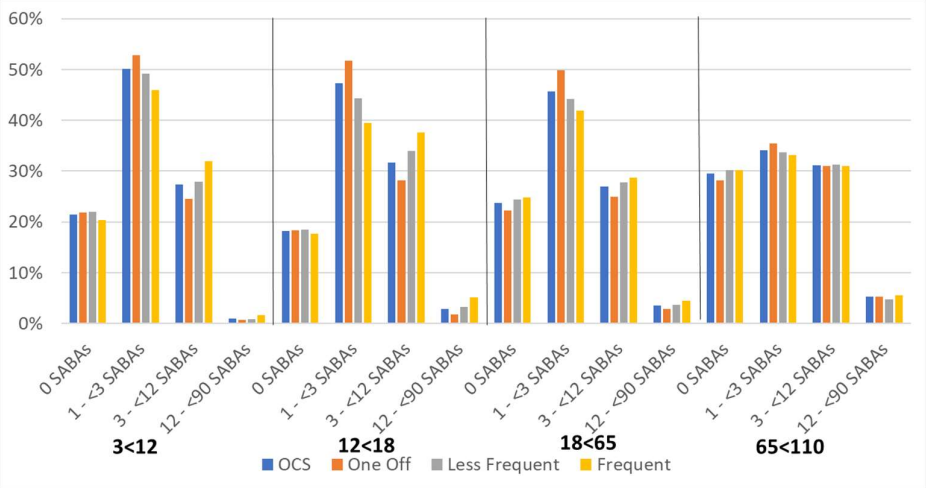


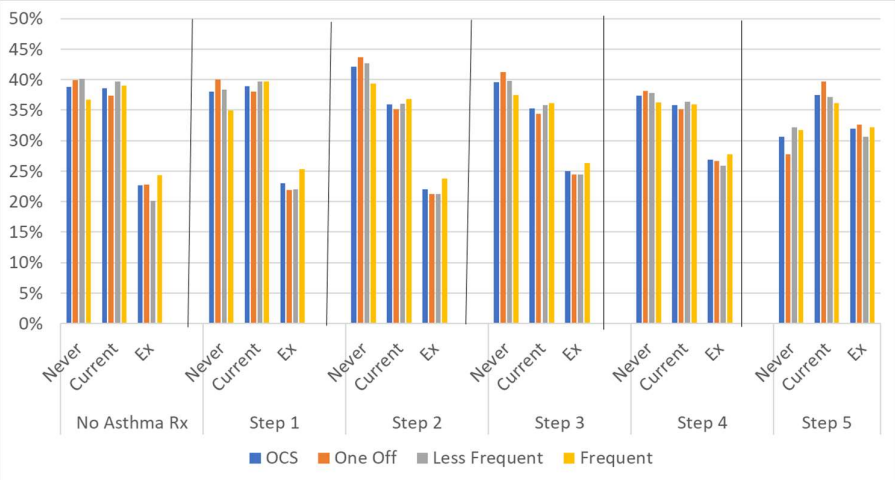
Figure 15 Prior SABA use categories of patients stratified by age categories



7.4.1.5 Stratification by GINA treatment steps

The distribution of age groups (Supplemental Table 24) and sexes (Supplemental Table 25) were similar between patients on different GINA treatment groups, regardless of OCS sequence categories. We observed no differences body mass index categories between GINA treatment steps (Supplemental Table 26). Meanwhile, the proportion of never-smokers declined and the proportion of ex-smokers increased going up the GINA treatment steps (Figure 16). This was consistent across all OCS use pattern categories, although the differences diminished in more frequent OCS users (Supplemental Table 27).

Figure 16 Smoking statuses of patients stratified by prior GINA treatment steps



As expected, SABA and ICS use increased going up the GINA treatment steps (Figure 17 and Figure 18, Supplemental Tables 28 and 29).

Figure 17 Prior SABA use category of patients stratified by prior GINA treatment steps

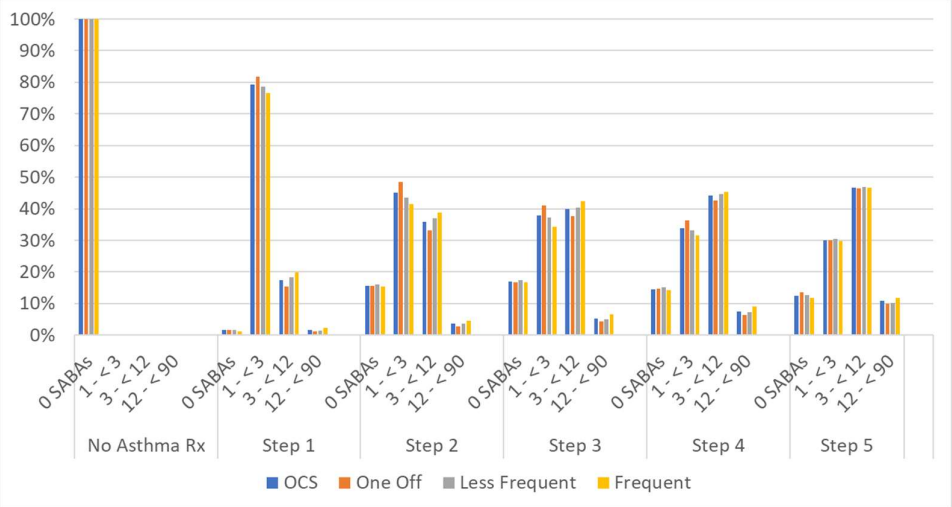
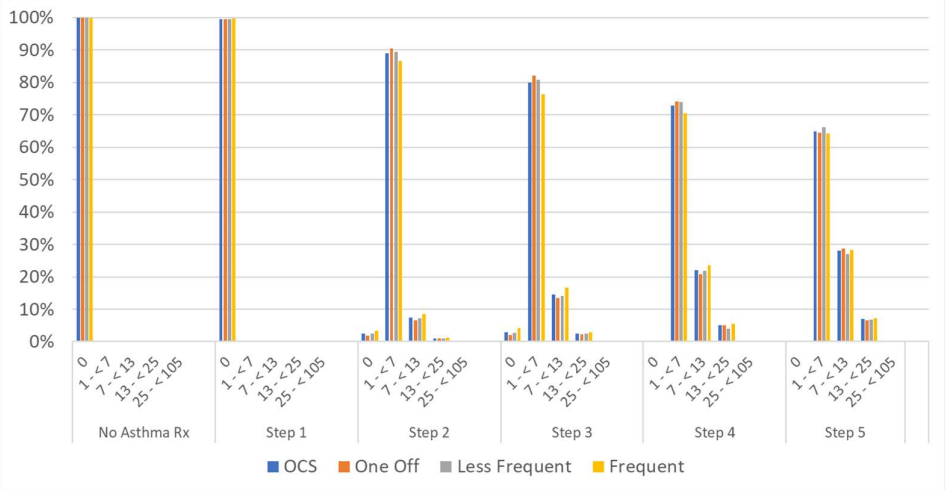


Figure 18 Prior ICS use category of patients stratified by prior GINA treatment steps



7.4.2 Objective 2

Patients in the OCS cohort had a follow-up of a median of 8.2 years (IQR 4.2-13.7 years), which was not significantly different from the follow-up duration of the control cohort (median 9.05 years, IQR 4.72-14.66 years).

7.4.2.1 Overall results in the unstratified cohort

All time-fixed analyses herein described were adjusted for age, gender, BMI, and smoking, while all time-varying analyses were further adjusted for cumulative OCS dose. Compared to OCS-naïve patients, all OCS use categories were associated with higher risks of adverse

events in both time-fixed and time-varying analyses, with frequent OCS users having the highest risk (HR 1.42 [1.41, 1.43] on time-varying analysis; Table 17 and Figure 19).

Table 17 Results of multivariable Cox regression comparing the occurrence of any adverse events between OCS use categories

Any Adverse Event						
n = 231196	**Time Fixed Analysis**			**Time Variable Analysis**		
	HR	**95% CI**		**HR**	**95% CI**	
OCS Naïve	1			1		
One Off OCS	1.2	1.19	1.21	1.19	1.18	1.2
Less frequent OCS	1.38	1.36	1.38	1.35	1.34	1.36
Frequent OCS	1.44	1.43	1.45	1.42	1.48	1.43

Figure 19 Kaplan-Meier curve showing the cumulative freedom from any adverse event, stratified by OCS use categories

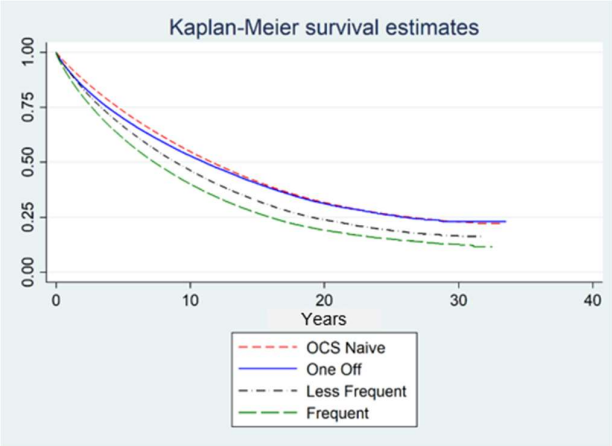
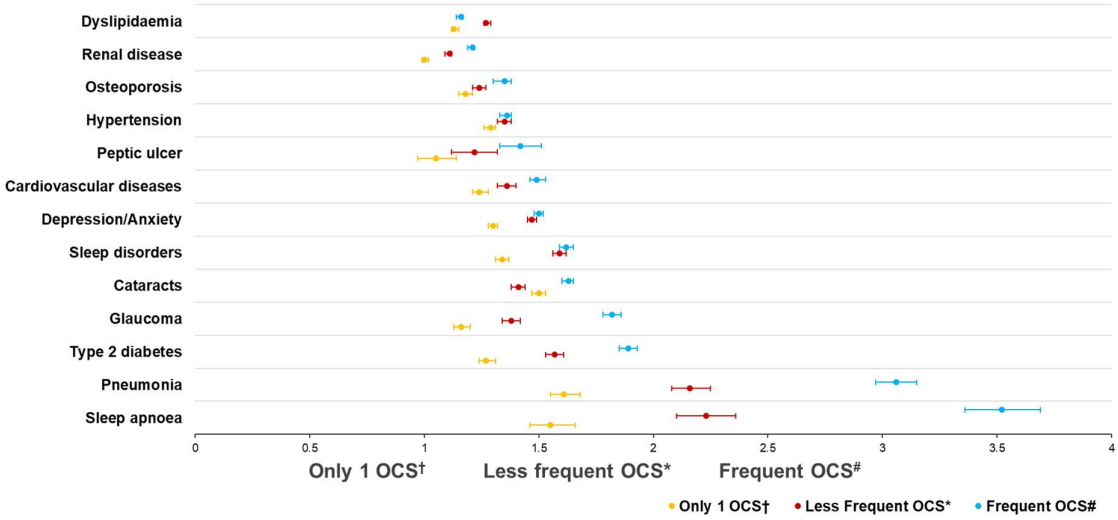


Figure 20 summarizes the hazard ratios of specific adverse effects comparing different OCS use categories against OCS-naïve patients. Except for behavioural issues, the risk of all outcomes were higher in the OCS cohort. Except dyslipidaemia and cataracts, all outcomes showed clear trends for significantly higher risks in more frequent use categories.

Figure 20 Forrest plot summarizing the hazard ratios for individual adverse events, stratifying by OCS use categories and comparing against OCS-naïve patients. All hazard ratios were calculated using Cox regression analysis, adjusted for age, gender, body-mass index, smoking and time varying OCS prescriptions



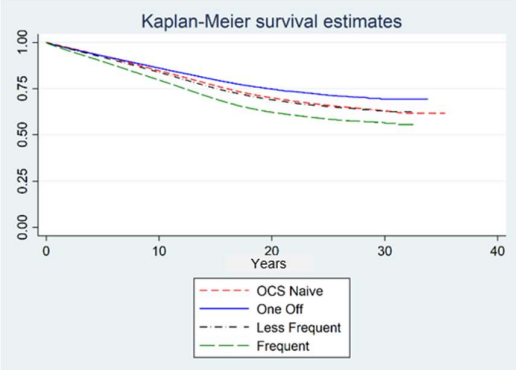
7.4.2.2 Specific outcomes in the unstratified cohort

Those in the frequent OCS category had the highest risk of renal disease for both time-fixed and time-varying analysis (HR 1.21 [1.19, 1.22]; Table 18 and Figure 21), which was higher than that of those in the less frequent category. Nonetheless, the risk was not observed to be significantly different in the one-off category.

Table 18 Results of multivariable Cox regression comparing the occurrence of renal disease between OCS use categories

Renal diagnosis						
n = 437297	**Time Fixed Analysis**			**Time Variable Analysis**		
	HR	**95% CI**		**HR**	**95% CI**	
OCS Naïve	1			1		
One Off OCS	1.05	0.99	1.02	1	0.99	1.02
Less frequent OCS	1.11	1.09	1.12	1.11	1.09	1.12
Frequent OCS	1.21	1.19	1.22	1.21	1.19	1.22

Figure 21 Kaplan-Meier curve showing the cumulative freedom from renal disease, stratified by OCS use categories

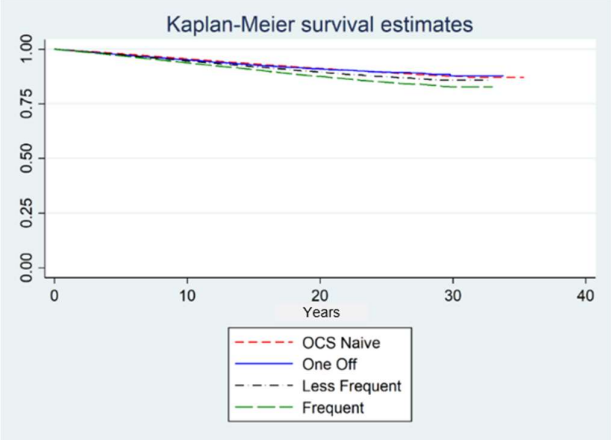


Results were similar for osteoporosis, with the frequent OCS users having the higher risk than both OCS-naïve patients (HR 1.35 [1.32, 1.38] on time-varying analysis; Table 19 and Figure 22) and less frequent or one off OCS users. Notably, even one off OCS users had significantly higher risks of osteoporosis (HR 1.18 [1.15, 1.21] on time-varying analysis).

Table 19 Results of multivariable Cox regression comparing the occurrence of osteoporosis between OCS use categories

Osteoporosis						
n = 447598	**Time Fixed Analysis**			**Time Variable Analysis**		
	HR	**95% CI**		**HR**	**95% CI**	
OCS Naïve	1			1		
One Off OCS	1.18	1.15	1.21	1.18	1.15	1.21
Less frequent OCS	1.25	1.21	1.28	1.24	1.21	1.27
Frequent OCS	1.36	1.33	1.39	1.35	1.38	1.38

Figure 22 Kaplan-Meier curve showing the cumulative freedom from osteoporosis, stratified by OCS use categories



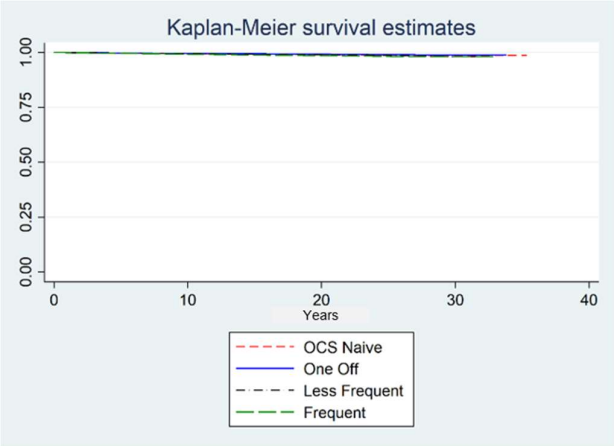
Similarly, patients with frequent OCS use had higher risks of peptic ulcer compared to both OCS-naïve patients (HR 1.42 [1.33, 1.51] on time-varying analysis; Table 20, Figure 23) and less frequent or one off OCS users. Nonetheless, one off OCS users did not show

significantly different risk of peptic ulcer compared to OCS-naïve patients (HR 1.05 [0.97, 1.14] on time-varying analysis).

Table 20 Results of multivariable Cox regression comparing the occurrence of peptic ulcer between OCS use categories

Peptic Ulcer n = 469345	**Time Fixed Analysis**			**Time Variable Analysis**		
	HR	**95% CI**		**HR**	**95% CI**	
OCS Naïve	1			1		
One Off OCS	1.05	0.96	1.14	1.05	0.97	1.14
Less frequent OCS	1.22	1.13	1.33	1.22	1.12	1.32
Frequent OCS	1.41	1.32	1.51	1.42	1.33	1.51

Figure 23 Kaplan-Meier curve showing the cumulative freedom from peptic ulcer, stratified by OCS use categories

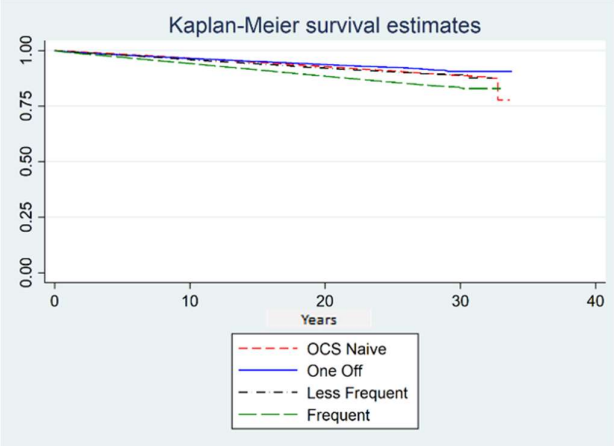


In terms of cardiovascular disease, the risks increased significantly with more frequent OCS use categories compared to the non-OCS group. While frequent OCS use expectedly increased the risk of cardiovascular disease (HR 1.49 [1.46, 1.53] on time-varying analysis; Table 21 and Figure 24), even one off OCS use increased such risk significantly (HR 1.54 [1.21, 1.28] on time-varying analysis).

Table 21 Results of multivariable Cox regression comparing the occurrence of cardiovascular disease between OCS use categories

Cardiovascular n = 460277	**Time Fixed Analysis**			**Time Variable Analysis**		
	HR	**95% CI**		**HR**	**95% CI**	
OCS Naïve	1			1		
One Off OCS	1.25	1.21	1.28	1.24	1.21	1.28
Less frequent OCS	1.37	1.33	1.41	1.36	1.32	1.4
Frequent OCS	1.5	1.47	1.54	1.49	1.46	1.53

Figure 24 Kaplan-Meier curve showing the cumulative freedom from cardiovascular disease, stratified by OCS use categories



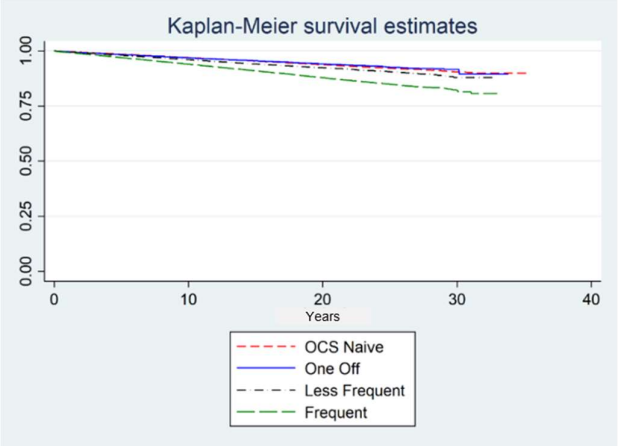
Similarly, the risks of glaucoma increased significantly with more frequent OCS use categories compared to the non-OCS group. One off OCS use increased the risk of glaucoma (HR 1.16 [1.13, 1.20] on time-varying analysis; Table 22 and Figure 25), and less frequent (HR 1.38 [1.34, 1.42] on time-varying analysis) and frequent (HR 1.82 [1.78, 1.86] on time-varying analysis) OCS use further increased such risk.

Table 22 Results of multivariable Cox regression comparing the occurrence of glaucoma between OCS use categories

Glaucoma						
n = 460600	**Time Fixed Analysis**			**Time Variable Analysis**		
	HR	**95% CI**		**HR**	**95% CI**	
OCS Naïve	1			1		
One Off OCS	1.16	1.12	1.19	1.16	1.13	1.2
Less frequent OCS	1.38	1.34	1.42	1.38	1.34	1.42
Frequent OCS	1.82	1.78	1.87	1.82	1.78	1.86

Figure 25 Kaplan-Meier curve showing the cumulative freedom from glaucoma, stratified by OCS use categories

Years

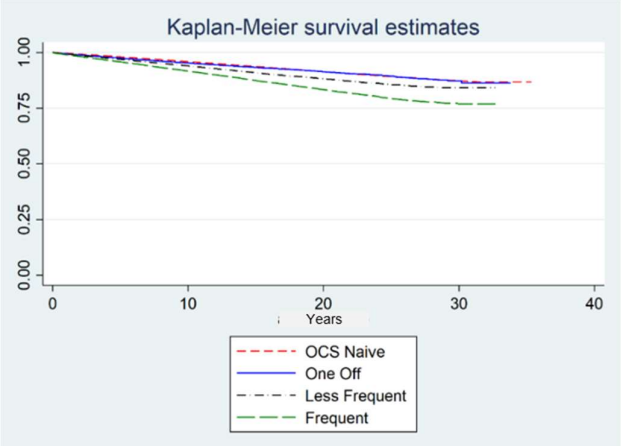


Results were similar for type 2 diabetes mellitus, the risks of which was higher in frequent OCS users than the non-OCS group (HR 1.89 [1.85, 1.93] on time-varying analysis; Table 23 and Figure 26). One off OCS users also had significantly elevated risks, albeit to lesser extents (HR 1.27 [1.24, 1.31] on time-varying analysis).

Table 23 Results of multivariable Cox regression comparing the occurrence of type 2 diabetes mellitus between OCS use categories

Type 2 Diabetes						
n = 455035	**Time Fixed Analysis**			**Time Variable Analysis**		
	HR	**95% CI**		**HR**	**95% CI**	
OCS Naïve	1			1		
One Off OCS	1.28	1.25	1.31	1.27	1.24	1.31
Less frequent OCS	1.57	1.54	1.61	1.57	1.53	1.61
Frequent OCS	1.9	1.86	1.94	1.89	1.85	1.93

Figure 26 Kaplan-Meier curve showing the cumulative freedom from type 2 diabetes mellitus, stratified by OCS use categories

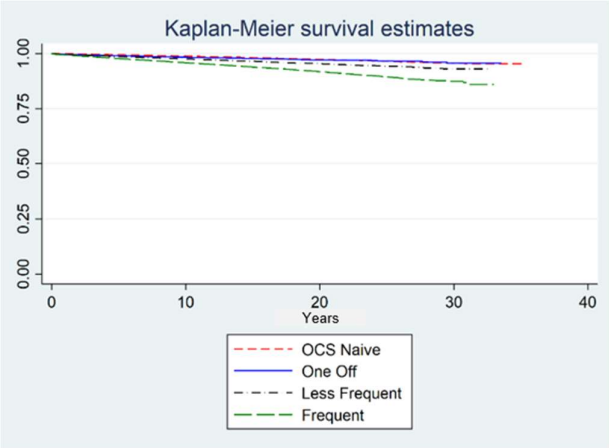


The risks of pneumonia similarly increased with each OCS use category compared to the non-OCS group, with a HR of 1.61 [1.55, 1.68] on time-varying analysis for one off OCS users, and 3.06 [2.97, 3.15] for frequent users (Table 24 and Figure 27).

Table 24 Results of multivariable Cox regression comparing the occurrence of pneumonia between OCS use categories

Pneumonia						
n = 476167	**Time Fixed Analysis**			**Time Variable Analysis**		
	HR	**95% CI**		**HR**	**95% CI**	
OCS Naïve	1			1		
One Off OCS	4.74	4.51	4.95	1.61	1.55	1.68
Less frequent OCS	6.33	6.06	6.62	2.16	2.08	2.25
Frequent OCS	9.11	8.77	9.45	3.06	2.97	3.15

Figure 27 Kaplan-Meier curve showing the cumulative freedom from pneumonia, stratified by OCS use categories

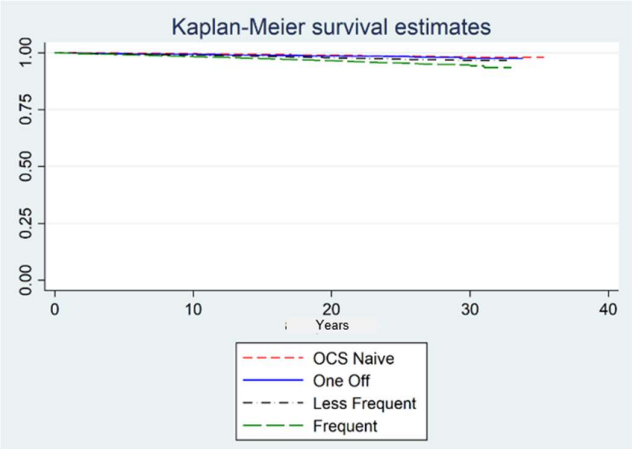


The most drastic increase in risks was observed for sleep apnoea. One time OCS users showed a HR of 1.55 [1.46, 1.66] on time-varying analysis compared to the non-OCS group, which leaped to 2.23 [2.10, 2.36] for less frequent OCS users, and to 3.52 [3.36, 3.69] in frequent users (Table 25 and Figure 28).

Table 25 Results of multivariable Cox regression comparing the occurrence of sleep apnoea between OCS use categories

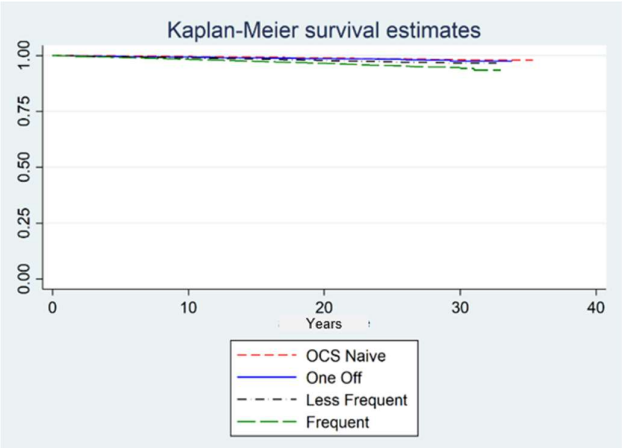
Sleep Apnoea						
n = 473910	**Time Fixed Analysis**			**Time Variable Analysis**		
	HR	**95% CI**		**HR**	**95% CI**	
OCS Naïve	1			1		
One Off OCS	1.55	1.46	1.65	1.55	1.46	1.66
Less frequent OCS	2.23	2.1	2.36	2.23	2.1	2.36
Frequent OCS	3.53	3.37	3.69	3.52	3.36	3.69

Figure 28 Kaplan-Meier curve showing the cumulative freedom from sleep apnoea, stratified by OCS use categories



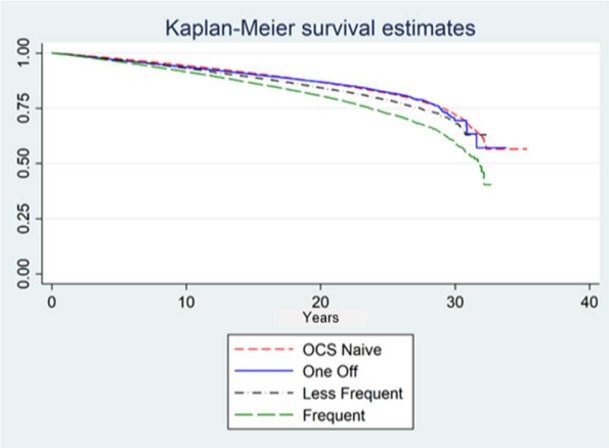
The risk of hypertension was elevated in one off OCS users compared to the non-OCS group (HR 1.29 [1.26, 1.31] on time-varying analysis; Table 26 and Figure 29). Both less frequent (HR 1.35 [1.32, 1.38] on time-varying analysis) and frequent (HR 1.36 [1.33, 1.38] on time-varying analysis) OCS users had higher risks of hypertension than one off OCS users.

Table 26 Results of multivariable Cox regression comparing the occurrence of hypertension between OCS use categories



Hypertension						
n = 418362	**Time Fixed Analysis**			**Time Variable Analysis**		
	HR	**95% CI**		**HR**	**95% CI**	
OCS Naïve	1			1		
One Off OCS	1.29	1.26	1.32	1.29	1.26	1.31
Less frequent OCS	1.36	1.33	1.39	1.35	1.32	1.38
Frequent OCS	1.37	1.34	1.39	1.36	1.33	1.38

Figure 29 Kaplan-Meier curve showing the cumulative freedom from hypertension, stratified by OCS use categories

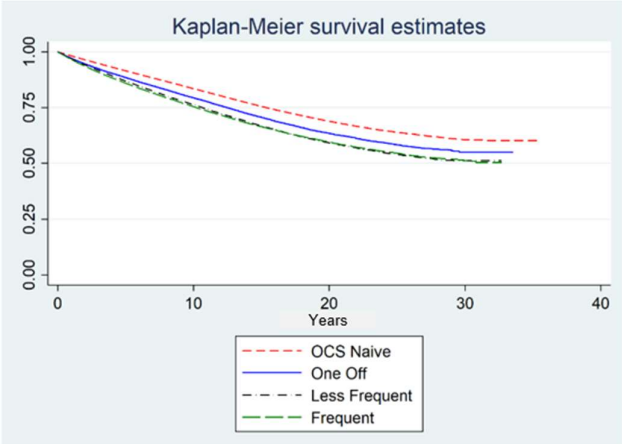


Similar trends were observed for anxiety and depression, where one-off (HR 1.3 [1.28, 1.32] on time-varying analysis), less frequent (HR 1.47 [1.45, 1.49] on time-varying analysis),and frequent (HR 1.50 [1.48, 1.52] on time-varying analysis; Table 27 and Figure 30) OCS users all had higher risks compared to OCS-naïve patients.

Table 27 Results of multivariable Cox regression comparing the occurrence of anxiety and depression between OCS use categories

Anxiety and Depression						
n = 359678	**Time Fixed Analysis**			**Time Variable Analysis**		
	HR	**95% CI**		**HR**	**95% CI**	
OCS Naïve	1			1		
One Off OCS	1.31	1.29	1.32	1.3	1.28	1.32
Less frequent OCS	1.47	1.45	1.49	1.47	1.45	1.49
Frequent OCS	1.5	1.48	1.52	1.5	1.48	1.52

Figure 30 Kaplan-Meier curve showing the cumulative freedom from anxiety and depression, stratified by OCS use categories

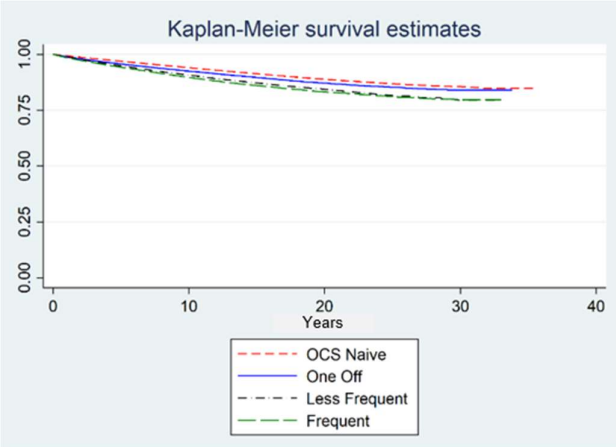


Similar observations were made for sleep disorders, where frequent (HR 1.62 [1.59, 1.65] on time-varying analysis; Table 28 and Figure 31) and less frequent (HR 1.59 [1.56, 1.62] on time-varying analysis) OCS users had similarly elevated risks compared to OCS-naïve patients, with the increase in risk being more drastic than that for one off OCS (HR 1.34 [1.31, 1.37] on time-varying analysis).

Table 28 Results of multivariable Cox regression comparing the occurrence of sleep disorder between OCS use categories

Sleep Disorder						
n = 440024	**Time Fixed Analysis**			**Time Variable Analysis**		
	HR	**95% CI**		**HR**	**95% CI**	
OCS Naïve	1			1		
One Off OCS	1.35	1.32	1.38	1.34	1.31	1.37
Less frequent OCS	1.59	1.56	1.63	1.59	1.56	1.62
Frequent OCS	1.62	1.59	1.65	1.62	1.59	1.65

Figure 31 Kaplan-Meier curve showing the cumulative freedom from sleep disorder, stratified by OCS use categories

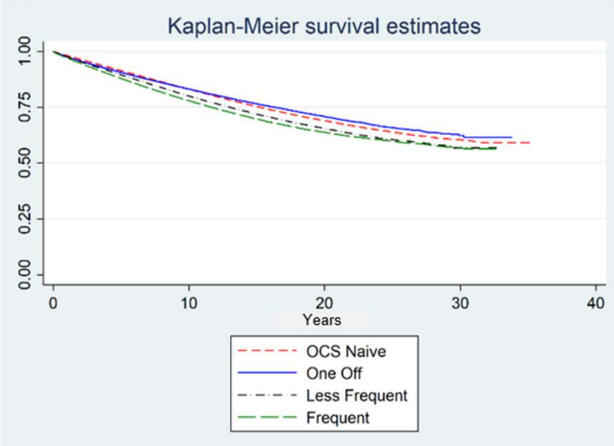


In contrast, a different pattern was observed for dyslipidaemia, where less frequent OCS users had the highest increase in risk compared to the non-OCS group (HR 1.27 [1.26, 1.29] on time-varying analysis; Table 29 and Figure 32), followed by frequent (HR 1.16 [1.14, 1.17] on time-varying analysis) and one off OCS users (HR 1.13 [1.12, 1.15] on time-varying analysis).

Table 29 Results of multivariable Cox regression comparing the occurrence of dyslipidaemia between OCS use categories

Dyslipidaemia						
n = 401314	**Time Fixed Analysis**			**Time Variable Analysis**		
	HR	**95% CI**		**HR**	**95% CI**	
OCS Naïve	1			1		
One Off OCS	1.14	1.13	1.16	1.13	1.12	1.15
Less frequent OCS	1.28	1.26	1.3	1.27	1.26	1.29
Frequent OCS	1.17	1.15	1.18	1.16	1.14	1.17

Figure 32 Kaplan-Meier curve showing the cumulative freedom from dyslipidaemia, stratified by OCS use categories

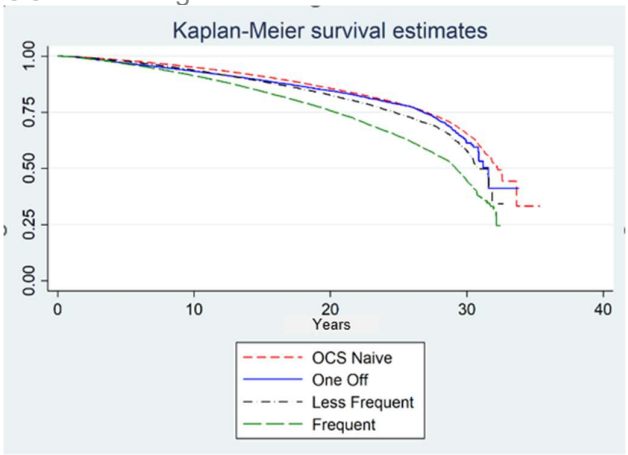


Unexpected trends were also observed for cataract, of which frequent OCS users had the highest risk compared with the non-OCS group (HR 1.63 [1.60, 1.65] on time-varying analysis; Table 30 and Figure 33), followed by one off OCS users (HR 1.50 [1.47, 1.53] on time-varying analysis) and then by less frequent OCS users (HR 1.41 [1.38, 1.44] on time-varying analysis).

Table 30 Results of multivariable Cox regression comparing the occurrence of cataract between OCS use categories

Cataracts						
n = 463805	**Time Fixed Analysis**			**Time Variable Analysis**		
	HR	**95% CI**		**HR**	**95% CI**	
OCS Naïve	1			1		
One Off OCS	1.49	1.46	1.52	1.5	1.47	1.53
Less frequent OCS	1.42	1.39	1.45	1.41	1.38	1.44
Frequent OCS	1.64	1.61	1.66	1.63	1.6	1.65

Figure 33 Kaplan-Meier curve showing the cumulative freedom from cataract, stratified by OCS use categories

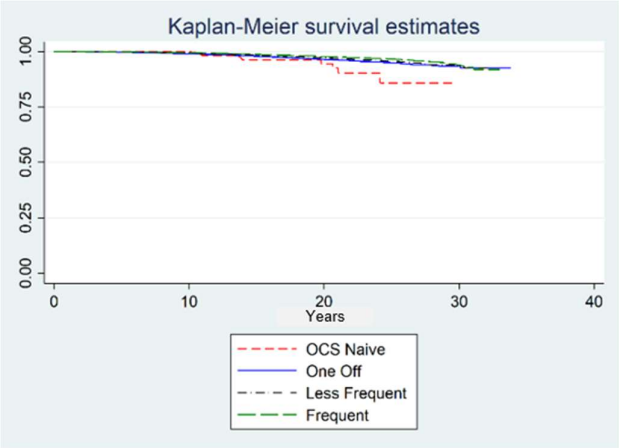


Lastly, the risks of behvaioural issues were not different between patients in the OCS cohort and those in the control cohort (Table 31 and Figure 34).

Table 31 Results of multivariable Cox regression comparing the occurrence of behavioural issues between OCS use categories

Behavoural Issues						
n = 424290	**Time Fixed Analysis**			**Time Variable Analysis**		
	HR	**95% CI**		**HR**	**95% CI**	
OCS Naïve	1			1		
One Off OCS	1.25	1.19	1.32	1.29	0.72	2.34
Less frequent OCS	1.02	0.96	1.08	1.14	0.63	2.07
Frequent OCS	0.99	0.93	1.05	1.20	0.66	2.18

Figure 34 Kaplan-Meier curve showing the cumulative freedom from behavioural issues, stratified by OCS use categories



7.4.2.3 Stratification by baseline age

The HR of different OCS prescription patterns, as compared against the non-OCS group, for AEs in different baseline age groups were summarized in Table 32 (4-<12 years old), Table 33 (12-<18 years old), Table 34 (18-<65 years old) and Table 35 (>65 years old). As expected, the younger age groups had longer mean follow-up durations (4-<12 years old: 11.4 years; 12-<18 years old: 10.4 years; 18-<65 years old: 9.4 years; >65 years old: 8.8 years)). Generally, more frequent OCS users had higher risks for AEs. The risk increase for pneumonia was consistently the biggest throughout all age groups.

Table 32 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients aged 4-<12 years

Age 4 - <12

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.11	1.08	1.14	1.21	1.17	1.24	1.32	1.29	1.36
Diabetes	1	1.20	1.05	1.38	1.14	0.97	1.35	1.18	1.00	1.38
Osteoporosis	1	1.02	0.97	1.07	1.09	1.03	1.15	1.17	1.10	1.24
Hypertension	1	1.01	0.86	1.18	0.84	0.71	1.00	0.88	0.74	1.05
Glaucoma	1	1.04	0.88	1.22	1.01	0.84	1.20	1.06	0.89	1.27
Sleep disorders	1	1.28	1.20	1.36	1.54	1.44	1.64	1.60	1.49	1.72
Sleep apnoea	1	1.25	0.96	1.63	1.24	0.93	1.65	1.74	1.34	2.26
Depression/Anxiety	1	1.12	1.08	1.16	1.22	1.18	1.26	1.30	1.26	1.35
Pneumonia	1	7.07	5.88	8.51	11.38	9.50	13.64	17.10	14.33	20.40
Cataracts	1	1.03	0.88	1.20	0.81	0.68	0.97	0.94	0.79	1.10
Cardiovascular diseases	1	1.02	0.69	1.49	0.84	0.53	1.32	0.94	0.59	1.49
Renal disease	1	0.74	0.70	0.79	0.82	0.77	0.87	0.99	0.93	1.05
Dyslipidaemia	1	1.48	1.38	1.59	1.50	1.38	1.63	1.38	1.25	1.53
Peptic ulcer	1	0.76	0.40	1.44	1.41	0.83	2.41	1.41	0.78	2.53

Mean follow-up 11.4yrs, median 10.7 (IQR 5.8-16.1), maximum follow-up 33.8yrs

Table 33 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients aged 12-<18 years

Age 12 - <18

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.17	1.14	1.20	1.33	1.29	1.37	1.45	1.40	1.50
Diabetes	1	1.14	0.97	1.35	1.28	1.07	1.53	1.45	1.20	1.74
Osteoporosis	1	1.04	0.96	1.12	1.28	1.18	1.40	1.26	1.14	1.39
Hypertension	1	0.94	0.79	1.12	1.05	0.88	1.25	1.06	0.88	1.27
Glaucoma	1	0.93	0.75	1.15	1.29	1.05	1.59	1.51	1.23	1.86
Sleep disorders	1	1.47	1.37	1.57	1.66	1.53	1.79	1.83	1.67	1.99
Sleep apnoea	1	1.14	0.82	1.60	1.34	0.94	1.90	2.29	1.67	3.14
Depression/Anxiety	1	1.27	1.22	1.31	1.45	1.40	1.51	1.53	1.46	1.59
Pneumonia	1	4.50	3.37	6.01	9.17	6.97	12.07	17.77	13.72	23.02
Cataracts	1	0.88	0.73	1.05	0.91	0.75	1.10	1.13	0.95	1.35
Cardiovascular diseases	1	1.09	0.72	1.64	1.22	0.77	1.93	2.11	1.39	3.20
Renal disease	1	0.82	0.77	0.87	0.92	0.86	0.98	1.03	0.96	1.10
Dyslipidaemia	1	1.26	1.16	1.35	1.33	1.21	1.45	1.32	1.19	1.47
Peptic ulcer	1	1.90	1.17	3.07	2.15	1.27	3.62	2.25	1.28	3.96

Mean follow-up 10.4yrs, median 9.2 (IQR 5.0-14.5), maximum follow-up 32.4yrs

Table 34 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients aged 18-<65 years

Age 18 - <65

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.24	1.23	1.26	1.39	1.38	1.41	1.48	1.47	1.50
Diabetes	1	1.40	1.36	1.45	1.63	1.58	1.67	2.01	1.96	2.06
Osteoporosis	1	1.22	1.17	1.27	1.31	1.26	1.36	1.56	1.51	1.61
Hypertension	1	1.44	1.41	1.48	1.43	1.40	1.47	1.47	1.43	1.50
Glaucoma	1	1.27	1.23	1.32	1.46	1.41	1.51	1.98	1.93	2.04
Sleep disorders	1	1.38	1.35	1.42	1.65	1.61	1.69	1.72	1.68	1.76
Sleep apnoea	1	1.68	1.57	1.80	2.30	2.16	2.44	3.59	3.41	3.77
Depression/Anxiety	1	1.38	1.36	1.40	1.57	1.55	1.60	1.64	1.61	1.66
Pneumonia	1	5.21	4.84	5.60	7.37	6.90	7.89	12.82	12.11	13.57
Cataracts	1	1.67	1.62	1.71	1.45	1.41	1.49	1.76	1.72	1.80
Cardiovascular diseases	1	1.29	1.24	1.35	1.34	1.28	1.39	1.58	1.53	1.63
Renal disease	1	1.04	1.03	1.06	1.11	1.09	1.13	1.25	1.23	1.26
Dyslipidaemia	1	1.27	1.25	1.29	1.30	1.28	1.32	1.16	1.15	1.18
Peptic ulcer	1	1.09	0.98	1.22	1.22	1.10	1.35	1.52	1.40	1.65

Mean follow-up 9.4yrs, median 8 (IQR 4.1-13.3), maximum follow-up 33yrs

Table 35 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients aged >65 years

Age >65

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.20	1.18	1.23	1.35	1.33	1.38	1.35	1.33	1.37
Diabetes	1	1.24	1.18	1.30	1.44	1.37	1.52	1.50	1.44	1.57
Osteoporosis	1	1.12	1.07	1.18	1.27	1.21	1.34	1.30	1.25	1.36
Hypertension	1	1.26	1.21	1.32	1.17	1.12	1.23	1.08	1.03	1.12
Glaucoma	1	1.10	1.04	1.17	1.16	1.09	1.23	1.38	1.31	1.44
Sleep disorders	1	1.27	1.21	1.34	1.43	1.35	1.50	1.35	1.29	1.41
Sleep apnoea	1	1.77	1.39	2.25	2.25	1.78	2.83	3.15	2.65	3.75
Depression/Anxiety	1	1.29	1.23	1.34	1.47	1.41	1.53	1.36	1.32	1.41
Pneumonia	1	4.11	3.85	4.39	5.19	4.86	5.54	6.06	5.74	6.40
Cataracts	1	1.46	1.41	1.51	1.33	1.28	1.38	1.34	1.30	1.38
Cardiovascular diseases	1	1.30	1.25	1.35	1.38	1.33	1.44	1.39	1.34	1.43
Renal disease	1	1.09	1.05	1.12	1.18	1.15	1.22	1.13	1.10	1.16
Dyslipidaemia	1	1.14	1.10	1.19	1.26	1.21	1.30	1.06	1.03	1.09
Peptic ulcer	1	1.06	0.93	1.22	1.18	1.03	1.35	1.19	1.06	1.33

Mean follow-up 8.2yrs, median 6.6 (IQR 3.4-11.4), maximum follow-up 33.5yrs

7.4.2.4 Stratification by baseline GINA step

The incidence of AEs in patients treated with different GINA steps at baseline were compared. The increase in risks of AEs with OCS use compared with the non-OCS group were generally similar across GINA steps 0-3 (Table 36, Table 37, Table 38, and Table 39), while the risks of AEs for patients who were already treated with GINA step 4 (Table 40) or 5 (Table 41) were further elevated compared to those treated with lower GINA steps. The risks for AEs were generally the highest in frequent OCS users.

Table 36 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients taking no asthma treatment (GINA step 0).

GINA Step 0

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.25	1.22	1.28	1.43	1.40	1.47	1.46	1.43	1.49
Diabetes	1	1.41	1.32	1.51	1.64	1.54	1.75	1.96	1.86	2.07
Osteoporosis	1	1.16	1.08	1.24	1.24	1.15	1.32	1.32	1.24	1.40
Hypertension	1	1.24	1.18	1.32	1.41	1.34	1.49	1.36	1.29	1.43
Glaucoma	1	1.32	1.22	1.43	1.27	1.17	1.37	1.89	1.78	2.02
Sleep disorders	1	1.28	1.22	1.36	1.63	1.55	1.71	1.57	1.50	1.65
Sleep apnoea	1	1.39	1.16	1.68	1.91	1.61	2.27	3.19	2.77	3.68
Depression/Anxiety	1	1.27	1.23	1.32	1.57	1.51	1.62	1.47	1.42	1.52
Pneumonia	1	3.78	3.34	4.28	5.02	4.46	5.65	6.84	6.16	7.59
Cataracts	1	1.58	1.50	1.67	1.38	1.30	1.46	1.74	1.66	1.82
Cardiovascular diseases	1	1.27	1.18	1.36	1.48	1.39	1.59	1.54	1.46	1.63
Renal disease	1	1.16	1.12	1.21	1.17	1.13	1.22	1.32	1.27	1.36
Dyslipidaemia	1	1.12	1.08	1.16	1.39	1.34	1.43	1.19	1.15	1.23
Peptic ulcer	1	1.08	0.88	1.33	1.37	1.12	1.66	1.41	1.19	1.67

Table 37 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients taking GINA step 1 treatment.

GINA Step 1

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.21	1.19	1.23	1.35	1.33	1.38	1.40	1.38	1.43
Diabetes	1	1.26	1.20	1.33	1.62	1.54	1.71	1.94	1.85	2.03
Osteoporosis	1	1.17	1.11	1.24	1.21	1.14	1.28	1.31	1.24	1.38
Hypertension	1	1.31	1.25	1.38	1.31	1.24	1.38	1.43	1.37	1.50
Glaucoma	1	1.21	1.14	1.29	1.48	1.39	1.58	1.85	1.75	1.95
Sleep disorders	1	1.29	1.24	1.35	1.56	1.49	1.63	1.54	1.47	1.60
Sleep apnoea	1	1.65	1.45	1.88	2.38	2.10	2.70	3.46	3.10	3.87
Depression/Anxiety	1	1.27	1.23	1.30	1.39	1.35	1.43	1.42	1.38	1.46
Pneumonia	1	4.75	4.23	5.34	6.31	5.63	7.08	8.59	7.74	9.54
Cataracts	1	1.47	1.40	1.53	1.42	1.35	1.48	1.69	1.62	1.76
Cardiovascular diseases	1	1.32	1.24	1.41	1.46	1.37	1.56	1.56	1.47	1.64
Renal disease	1	0.99	0.96	1.02	1.09	1.06	1.13	1.18	1.14	1.21
Dyslipidaemia	1	1.16	1.12	1.19	1.23	1.19	1.27	1.16	1.12	1.19
Peptic ulcer	1	1.12	0.94	1.33	1.10	0.91	1.33	1.54	1.33	1.79

Table 38 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients taking GINA step 2 treatment.

GINA Step 2

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.16	1.15	1.18	1.32	1.30	1.34	1.38	1.36	1.41
Diabetes	1	1.27	1.21	1.33	1.49	1.42	1.56	1.83	1.75	1.90
Osteoporosis	1	1.16	1.11	1.22	1.20	1.15	1.26	1.34	1.29	1.40
Hypertension	1	1.30	1.25	1.36	1.34	1.28	1.39	1.33	1.27	1.38
Glaucoma	1	1.16	1.09	1.23	1.42	1.35	1.50	1.82	1.74	1.91
Sleep disorders	1	1.31	1.26	1.37	1.53	1.47	1.59	1.60	1.54	1.66
Sleep apnoea	1	1.42	1.25	1.62	2.06	1.82	2.32	3.48	3.14	3.85
Depression/Anxiety	1	1.26	1.23	1.29	1.41	1.38	1.45	1.46	1.42	1.49
Pneumonia	1	4.47	4.02	4.97	6.19	5.60	6.85	9.23	8.42	10.11
Cataracts	1	1.52	1.46	1.58	1.42	1.37	1.48	1.42	1.50	1.61
Cardiovascular diseases	1	1.09	1.03	1.16	1.17	1.11	1.24	1.38	1.32	1.45
Renal disease	1	0.94	0.92	0.97	1.04	1.01	1.07	1.11	1.08	1.13
Dyslipidaemia	1	1.10	1.07	1.13	1.22	1.19	1.26	1.13	1.11	1.16
Peptic ulcer	1	0.98	0.84	1.16	1.25	1.07	1.46	1.39	1.22	1.59

Table 39 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients taking GINA step 3 treatment.

GINA Step 3

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.19	1.17	1.21	1.38	1.35	1.41	1.46	1.43	1.49
Diabetes	1	1.19	1.12	1.27	1.54	1.45	1.64	1.93	1.83	2.04
Osteoporosis	1	1.22	1.14	1.30	1.35	1.27	1.44	1.42	1.34	1.51
Hypertension	1	1.21	1.14	1.28	1.35	1.28	1.43	1.30	1.24	1.37
Glaucoma	1	1.04	0.96	1.13	1.36	1.26	1.47	1.92	1.81	2.05
Sleep disorders	1	1.35	1.28	1.43	1.54	1.46	1.62	1.60	1.52	1.67
Sleep apnoea	1	1.53	1.30	1.81	2.13	1.82	2.49	3.49	3.06	3.98
Depression/Anxiety	1	1.33	1.29	1.38	1.46	1.41	1.51	1.52	1.47	1.57
Pneumonia	1	3.89	3.45	4.40	5.11	4.54	5.75	7.52	6.78	8.34
Cataracts	1	1.45	1.38	1.53	1.48	1.40	1.56	1.65	1.58	1.73
Cardiovascular diseases	1	1.30	1.21	1.39	1.44	1.34	1.54	1.51	1.42	1.60
Renal disease	1	1.01	0.97	1.05	1.20	1.15	1.24	1.27	1.23	1.32
Dyslipidaemia	1	1.12	1.08	1.16	1.21	1.16	1.25	1.09	1.05	1.12
Peptic ulcer	1	1.09	0.89	1.34	1.18	0.96	1.45	1.50	1.27	1.77

Table 40 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients taking GINA step 4 treatment.

GINA Step 4

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.28	1.24	1.32	1.47	1.43	1.52	1.58	1.54	1.63
Diabetes	1	1.40	1.27	1.55	1.77	1.61	1.94	2.03	1.88	2.19
Osteoporosis	1	1.19	1.08	1.32	1.32	1.20	1.46	1.47	1.35	1.60
Hypertension	1	1.38	1.27	1.50	1.37	1.26	1.49	1.43	1.34	1.54
Glaucoma	1	1.32	1.17	1.48	1.55	1.39	1.73	2.07	1.89	2.26
Sleep disorders	1	1.40	1.29	1.53	1.62	1.49	1.76	1.82	1.69	1.95
Sleep apnoea	1	2.14	1.69	2.70	3.79	3.08	4.67	5.02	4.18	6.04
Depression/Anxiety	1	1.38	1.31	1.46	1.58	1.49	1.67	1.57	1.50	1.65
Pneumonia	1	4.86	4.05	5.83	6.75	5.68	8.04	9.47	8.11	11.06
Cataracts	1	1.69	1.58	1.82	1.57	1.46	1.69	1.74	1.64	1.84
Cardiovascular diseases	1	1.34	1.21	1.49	1.35	1.21	1.50	1.56	1.43	1.70
Renal disease	1	1.21	1.15	1.28	1.39	1.32	1.47	1.51	1.45	1.58
Dyslipidaemia	1	1.09	1.03	1.16	1.31	1.24	1.39	1.22	1.17	1.28
Peptic ulcer	1	1.11	0.81	1.51	1.24	0.92	1.68	1.30	1.01	1.68

Table 41 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients taking GINA step 5 treatment.

GINA Step 5

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.33	1.24	1.43	1.59	1.49	1.70	1.89	1.80	1.99
Diabetes	1	1.29	1.05	1.59	2.03	1.70	2.43	2.07	1.80	2.39
Osteoporosis	1	1.52	1.21	1.91	1.54	1.23	1.92	1.85	1.56	2.18
Hypertension	1	1.73	1.46	2.06	1.75	1.48	2.07	1.49	1.30	1.70
Glaucoma	1	1.25	0.99	1.58	1.89	1.54	2.32	1.79	1.52	2.10
Sleep disorders	1	1.43	1.16	1.77	1.74	1.43	2.12	1.88	1.61	2.19
Sleep apnoea	1	3.00	2.01	4.50	3.34	2.25	4.96	4.53	3.29	6.24
Depression/Anxiety	1	1.64	1.43	1.88	1.77	1.55	2.02	2.07	1.87	2.29
Pneumonia	1	14.53	9.25	22.84	15.51	9.86	24.39	27.76	18.33	42.05
Cataracts	1	1.95	1.70	2.24	1.99	1.74	2.27	1.85	1.67	2.06
Cardiovascular diseases	1	1.38	1.11	1.73	1.53	1.23	1.91	1.75	1.48	2.06
Renal disease	1	1.22	1.09	1.37	1.38	1.23	1.54	1.63	1.50	1.77
Dyslipidaemia	1	1.11	0.96	1.27	1.44	1.27	1.63	1.35	1.22	1.49
Peptic ulcer	1	0.83	0.36	1.87	0.63	0.51	4.58	1.46	0.86	2.47

7.4.2.5 Stratification by ICS prescriptions

The risks of AEs in patients in relation to intermittent OCS patterns by different numbers of ICS prescriptions were compared (Table 42, Table 43, Table 44, and Table 45). The increases in risks of AEs were highest in those with the most ICS prescriptions compared to

those with less ICS prescriptions. The risks for AEs were generally the highest in frequent OCS users.

Table 42 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients without any ICS prescription

ICS 0

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.22	1.20	1.23	1.38	1.36	1.40	1.42	1.40	1.44
Diabetes	1	1.31	1.26	1.37	1.62	1.56	1.69	1.95	1.88	2.02
Osteoporosis	1	1.17	1.12	1.22	1.22	1.17	1.27	1.32	1.27	1.37
Hypertension	1	1.28	1.23	1.32	1.36	1.31	1.41	1.39	1.35	1.44
Glaucoma	1	1.25	1.19	1.32	1.39	1.32	1.46	1.87	1.79	1.95
Sleep disorders	1	1.29	1.24	1.33	1.60	1.55	1.66	1.55	1.51	1.60
Sleep apnoea	1	1.57	1.42	1.74	2.17	1.96	2.40	3.31	3.04	3.61
Depression/Anxiety	1	1.27	1.24	1.30	1.46	1.42	1.49	1.46	1.41	1.48
Pneumonia	1	4.37	4.02	4.75	5.79	5.34	6.27	7.78	7.24	8.37
Cataracts	1	1.51	1.46	1.57	1.40	1.36	1.45	1.71	1.66	1.76
Cardiovascular diseases	1	1.29	1.23	1.35	1.45	1.38	1.52	1.53	1.47	1.59
Renal disease	1	1.06	1.03	1.08	1.12	1.09	1.15	1.23	1.20	1.25
Dyslipidaemia	1	1.14	1.11	1.16	1.30	1.27	1.33	1.17	1.15	1.20
Peptic ulcer	1	1.10	0.97	1.26	1.20	1.05	1.37	1.48	1.33	1.65

Table 43 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients with 1-<7 ICS prescriptions.

ICS 1 <7

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.19	1.17	1.20	1.35	1.36	1.40	1.44	1.43	1.46
Diabetes	1	1.24	1.19	1.29	1.53	1.56	1.69	1.86	1.80	1.93
Osteoporosis	1	1.18	1.13	1.23	1.25	1.17	1.27	1.39	1.34	1.44
Hypertension	1	1.27	1.22	1.31	1.34	1.31	1.41	1.35	1.31	1.40
Glaucoma	1	1.13	1.07	1.18	1.42	1.32	1.46	1.86	1.79	1.93
Sleep disorders	1	1.33	1.29	1.38	1.53	1.55	1.66	1.64	1.59	1.69
Sleep apnoea	1	1.54	1.39	1.70	2.33	1.96	2.40	3.86	3.56	4.18
Depression/Anxiety	1	1.30	1.27	1.32	1.45	1.42	1.49	1.50	1.47	1.53
Pneumonia	1	4.26	3.91	4.63	6.07	5.34	6.27	9.30	8.65	10.00
Cataracts	1	1.48	1.43	1.52	1.41	1.36	1.45	1.61	1.56	1.65
Cardiovascular diseases	1	1.17	1.12	1.23	1.26	1.38	1.52	1.44	1.38	1.50
Renal disease	1	0.99	0.96	1.01	1.12	1.09	1.15	1.21	1.18	1.23
Dyslipidaemia	1	1.11	1.09	1.14	1.24	1.27	1.33	1.14	1.12	1.17
Peptic ulcer	1	1.00	0.88	1.14	1.22	1.07	1.38	1.40	1.26	1.56

Table 44 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients with 7-<13 ICS prescriptions.

ICS 7 <13

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.21	1.17	1.24	1.41	1.37	1.46	1.49	1.45	1.53
Diabetes	1	1.38	1.26	1.52	1.66	1.52	1.82	1.93	1.79	2.08
Osteoporosis	1	1.21	1.09	1.34	1.43	1.30	1.57	1.47	1.35	1.59
Hypertension	1	1.44	1.33	1.56	1.42	1.31	1.54	1.28	1.19	1.37
Glaucoma	1	1.20	1.06	1.35	1.48	1.32	1.66	1.95	1.78	2.13
Sleep disorders	1	1.42	1.30	1.55	1.59	1.47	1.73	1.61	1.49	1.73
Sleep apnoea	1	1.65	1.28	2.12	2.34	1.86	2.95	3.35	2.77	4.06
Depression/Anxiety	1	1.38	1.30	1.46	1.50	1.41	1.59	1.50	1.42	1.58
Pneumonia	1	4.84	4.13	5.68	5.42	4.63	6.35	8.20	7.15	9.39
Cataracts	1	1.75	1.64	1.88	1.67	1.55	1.79	1.66	1.56	1.76
Cardiovascular diseases	1	1.33	1.21	1.46	1.43	1.30	1.57	1.52	1.41	1.65
Renal disease	1	1.05	0.99	1.11	1.20	1.14	1.27	1.34	1.28	1.40
Dyslipidaemia	1	1.11	1.05	1.17	1.20	1.13	1.27	1.09	1.04	1.15
Peptic ulcer	1	1.17	0.87	1.57	1.52	1.15	2.00	1.45	1.15	1.84

Table 45 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients with >12 ICS prescriptions.

ICS >12

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.26	1.18	1.36	1.49	1.38	1.60	1.65	1.56	1.76
Diabetes	1	1.36	1.09	1.69	1.91	1.55	2.36	2.46	2.08	2.90
Osteoporosis	1	1.24	0.97	1.57	1.33	1.04	1.69	1.59	1.32	1.92
Hypertension	1	1.64	1.38	1.95	1.63	1.35	1.96	1.57	1.35	1.84
Glaucoma	1	1.27	0.96	1.66	1.73	1.34	2.23	2.23	1.82	2.73
Sleep disorders	1	1.33	1.09	1.63	1.78	1.47	2.15	1.79	1.52	2.10
Sleep apnoea	1	3.49	2.01	6.05	3.88	2.20	6.85	5.35	3.30	8.65
Depression/Anxiety	1	1.40	1.21	1.62	1.36	1.17	1.59	1.71	1.52	1.93
Pneumonia	1	4.83	3.47	6.73	6.64	4.79	9.19	8.96	6.73	11.93
Cataracts	1	2.03	1.75	2.36	2.12	1.82	2.48	2.13	1.88	2.42
Cardiovascular diseases	1	1.21	0.98	1.48	1.48	1.19	1.83	1.83	1.55	2.16
Renal disease	1	1.14	1.00	1.31	1.39	1.22	1.59	1.54	1.38	1.71
Dyslipidaemia	1	1.11	0.97	1.27	1.29	1.12	1.47	1.07	0.96	1.20
Peptic ulcer	1	1.07	0.60	1.92	1.52	0.87	2.66	1.28	0.78	2.09

7.4.2.6 Stratification by SABA prescriptions

The risks of AEs in patients with different numbers of SABA prescriptions were shown in Table 46, Table 47, Table 48, and Table 49. The increases in risks of AEs were lowest in those without SABA prescriptions, compared to those with SABA prescriptions. The risks for AEs were generally the highest in frequent OCS users.

Table 46 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients without SABA prescriptions.

SABA 0

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.25	1.23	1.27	1.42	1.40	1.45	1.46	1.44	1.48
Diabetes	1	1.30	1.24	1.37	1.53	1.45	1.60	1.87	1.79	1.94
Osteoporosis	1	1.21	1.15	1.28	1.26	1.20	1.33	1.33	1.27	1.40
Hypertension	1	1.21	1.16	1.27	1.38	1.32	1.44	1.29	1.25	1.35
Glaucoma	1	1.24	1.16	1.32	1.26	1.18	1.34	1.81	1.72	1.90
Sleep disorders	1	1.29	1.23	1.34	1.61	1.54	1.67	1.57	1.51	1.63
Sleep apnoea	1	1.37	1.18	1.59	1.92	1.68	2.20	3.10	2.76	3.47
Depression/Anxiety	1	1.28	1.24	1.31	1.50	1.46	1.54	1.45	1.41	1.49
Pneumonia	1	3.42	3.12	3.75	4.41	4.04	4.82	6.21	5.74	6.71
Cataracts	1	1.51	1.44	1.57	1.37	1.31	1.43	1.67	1.61	1.73
Cardiovascular diseases	1	1.25	1.19	1.32	1.43	1.35	1.50	1.51	1.44	1.58
Renal disease	1	1.20	1.16	1.23	1.21	1.18	1.25	1.36	1.32	1.39
Dyslipidaemia	1	1.13	1.10	1.16	1.35	1.31	1.38	1.17	1.14	1.20
Peptic ulcer	1	1.08	0.92	1.27	1.24	1.06	1.45	1.36	1.19	1.55

Table 47 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients with 1-<4 SABA prescriptions.

SABA 1<4

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.20	1.18	1.21	1.35	1.33	1.37	1.42	1.40	1.43
Diabetes	1	1.25	1.19	1.30	1.60	1.54	1.67	1.91	1.85	1.99
Osteoporosis	1	1.15	1.11	1.20	1.21	1.15	1.26	1.35	1.30	1.41
Hypertension	1	1.30	1.26	1.35	1.30	1.25	1.35	1.39	1.34	1.44
Glaucoma	1	1.17	1.12	1.23	1.46	1.39	1.54	1.88	1.80	1.96
Sleep disorders	1	1.31	1.26	1.35	1.51	1.46	1.56	1.58	1.53	1.64
Sleep apnoea	1	1.64	1.48	1.81	2.42	2.19	2.66	3.68	3.38	4.00
Depression/Anxiety	1	1.30	1.27	1.33	1.43	1.40	1.46	1.46	1.43	1.49
Pneumonia	1	4.79	4.36	5.27	6.71	6.11	7.36	9.89	9.08	10.76
Cataracts	1	1.43	1.38	1.48	1.39	1.34	1.44	1.59	1.54	1.64
Cardiovascular diseases	1	1.20	1.14	1.26	1.30	1.24	1.37	1.43	1.37	1.49
Renal disease	1	0.98	0.96	1.00	1.09	1.07	1.12	1.16	1.13	1.18
Dyslipidaemia	1	1.15	1.13	1.18	1.24	1.21	1.27	1.15	1.13	1.18
Peptic ulcer	1	0.94	0.82	1.09	1.21	1.05	1.39	1.36	1.20	1.54

Table 48 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients with 3-<13 SABA prescriptions.

SABA 3<13

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.19	1.17	1.21	1.35	1.33	1.37	1.46	1.44	1.49
Diabetes	1	1.32	1.25	1.39	1.60	1.52	1.68	1.96	1.88	2.05
Osteoporosis	1	1.22	1.15	1.28	1.28	1.21	1.35	1.40	1.34	1.47
Hypertension	1	1.34	1.28	1.40	1.38	1.32	1.45	1.43	1.37	1.49
Glaucoma	1	1.16	1.09	1.24	1.48	1.40	1.58	1.93	1.84	2.03
Sleep disorders	1	1.39	1.33	1.45	1.58	1.52	1.65	1.66	1.60	1.73
Sleep apnoea	1	1.65	1.44	1.89	2.39	2.12	2.70	3.94	3.56	4.37
Depression/Anxiety	1	1.31	1.27	1.34	1.44	1.40	1.48	1.51	1.47	1.55
Pneumonia	1	5.61	5.04	6.25	7.19	6.48	7.98	10.60	9.65	11.65
Cataracts	1	1.62	1.56	1.69	1.54	1.47	1.60	1.71	1.65	1.77
Cardiovascular diseases	1	1.30	1.23	1.38	1.35	1.27	1.43	1.57	1.50	1.65
Renal disease	1	0.94	0.91	0.97	1.11	1.08	1.14	1.21	1.18	1.24
Dyslipidaemia	1	1.09	1.06	1.13	1.21	1.17	1.24	1.14	1.11	1.17
Peptic ulcer	1	1.30	1.11	1.53	1.24	1.05	1.47	1.63	1.43	1.87

Table 49 Results of multivariable Cox regression comparing the occurrence of adverse events between OCS use categories in patients with >12 SABA prescriptions.

SABA >12

	OCS-naïve	Only 1 OCS			Less frequent OCS			Frequent OCS		
Adverse Events	HR	HR	95% CI		HR	95% CI		HR	95% CI	
Any adverse event	1	1.08	1.03	1.13	1.41	1.35	1.48	1.45	1.40	1.51
Diabetes	1	1.47	1.27	1.69	1.80	1.57	2.05	1.97	1.77	2.20
Osteoporosis	1	0.99	0.83	1.18	1.50	1.29	1.73	1.50	1.33	1.69
Hypertension	1	1.50	1.33	1.69	1.45	1.28	1.64	1.29	1.16	1.43
Glaucoma	1	1.21	1.01	1.44	1.53	1.30	1.81	1.87	1.64	2.13
Sleep disorders	1	1.40	1.23	1.59	1.82	1.62	2.04	1.65	1.49	1.83
Sleep apnoea	1	1.74	1.21	2.51	2.31	1.66	3.21	3.42	2.62	4.47
Depression/Anxiety	1	1.19	1.08	1.30	1.53	1.41	1.66	1.66	1.55	1.78
Pneumonia	1	4.42	3.47	5.63	6.43	5.12	8.08	8.13	6.65	9.93
Cataracts	1	1.94	1.74	2.15	1.87	1.68	2.08	1.87	1.72	2.05
Cardiovascular diseases	1	1.19	1.02	1.37	1.44	1.24	1.66	1.46	1.30	1.64
Renal disease	1	0.93	0.85	1.02	1.08	0.99	1.17	1.26	1.18	1.35
Dyslipidaemia	1	1.05	0.96	1.15	1.20	1.10	1.30	1.08	1.01	1.16
Peptic ulcer	1	0.82	0.51	1.30	1.57	1.08	2.27	1.43	1.05	1.96

7.4.3 Objective 3

Analyses for Objective 3 were limited to patients in CPRD with HES and ONS linkage. Their baseline characteristics are summarized in Table 50.

Table 50 Baseline characteristics of patients included in Objective 3 analyses

	OCS-naïve n=149,191†		Any OCS n=149,191 (100%)		One-off OCS n=74,999 (50.3%)		Less frequent OCS‡ n=40,890 (27.4%)		Frequent OCS§ n=33,302 (22.3%)	
Age, mean, years (SD)	38.7	(22.4)	38.7	(22.4)	35.9	(22.7)	38.6	(23.1)	45.2	(23.3)
Female, %	52.6		52.6		50.7		54.1	0	55.1	0
Follow-up, median years (IQR)	20.9	(13.5-29.8)	19.1	(11.6-28.0)	17.8	(10.4-26.2)	20.9	(13.4-29.6)	20.2	(12.3-29.8)
GINA step, n (%)										
0	143,524	96.2	24,111	16.16	9,482	12.65	7,894	19.31	6,737	20.21
1	4,997	3.35	35,761	23.97	19,612	26.15	8,877	21.71	7,276	21.85
2	208	0.14	41,504	27.82	21,682	28.91	11,469	28.05	8,348	25.07
3	462	0.31	35,015	23.47	18,164	24.22	9,269	22.67	7,579	22.76
4	0	0	11,562	7.75	5,557	7.41	3,083	7.54	2,920	8.77
5	0	0	1,238	0.83	502	0.67	298	0.73	442	1.33
BMI										
Underweight, n (%)	1,852	1.24	1,851	1.24	909	1.2	469	1.14	481	1.45
Normal, n (%)	32,359	21.69	29,554	19.81	14,902	19.87	7,993	19.55	6,657	19.99
Overweight, n (%)	25,108	16.83	28,212	18.91	13,589	18.12	7,613	18.62	7,006	21.04
Obese, n (%)	15,292	10.25	23,945	16.05	11,122	14.83	6,566	16.06	6,254	18.78
Unknown, n (%)	74,580	49.99	65,629	43.99	34,477	45.97	18,249	44.63	12,904	38.75
Mean (SD)	26.326	(5.4)	27.62	(6.2)	27.42	(6.1)	27.63	(6.2)	27.99	(6.4}
Smoking status, n (%)										
Never	42,715	46.7	45,922	41.5	24,137	43.8	12,293	41.4	9,510	37.0
Current	31,867	34.9	41,102	37.2	19,439	35.3	11,465	38.6	10,193	39.6
Ex	16,858	18.4	23,527	21.3	11,549	21.0	5,961	20.1	6,007	23.4
Unknown	57,751	38.71	38,640	25.9	19,874	26.5	11,171	27.32	7,592	22.8
SABA fills; n (%)										
0	143,986	96.51	45,848	30.73	19,134	25.51	14,571	35.63	12,139	36.45
1–2	3,505	2.35	59,437	39.84	33,614	44.82	14,712	35.98	11,112	33.37

	OCS-naïve n=149,191†		Any OCS n=149,191 (100%)		One-off OCS n=74,999 (50.3%)		Less frequent OCS‡ n=40,890 (27.4%)		Frequent OCS§ n=33,302 (22.3%)	
3–11	1,476	0.99	38,670	25.92	19,934	26.58	10,197	24.94	8,538	25.64
≥12	223	0.15	5,236	3.51	2,317	3.09	1,410	3.45	1,511	4.54
ICS fills; n (%)										
0	145,522	97.54	61,006	40.89	29,566	39.42	17,069	41.74	14,385	43.19
1–3	2,329	1.56	53,651	35.96	29,109	38.81	14,374	35.15	10,175	30.55
4–6	747	0.5	18,934	12.69	9,196	12.26	5,260	12.86	4,487	13.47
7–9	315	0.21	8,505	5.7	3,931	5.24	2,344	5.73	2,233	6.7
10–12	181	0.12	4,343	2.91	1,974	2.63	1,167	2.85	1,200	3.6
≥13	121	0.08	2,747	1.84	1,239	1.65	680	1.66	831	2.49

BMI, body mass index; **GINA**, Global Initiative for Asthma; **ICS**, inhaled corticosteroid; **IQR**, interquartile range; **SABA**, short-acting β_2-agonist; **SD**, standard deviation.

[a]The doses of systemic corticosteroids contributing to OCS exposure were converted to prednisolone equivalents using the DDD obtained from the ATC/DDD classification system.[13]

[b]GINA treatment step is based on GINA 2020 guidelines; treatment step 0 refers to patients with no prescribed asthma medication.

[c]Number of fills in the 12 months prior to the index date.

Overall, OCS users had higher use of healthcare resources over the study period. The total all-cause per-patient healthcare cost was £8935 for OCS users and £4635 for OCS non-users, with patients with more frequent OCS use patterns incurring higher per-patient healthcare costs (£6955 for one-off OCS users, £10,125 for less frequent OCS users, and £11,937 for frequent OCS users; Table 51). Such observations were consistent for setting-specific healthcare costs (Table 51 and Figure 35). Similar patterns were generally observed for both total all-cause and setting-specific annualized healthcare costs (Table 52 and Figure 36), except annualized A&E, outpatient, and in-patient costs which were higher in one-off OCS users than less frequent OCS users.

Table 51 Overall and setting-specific per-patient healthcare costs.

Per Patient	OCS	95% CI			OCS Naïve	95% CI			One Off	95% CI			Less Frequent	95% CI			Frequent	95% CI		
A&E	£156	£152	£159	2%	£57	£56	£58	1%	£147	£142	£152	2%	£165	£160	£171	2%	£162	£156	£168	1%
Outpatients	£1,337	£1,303	£1,370	15%	£552	£538	£566	12%	£1,173	£1,114	£1,232	17%	£1,441	£1,396	£1,485	14%	£1,578	£1,528	£1,627	13%
GP Consultations	£2,292	£2,279	£2,305	26%	£1,670	£1,658	£1,683	36%	£1,681	£1,667	£1,695	24%	£2,795	£2,768	£2,822	28%	£3,051	£3,018	£3,084	26%
In Patients	£3,396	£3,310	£3,482	38%	£1,367	£1,318	£1,417	30%	£2,781	£2,659	£2,903	40%	£3,600	£3,459	£3,741	36%	£4,532	£4,326	£4,738	38%
Prescriptions	£1,755	£1,735	£1,776	20%	£988	£970	£1,005	21%	£1,173	£1,151	£1,195	17%	£2,124	£2,084	£2,164	21%	£2,614	£2,557	£2,671	22%
Total Cost	£8,935				£4,635				£6,955				£10,125				£11,937			

Figure 35 Comparison of setting-specific healthcare costs by OCS use patterns.

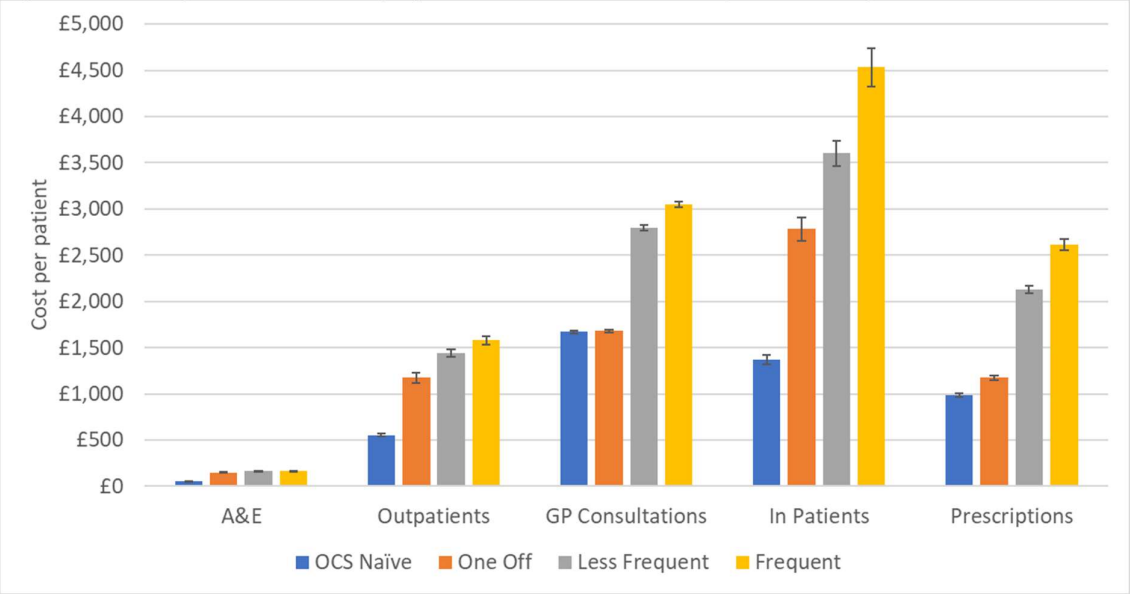
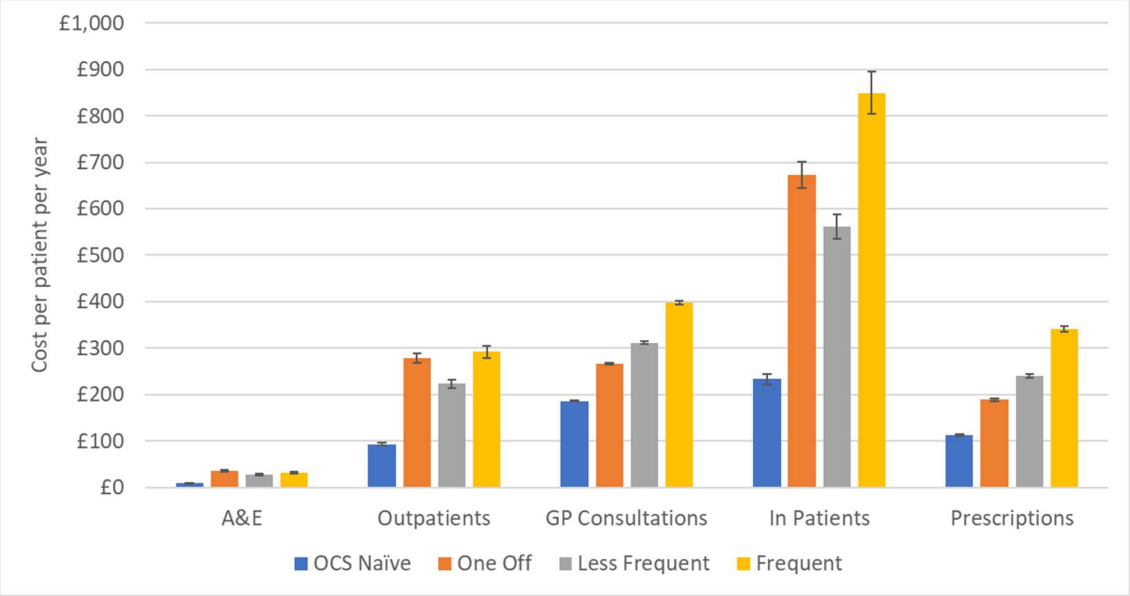


Table 52 Overall and setting-specific annualized per-patient healthcare costs

Per Patient/Year	OCS	95% CI			OCS Naïve	95% CI			One Off	95% CI			Less Frequent	95% CI			Frequent	95% CI		
A&E	£33	£32	£34	2%	£10	£10	£10	2%	£36	£34	£37	2%	£27	£26	£29	2%	£32	£30	£34	2%
Outpatients	£266	£260	£273	17%	£93	£90	£95	15%	£279	£268	£289	19%	£223	£214	£232	16%	£292	£279	£304	15%
GP Consultations	£308	£306	£309	20%	£186	£185	£187	29%	£266	£264	£268	18%	£311	£309	£314	23%	£398	£395	£402	21%
In Patients	£682	£663	£701	45%	£233	£222	£245	37%	£673	£645	£701	47%	£561	£535	£587	41%	£849	£804	£895	44%
Prescriptions	£237	£235	£240	16%	£112	£110	£114	18%	£189	£186	£192	13%	£240	£236	£245	18%	£341	£334	£348	18%
Total Cost	£1,526				£634				£1,443				£1,363				£1,913			

Figure 36 Comparison of setting-specific annualized healthcare costs by OCS use patterns.



The mean episodes and annualized rates of general practitioner consultations (Table 53), accident and emergency attendances (Table 54), and outpatient attendances (Table 55) were all higher in OCS users compared to the non-OCS group. This was consistently observed for both respiratory and non-respiratory events, as well as those with unknown diagnoses. Among OCS users, further stratification by OCS use pattern showed that the highest rate of general practitioner consultations occurred in frequent OCS users, and the lowest in one-off users (Table 53). A different trend was observed for accident and emergency and outpatient attendances, which were both highest in one-off OCS users, followed by frequent and less-frequent users (Table 54 and Table 55). Such trends were observed across different types of events (respiratory, non-respiratory, and unknown diagnoses).

Table 53 Comparison of general practitioner consultations by OCS use patterns, with stratification by type of consultations

GP Consultations

	All Consultations								
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate/yr	P value
Non OCS	136,266	6,336,992	46.50	46.17	46.84	55.38	25	(9-58)	3.29	
OCS	147,782	8,710,937	58.94	58.61	59.28	48.09	38	(18-76)	3.52	p<0.0001*
Non OCS	136,266	6,336,992	46.50	46.17	46.84	63.12	25	(9-58)	3.29	
One Off	74,257	3,211,507	43.25	42.89	43.60	49.35	28	(13-55)	2.95	
Less Frequent	40,591	2,911,461	71.73	71.04	72.41	70.72	51	(27-92)	3.59	
Frequent	32,934	2,587,969	78.58	77.74	79.42	77.94	54	(28-103)	4.50	p<0.0001**

	Respiratory								
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	54,700	206,828	3.78	3.74	3.82	5.01	2	(1-4)	0.33	
OCS	141,747	1,279,411	9.03	8.98	9.07	8.57	6	(3-12)	1.05	p<0.0001*
Non OCS	54,700	206,828	3.78	3.74	3.82	5.01	2	(1-4)	0.33	
One Off	69,952	431,592	6.17	6.13	6.21	5.68	4	(2-8)	0.81	
Less Frequent	39,735	433,080	10.90	10.81	10.98	8.67	9	(5-14)	1.08	
Frequent	32,060	414,739	12.94	12.81	13.06	11.11	10	(5-17)	1.46	p<0.0001**

	Non Respiratory								
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	136,025	6,130,164	45.07	44.74	45.39	61.66	24	(9-56)	4.70	
OCS	146,775	7,431,526	50.63	50.32	50.94	60.20	31	(14-64)	5.93	p<0.0001*
Non OCS	136,025	6,130,164	45.07	44.74	45.39	61.66	24	(9-56)	4.70	
One Off	73,430	2,779,915	37.86	37.52	38.19	46.46	23	(10-47	5.00	
Less Frequent	40,478	2,478,381	61.23	60.58	61.87	66.22	41	(20-79)	6.08	
Frequent	32,867	2,173,230	66.12	65.34	66.90	72.24	43	(20-86)	7.49	p<0.0001**

* p Values caclulated using Mann-Whitney test

** p values calculated using Chi squared test

Table 54 Comparison of accident and emergency attendances by OCS use patterns, with stratification for the type of attendances

A&E Attendances

	All Consultations									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate/yr	P value
Non OCS	14,758	50,253	3.41	3.34	3.47	3.92	2	(1-4)	0.66	
OCS	33,950	137,973	4.06	3.99	4.14	6.97	3	(1-5)	1.09	p<0.0001*
Non OCS	14,758	50,253	3.41	3.34	3.47	3.92	2	(1-4)	0.66	
One Off	16,976	65,478	3.86	3.74	3.98	8.11	2	(1-5)	1.55	
Less Frequent	9,639	40,183	4.17	4.06	4.28	5.48	3	(1-5)	0.70	
Frequent	7,335	32,312	4.41	4.27	4.54	5.76	3	(1-5)	0.84	p<0.0001**
	Respiratory									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	1,172	1,606	1.37	1.31	1.43	1.09	1	(1-1)	0.23	
OCS	6,174	10,937	1.77	1.71	1.83	2.46	1	(1-2)	0.72	p<0.0001*
Non OCS	1,172	1,606	1.37	1.31	1.43	1.09	1	(1-1)	0.23	
One Off	2,455	3,880	1.58	1.52	1.64	1.59	1	(1-2)	0.53	
Less Frequent	1,920	3,530	1.84	1.71	1.96	2.82	1	(1-2)	0.76	
Frequent	1,799	3,527	1.96	1.82	2.10	2.96	1	(1-2)	0.84	p<0.0001**
	Non Respiratory									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	10,564	27,852	2.64	2.57	2.70	3.26	2	(1-3)	0.67	
OCS	24,397	71,728	2.94	2.88	3.00	4.51	2	(1-3)	1.14	p<0.0001*
Non OCS	10,564	27,852	2.64	2.57	2.70	3.26	2	(1-3)	0.67	
One Off	12,021	33,799	2.81	2.72	2.90	4.98	2	(1-3)	1.55	
Less Frequent	6,987	20,832	2.98	2.89	3.07	3.76	2	(1-3)	0.77	
Frequent	5,389	17,097	3.17	3.06	3.29	4.28	2	(1-3)	0.98	p<0.0001**
	Missing diagnosis									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	9,657	20,795	2.15	2.11	2.19	2.03	1	(1-3)	0.40	
OCS	23,032	55,308	2.40	2.35	2.45	3.96	2	(1-3)	1.00	p<0.0001*
Non OCS	9,657	20,795	2.15	2.11	2.19	4.36	1	(1-3)	0.40	
One Off	11,688	27,799	2.38	2.29	2.47	56.74	2	(1-3)	1.57	
Less Frequent	6,535	15,821	2.42	2.36	2.49	8.27	2	(1-3)	0.53	
Frequent	4,809	11,688	2.43	2.35	2.51	8.38	2	(1-3)	0.57	p<0.0001**

* p Values caclulated using Mann-Whitney test

** p values calculated using Chi squared test

Table 55 Comparison of outpatient attendances by OCS use patterns, with stratification for the type of attendances

Outpatients

	All Consultations									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate/yr	P value
Non OCS	20,182	465,032	23.04	22.60	23.48	32.11	12	(5-29)	0.10	
OCS	43,820	1,116,590	25.48	24.89	26.07	63.35	14	(6-32)	0.11	p=0.0069*
Non OCS	20,182	465,032	23.04	22.60	23.48	32.11	12	(5-29)	0.10	
One Off	21,909	503,945	23.00	21.92	24.08	81.49	12	(5-29)	0.13	
Less Frequent	12,310	326,936	26.56	25.91	27.21	36.78	15	(6-34)	0.10	
Frequent	9,601	285,709	29.76	29.01	30.51	37.35	18	(7-38)	0.11	p<0.0001**
	Respiratory									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	1,330	5,404	4.06	3.74	4.38	5.92	2	(1-4)	0.10	
OCS	5,778	29,892	5.17	4.98	5.37	7.68	4	(1-6)	0.12	p<0.0001*
Non OCS	1,330	5,404	4.06	3.74	4.38	5.92	2	(1-4)	0.10	
One Off	2,162	10,518	4.86	4.57	5.16	6.92	3	(1-5)	0.15	
Less Frequent	1,736	8,581	4.94	4.61	5.28	7.09	3	(1-6)	0.11	
Frequent	1,880	10,793	5.74	5.34	6.14	8.92	3	(1-6)	0.12	p<0.0001**
	Non Respiratory									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	20,146	457,352	22.70	22.27	23.14	31.64	12	(5-28)	0.10	
OCS	43,649	1,081,474	24.78	24.19	25.36	62.56	14	(5-32)	0.11	p<0.0001*
Non OCS	20,146	457,352	22.70	22.27	23.14	31.64	12	(5-28)	0.10	
One Off	21,840	491,265	22.49	21.42	23.56	80.65	12	(5-28)	0.13	
Less Frequent	12,263	316,801	25.83	25.20	26.47	36.07	15	(6-33)	0.10	
Frequent	9,546	273,408	28.64	27.91	29.37	36.21	17	(7-37)	0.11	p<0.0001**
	Unknown diagnosis									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	749	2,276	3.04	2.64	3.43	5.53	2	(1-3)	0.09	
OCS	1,920	5,224	2.72	2.55	2.89	3.82	1	(1-3)	0.11	p=0.2725*
Non OCS	749	2,276	3.04	2.64	3.43	5.53	2	(1-3)	0.09	
One Off	814	2,162	2.66	2.42	2.90	3.50	1	(1-3)	0.11	
Less Frequent	575	1,554	2.70	2.43	2.98	3.36	1	(1-3)	0.09	
Frequent	531	1,508	2.84	2.44	3.24	4.69	1	(1-3)	0.11	p<0.0001**

* p Values caclulated using Mann-Whitney test
** p values calculated using Chi squared test

In regression analysis, OCS users had significantly higher incidence rate of general practitioner consultations, outpatient attendances, and accident and emergency attendances than OCS non-users (Table 56). The highest adjusted incidence rate ratios were observed in frequent OCS users (1.86 [95% confidence interval: 1.82, 1.90], 2.83 [2.61, 3.07], and 1.64 [1.55, 1.73], respectively; adjusted for gender, age, smoking status, BMI, and GINA step; all compared against OCS non-users). Similar patterns were observed for both non-respiratory and respiratory general practitioner consultations (adjusted incidence rate ratios for frequent OCS users vs OCS non-users: 1.64 [1.61, 1.68] and 7.63 [7.40, 7.87], respectively).

Table 56 Incidence rate ratios of GP consultations, outpatient attendances, and accidence and emergency attendances of OCS users, with OCS non-users as reference.

All Events

		Crude IRR			Adjusted IRR		
		IRR	95% CI		IRR	95% CI	
GP Consultation	No OCS	1 (ref)			1 (ref)		
	One Off	1.01	0.99	1.02	1.13	1.11	1.16
	Less Frequent (>=90 days)	1.67	1.65	1.70	1.83	1.79	1.87
	Frequent (<90 days)	1.83	1.80	1.85	1.86	1.82	1.90

		IRR	95% CI		IRR	95% CI	
Outpatients	No OCS	1 (ref)			1 (ref)		
	One Off	2.12	2.03	2.22	2.33	2.18	2.50
	Less Frequent (>=90 days)	2.61	2.46	2.76	2.80	2.59	3.03
	Frequent (<90 days)	2.85	2.68	3.04	2.83	2.61	3.07

		IRR	95% CI		IRR	95% CI	
A&E	No OCS	1 (ref)			1 (ref)		
	One Off	1.54	1.51	1.58	1.44	1.38	1.51
	Less Frequent (>=90 days)	1.71	1.66	1.76	1.63	1.55	1.72
	Frequent (<90 days)	1.72	1.67	1.78	1.64	1.55	1.73

Non Respiratory Events

	Crude IRR			Adjusted IRR		
	IRR	95% CI		IRR	95% CI	
No OCS	1 (ref)			1 (ref)		
One Off	0.90	0.89	0.91	1.04	1.02	1.06
Less Frequent (>=90 days)	1.47	1.45	1.49	1.64	1.60	1.67
Frequent (<90 days)	1.58	1.56	1.61	1.64	1.61	1.68

Respiratory Events

	Crude IRR			Adjusted IRR		
	IRR	95% CI		IRR	95% CI	
No OCS	1 (ref)			1 (ref)		
One Off	4.15	4.08	4.22	3.77	3.67	3.87
Less Frequent (>=90 days)	7.64	7.48	7.80	6.95	6.74	7.16
Frequent (<90 days)	8.98	8.78	9.19	7.63	7.40	7.87

OCS users also showed higher mean episodes and annualized rates of all admissions (

Table 57) and day case admissions (Table 58) than the non-OCS group. Although OCS users consistently had more admissions for a primary respiratory diagnosis (0.24 admissions per year for the OCS group vs 0.16 admissions per year for the non-OCS group, and 0.18 day cases per year for the OCS group vs 0.12 day cases per year for the non-OCS group) or any diagnoses that included asthma (0.37 admissions per year for the OCS group vs 0.27 admissions per year for the non-OCS group, and 0.29 day cases per year for the OCS group vs 0.21 day cases per year for the non-OCS group), there were no significant differences between OCS users and OCS-naïve patients in terms of admissions for a primary asthma diagnosis.

Table 57 Comparison of all admissions by OCS use patterns, with stratification for the type of admissions

All Admissions (spells)

	All Consultations									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate/yr	P value
Non OCS	16,503	92,193	5.59	5.34	5.83	16.01	3	(1-6)	0.57	
OCS	37,662	226,262	6.01	5.78	6.23	22.45	3	(2-7)	0.68	p<0.0001*
Non OCS	16,503	92,193	5.59	5.34	5.83	16.01	3	(1-6)	0.57	
One Off	17,864	94,223	5.27	5.02	5.53	17.67	3	(1-6)	0.67	
Less Frequent	10,760	63,513	5.90	5.74	6.06	8.52	4	(2-7)	0.57	
Frequent	9,038	68,526	7.58	6.81	8.35	37.34	4	(2-8)	0.82	p<0.0001**

	Respiratory as Primary									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	2,385	3,843	1.61	1.55	1.68	1.63	1	(1-2)	0.16	
OCS	10,213	20,607	2.02	1.96	2.08	3.23	1	(1-2)	0.24	p<0.0001*
Non OCS	2,385	3,843	1.61	1.55	1.68	1.63	1	(1-2)	0.16	
One Off	3,793	6,581	1.74	1.67	1.80	1.95	1	(1-2)	0.25	
Less Frequent	3,039	6,043	1.99	1.88	2.09	2.93	1	(1-2)	0.21	
Frequent	3,381	7,983	2.36	2.21	2.51	4.40	1	(1-2)	0.27	p<0.0001**

	Asthma as Primary									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	53	69	1.30	1.10	1.50	0.75	1	(1-1)	0.15	
OCS	2,701	4,357	1.61	1.48	1.75	3.52	1	(1-1)	0.21	p=0.4602*
Non OCS	53	69	1.30	1.10	1.50	0.75	1	(1-1)	0.15	
One Off	931	1,313	1.41	1.32	1.50	1.40	1	(1-1)	0.24	
Less Frequent	892	1,367	1.53	1.42	1.65	1.75	1	(1-1)	0.17	
Frequent	878	1,677	1.91	1.53	2.29	5.73	1	(1-1)	0.22	p<0.0001**

	Any Asthma									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	1,101	2,716	2.47	2.29	2.64	2.93	1	(1-3)	0.27	
OCS	23,510	75,685	3.22	3.11	3.33	8.68	2	(1-4)	0.37	p<0.0001*
Non OCS	1,101	2,716	2.47	2.29	2.64	2.93	1	(1-3)	0.27	
One Off	10,519	31,387	2.98	2.81	3.16	9.29	2	(1-3)	0.41	
Less Frequent	7,163	22,625	3.16	3.07	3.25	3.84	2	(1-4)	0.31	
Frequent	5,828	21,673	3.72	3.43	4.01	11.38	2	(1-4)	0.40	p<0.0001**

* p Values caclulated using Mann-Whitney test
** p values calculated using Chi squared test

Table 58 Comparison of day case admissions by OCS use patterns, with stratification for the type of admissions

Day cases (spells)

	All Consultations									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate/yr	P value
Non OCS	13,204	55,355	4.19	3.91	4.48	16.65	2	(1-4)	0.42	
OCS	30,564	129,045	4.22	3.97	4.48	22.72	2	(1-4)	0.47	p<0.0001*
Non OCS	13,204	55,355	4.19	3.91	4.48	16.65	2	(1-4)	0.42	
One Off	14,383	54,676	3.80	3.55	4.05	15.29	2	(1-4)	0.48	
Less Frequent	8,831	34,848	3.95	3.81	4.09	6.73	2	(1-4)	0.38	
Frequent	7,350	39,521	5.38	4.45	6.30	40.40	2	(1-5)	0.57	p<0.0001**
	Respiratory as Primary									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	659	779	1.18	1.13	1.23	0.64	1	(1-)	0.12	
OCS	3,202	4,636	1.45	1.35	1.55	2.89	1	(1-1)	0.18	p=0.0003*
Non OCS	659	779	1.18	1.13	1.23	0.64	1	(1-1)	0.12	
One Off	1,241	1,669	1.34	1.26	1.43	1.46	1	(1-1)	0.19	
Less Frequent	990	1,344	1.36	1.24	1.48	1.91	1	(1-1)	0.14	
Frequent	971	1,623	1.67	1.38	1.96	4.58	1	(1-1)	0.20	p<0.0001**
	Asthma as Primary									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	12	13	1.08	0.92	1.25	0.29	1	(1-1)	0.14	
OCS	849	1,199	1.41	1.15	1.67	3.87	1	(1-1)	0.19	p=0.5701*
Non OCS	12	13	1.08	0.92	1.25	0.29	1	(1-1)	0.14	
One Off	280	329	1.18	1.10	1.25	0.68	1	(1-1)	0.21	
Less Frequent	311	392	1.26	1.15	1.37	0.97	1	(1-1)	0.14	
Frequent	258	478	1.85	1.01	2.69	6.88	1	(1-1)	0.23	p<0.0001**
	Any Asthma									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	687	1,357	1.98	1.82	2.13	2.09	1	(1-2)	0.21	
OCS	16,203	40,504	2.50	2.35	2.65	9.51	1	(1-2)	0.29	p=0.0001*
Non OCS	687	1,357	1.98	1.82	2.13	2.09	1	(1-2)	0.21	
One Off	7,238	17,425	2.41	2.17	2.65	10.32	1	(1-2)	0.34	
Less Frequent	5,003	11,763	2.35	2.27	2.43	2.99	1	(1-3)	0.23	
Frequent	3,962	11,316	2.86	2.46	3.25	12.80	2	(1-3)	0.30	p<0.0001**

* p Values caclulated using Mann-Whitney test
** p values calculated using Chi squared test

Among OCS users, frequent users again had the most admissions (both p<0.0001). Nonetheless, despite this trend being observed for admissions for a primary respiratory diagnosis, one-off OCS users had the most admissions instead for a primary asthma diagnosis or any diagnosis that included asthma, followed by frequent OCS users. Similar patterns were observed when day cases were excluded from the analysis (Supplemental Table 30).

The increases in admission episodes were accompanied by longer mean and annualized lengths of admissions (Table 59) in OCS users as compared to the non-OCS group. When stratified for the diagnoses underlying these admissions, there was no significant difference

in length of stay for primary asthmatic admissions (p=0.3932). Meanwhile, the length of stay for any diagnosis that included asthma was significantly longer in OCS users, while that for a primary respiratory diagnosis was numerically longer in the same patients, with the difference approaching statistical significance. Among OCS users, frequent OCS users had the longest length of stay.

Table 59 Comparison of length of stay during all admissions by OCS use patterns, with stratification for the type of admissions. The rate of length of stay referred to the estimated days of attendance per year.

Admissions (Length of stay)

	All Consultations									
	Patients	Days	Mean	95% CI		SD	Median	IQR	Rate/yr	P value
Non OCS	16,503	315,101	19.09	17.97	20.22	73.55	3	(0-14)	1.95	
OCS	37,662	734,763	19.51	18.87	20.15	63.17	4	(1-15)	2.20	p<0.0001*
Non OCS	16,503	315,101	19.09	17.97	20.22	73.55	3	(0-14)	1.95	
One Off	17,864	285,565	15.99	15.10	16.87	60.50	3	(0-10)	2.04	
Less Frequent	10,760	213,589	19.85	18.53	21.17	69.71	4	(1-15)	1.93	
Frequent	9,038	235,609	26.07	24.84	27.30	59.51	6	(1-25	2.83	p<0.0001**
	Respiratory as Primary									
	Patients	Days	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	2,385	30,617	12.84	11.90	13.77	23.35	4	(1-15)	1.28	
OCS	10,213	127,736	12.51	11.98	13.04	27.36	3	(1-13)	1.51	p=0.0594*
Non OCS	2,385	30,617	12.84	11.90	13.77	23.35	4	(1-15)	1.28	
One Off	3,793	37,977	10.01	9.36	10.66	20.36	2	(1-10)	1.43	
Less Frequent	3,039	36,134	11.89	10.96	12.82	26.19	3	(1-1)	1.27	
Frequent	3,381	53,625	15.86	14.71	17.01	34.08	5	(1-16)	1.83	p<0.0001**
	Asthma as Primary									
	Patients	Days	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	53	266	5.02	2.96	7.07	7.63	2	(1-6)	0.57	
OCS	2,701	12,719	4.71	4.25	5.16	12.06	2	(1-5)	0.60	p=0.3932*
Non OCS	53	266	5.02	2.96	7.07	7.63	2	(1-6)	0.57	
One Off	931	3,846	4.13	3.46	4.81	10.50	2	(1-4)	0.70	
Less Frequent	892	3,497	3.92	3.40	4.44	7.96	2	(1-4)	0.43	
Frequent	878	5,376	6.12	5.05	7.20	16.22	3	(1-6)	0.71	p<0.0001**
	Any Asthma									
	Patients	Days	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	1,101	11,487	10.43	6.98	13.88	58.40	1	(0-6)	1.12	
OCS	23,510	220,395	9.37	8.98	9.77	30.61	2	(0-7)	1.08	p=0.0004*
Non OCS	1,101	11,487	10.43	6.98	13.88	58.40	1	(0-6)	1.12	
One Off	10,519	86,105	8.19	7.54	8.83	33.55	2	(0-6)	1.13	
Less Frequent	7,163	66,519	9.29	8.61	9.96	29.23	2	(0-7)	0.92	
Frequent	5,828	67,771	11.63	10.95	12.30	26.27	3	(0-11)	1.24	p<0.0001**

* p Values caclulated using Mann-Whitney test

** p values calculated using Chi squared test

However, when day cases were excluded from the analysis of length of stay, no significant differences were observed between OCS users and OCS-naïve patients (Table 60)

Nevertheless, OCS users still had longer hospitalizations for primary respiratory diagnoses (p=0.0014) or any diagnosis that included asthma. Among OCS users, frequent OCS users had the longest length of stay in all admissions and admissions for primary respiratory diagnoses. This was, however, not the case for admissions for a primary asthma diagnosis or any diagnosis that included asthma, for which one-off users had the longest stays.

Table 60 The rate of length of stay referred to the estimated days of attendance per year.

Admissions, excluding day cases (Length of stay)

	All Consultations									
	Patients	Days	Mean	95% CI		SD	Median	IQR	Rate/yr	P value
Non OCS	11,810	315,101	26.68	25.13	28.23	85.77	7	(2-24)	2.71	
OCS	28,343	734,763	25.92	25.09	26.76	71.67	7	(2-23)	2.91	p=0.4662*
Non OCS	11,810	315,101	26.68	25.13	28.23	85.77	7	(2-24)	2.71	
One Off	12,801	285,565	22.31	21.09	23.53	70.48	6	(2-17)	2.83	
Less Frequent	8,193	213,589	26.07	24.36	27.78	78.87	7	(3-23)	2.54	
Frequent	7,349	235,609	32.06	30.58	33.54	64.53	10	(3-34)	3.47	p<0.0001**
	Respiratory as Primary									
	Patients	Days	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	1,929	30,617	15.87	14.76	16.99	25.02	7	(2-19)	1.58	
OCS	8,322	127,736	15.35	14.71	15.98	29.58	5	(2-16)	1.87	p=0.0014*
Non OCS	1,929	30,617	15.87	14.76	16.99	25.02	7	(2-19)	1.58	
One Off	2,979	37,977	12.75	11.95	13.55	22.20	4	(2-14)	1.84	
Less Frequent	2,460	36,134	14.69	13.57	15.81	28.39	5	(2-15)	1.57	
Frequent	2,883	53,625	18.60	17.28	19.92	36.21	7	(3-20)	2.15	p<0.0001**
	Asthma as Primary									
	Patients	Days	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	43	266	6.19	3.78	8.59	8.04	3	(2-6)	0.69	
OCS	2,104	12,719	6.05	5.47	6.62	13.36	3	(1-6)	0.77	p=0.5253*
Non OCS	43	266	6.19	3.78	8.59	8.04	3	(1-6)	0.69	
One Off	719	3,846	5.35	4.50	6.20	11.68	2	(1-6)	0.91	
Less Frequent	671	3,497	5.21	4.55	5.88	8.80	3	(1-6)	0.59	
Frequent	714	5,376	7.53	6.23	8.83	17.70	3	(2-7)	0.86	p<0.0001**
	Any Asthma									
	Patients	Days	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	711	11,487	16.16	10.86	21.45	72.06	4	(2-10)	1.75	
OCS	16,115	220,395	13.68	13.12	14.23	36.17	5	(2-12)	1.58	p=0.0232*
Non OCS	711	11,487	16.16	10.86	21.45	72.06	4	(2-10)	1.75	
One Off	6,880	86,105	12.52	11.55	13.48	40.83	4	(2-11)	1.73	
Less Frequent	4,940	66,519	13.47	12.51	14.42	34.40	5	(2-12)	1.34	
Frequent	4,295	67,771	15.78	14.90	16.66	29.51	6	(2-16)	1.67	p<0.0001**

* p Values caclulated using Mann-Whitney test
** p values calculated using Chi squared test

Additionally, OCS users required significantly more prescriptions from any cause (median 74 prescriptions, IQR 27-205 prescriptions; 21.72 prescriptions per year) than non-users (median 33 prescriptions, IQR 8-139 prescriptions; 15.50 prescriptions per year; Table 61),

regardless of the type of prescriptions. Frequent OCS users had the most prescriptions, regardless of the type of prescriptions.

Table 61 Comparison of the number of prescriptions by OCS use patterns, with stratification for the type of prescriptions

Prescriptions

	All Consultations									
	Patients	Records	Mean	95% CI		SD	Median	IQR	Rate/yr	P value
Non OCS	128,497	18,301,835	142.43	140.82	144.04	293.90	33	(8-139)	15.50	
OCS	148,118	27,226,646	183.82	182.21	185.42	314.97	74	(27-205)	21.72	p<0.0001*
Non OCS	128,497	18,301,835	142.43	140.82	144.04	293.90	33	(8-139)	15.50	
One Off	73,976	9,346,657	126.35	124.56	128.13	247.67	46	(46-17)	16.89	
Less Frequent	40,870	9,023,645	220.79	217.52	224.06	337.35	102	(42-259)	21.99	
Frequent	33,272	8,856,344	266.18	262.02	270.34	386.86	132	(52-327)	30.43	p<0.0001**
	Respiratory[1]									
	Patients	Records	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	21,926	303,704	13.85	13.45	14.26	30.53	3	(1-12)	1.51	
OCS	132,373	4,914,211	37.12	36.84	37.41	53.00	18	(6-46)	4.39	p<0.0001*
Non OCS	21,926	303,704	13.85	13.45	14.26	30.53	3	(1-12)	1.51	
One Off	63,132	1,672,766	26.50	26.18	26.81	40.11	12	(4-31)	3.54	
Less Frequent	38,200	1,709,940	44.76	44.18	45.35	58.37	24	(9-58)	4.46	
Frequent	31,041	1,531,505	49.34	48.63	50.05	63.73	27	(10-63)	5.64	p<0.0001**
	Non Respiratory[2]									
	Patients	Records	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	128,053	17,998,131	140.55	138.95	142.15	291.91	31	(8-137)	15.30	
OCS	145,758	22,312,435	153.08	151.56	154.60	296.44	49	(15-160)	18.09	p<0.0001*
Non OCS	128,053	17,998,131	140.55	138.95	142.15	291.91	31	(8-137)	15.30	
One Off	71,774	7,673,891	106.92	105.19	108.65	236.48	30	(9-99)	14.30	
Less Frequent	40,782	7,313,705	179.34	176.26	182.41	317.03	65	(22-198)	17.86	
Frequent	33,202	7,324,839	220.61	216.71	224.51	362.53	91	(31-263)	25.22	p<0.0001**

* p values caclulated using Mann-Whitney test

** p values calculated using Chi squared test

ɜiratory defined by precriptions denoted asbeing in BNF Chapter 3

n respiratory defined as prescriptions ot being within BNF chapter 3

In regression analysis, less frequent and frequent OCS users, but not one-off OCS users, had significantly higher incidence rates of admissions and prescriptions than OCS non-users (Table 62). The highest adjusted incidence rate ratios were observed for frequent OCS users (2.25 [2.16, 2.50], and 1.73 [1.68, 1.79], respectively; adjusted for gender, age, smoking status, BMI, and GINA step; all compared against OCS non-users). For non-respiratory admissions and prescriptions, whilst both less frequent and frequent OCS users had significantly higher incidence rates than OCS non-users, with increase in incidence rates being more pronounced in frequent OCS users, one-off OCS users had significantly lower incidence rates of both admissions and prescriptions than OCS non-users. Meanwhile, OCS users had significantly higher adjusted incidence rates of respiratory admissions and prescriptions than OCS non-users across all OCS use patterns, with an increasing trend of adjusted incidence rate ratios with more frequent OCS use patterns (highest in frequent users: 7.92 [7.77, 8.17] for admissions, and 19.47 [18.53, 20.46] for prescriptions).

Table 62 Incidence rate ratios of admissions and prescriptions of OCS users, with OCS non-users as reference.

	All Events	Crude IRR			Adjusted IRR		
		IRR	95% CI		IRR	95% CI	
Admissions	No OCS	1 (ref)			1 (ref)		
	One Off	1.11	0.90	1.14	1.08	0.92	1.13
	Less Frequent (>=90 days)	1.59	1.49	1.65	1.55	1.46	1.61
	Frequent (<90 days)	2.34	2.18	2.52	2.25	2.16	2.50
Prescriptions	No OCS	1 (ref)			1 (ref)		
	One Off	0.89	0.87	0.90	0.97	0.95	1.00
	Less Frequent (>=90 days)	1.55	1.52	1.58	1.64	1.59	1.70
	Frequent (<90 days)	1.87	1.83	1.91	1.73	1.68	1.79

	Non Respiratory Events	Crude IRR			Adjusted IRR		
		IRR	95% CI		IRR	95% CI	
Admissions	No OCS	1 (ref)			1 (ref)		
	One Off	0.92	0.89	0.95	0.80	0.78	0.84
	Less Frequent (>=90 days)	1.31	1.26	1.36	1.25	1.22	1.28
	Frequent (<90 days)	1.97	1.93	2.02	1.88	2.58	2.08
Prescriptions	No OCS	1 (ref)			1 (ref)		
	One Off	0.74	0.73	0.75	0.85	0.82	0.87
	Less Frequent (>=90 days)	1.28	1.25	1.31	1.41	1.36	1.46
	Frequent (<90 days)	1.57	1.53	1.61	1.51	1.46	1.57

	Respiratory Events	Crude IRR			Adjusted IRR		
		IRR	95% CI		IRR	95% CI	
Admissions	No OCS	1 (ref)			1 (ref)		
	One Off	3.32	2.86	3.86	3.00	2.86	3.49
	Less Frequent (>=90 days)	4.95	4.39	5.75	4.66	4.06	4.95
	Frequent (<90 days)	8.17	7.39	9.03	7.92	7.77	8.17
Prescriptions	No OCS	1 (ref)			1 (ref)		
	One Off	9.57	9.22	9.93	9.57	9.22	9.93
	Less Frequent (>=90 days)	17.70	16.91	18.53	17.70	16.91	18.53
	Frequent (<90 days)	19.47	18.53	20.46	19.47	18.53	20.46

7.4.3.1 A&E and outpatient costs related to specific OCS-related morbidities

When broken down by causes that were OCS-related morbidities, OCS users had higher cause-specific per-patient healthcare costs for both A&E (Table 63 and Figure 37) and outpatient (Table 64 and Figure 39) attendances, which was also observed for annualized per-patient costs (A&E: Figure 38; outpatient: Figure 40) than the non-OCS group. Among OCS users, frequent OCS users had the highest overall and annualized healthcare costs for most causes of attendances. Among A&E attendances with non-missing causes that were OCS-related, attendances due to cardiovascular diseases incurred the highest costs, followed by peptic ulcer (Table 63). Among outpatient attendances with non-missing causes that were OCS-related, attendances due to T2DM incurred the highest costs, followed by osteoporosis (Table 64).

Table 63 Comparison of cause-specific per-patient healthcare costs for A&E attendances by OCS use patterns.

A&E		OCS	95% CI		OCS Naïve	95% CI		One Off	95% CI		Less Frequent	95% CI		Frequent	95% CI	
All Cause	Total Cost	£23,200,052			£8,502,815			£11,037,601			£6,755,844			£5,406,607		
	Patients	106,410			85,548			53,002			29,517			23,894		
	£ per patient	£155.57	£152.27	£158.86	£57.02	£55.63	£58.39	£147.21	£141.95	£152.46	£165.28	£159.99	£170.57	£162.47	£156.49	£168.44
A&E		OCS	95% CI		OCS Naïve	95% CI		One Off	95% CI		Less Frequent	95% CI		Frequent	95% CI	
Missing	Total Cost	£13,953,716			£5,231,254			£6,848,078			£4,016,722			£3,088,917		
	Patients	33,160			13,789			16,538			9,458			7,164		
	£ per patient	£93.57	£91.00	£96.00	£35.08	£34.00	£36.00	£91.33	£88.00	£95.00	£98.27	£95.00	£101.00	£92.82	£89.00	£96.00
Anxiety/	Total Cost	£313,339			£122,492			£162,047			£82,026			£69,266		
Depression	Patients	1,036			411			523			283			230		
	£ per patient	£2.10	£1.90	£2.31	£0.82	£0.70	£0.94	£2.16	£1.83	£2.49	£2.01	£1.66	£2.36	£2.08	£1.73	£2.43
Peptic ulcer	Total Cost	£1,240,962			£467,184			£572,177			£360,185			£308,600		
	Patients	4,401			1,774			2,087			1,271			1,043		
	£ per patient	£8.32	£7.93	£8.72	£3.13	£2.93	£3.33	£7.63	£7.17	£8.09	£8.81	£8.17	£9.46	£9.27	£8.07	£10.47
Other	Total Cost	£5,730,519			£1,839,205			£2,544,447			£1,717,078			£1,468,995		
Cause	Patients	20,529			7,387			9,626			6,009			4,894		
	£ per patient	£38.43	£37.42	£39.43	£12.33	£11.89	£12.78	£33.94	£32.65	£35.22	£42.01	£40.03	£43.98	£44.14	£41.71	£46.58
CVD	Total Cost	£1,268,669			£524,055			£568,714			£375,861			£324,094		
	Patients	4,822			2,099			2,177			1,404			1,241		
	£ per patient	£8.51	£8.14	£8.87	£3.51	£3.30	£3.72	£7.58	£7.04	£8.13	£9.20	£8.54	£9.85	£10	£9.04	£10.44
Cataract/	Total Cost	£597,332			£268,316			£301,856			£172,437			£123,039		
glaucoma	Patients	2,459			1,100			1,233			717			509		
	£ per patient	£4.01	£3.81	£4.21	£1.80	£1.66	£1.93	£4.03	£3.73	£4.32	£4.22	£3.84	£4.60	£3.70	£3.31	£4.09
T2DM	Total Cost	£95,515			£50,309			£40,284			£31,534			£23,696		
	Patients	378			181			161			123			94		
	£ per patient	£0.64	£0.55	£0.73	£0.34	£0.26	£0.42	£0.54	£0.42	£0.65	£0.77	£0.60	£0.95	£0.71	£0.52	£0.90

Figure 37 Comparison of cause-specific per-patient healthcare costs for A&E attendances by OCS use patterns. “Other causes” refer to causes that were non-missing and not any of anxiety / depression, peptic ulcer, cardiovascular disease, cataract / glaucoma, type 2 diabetes mellitus.

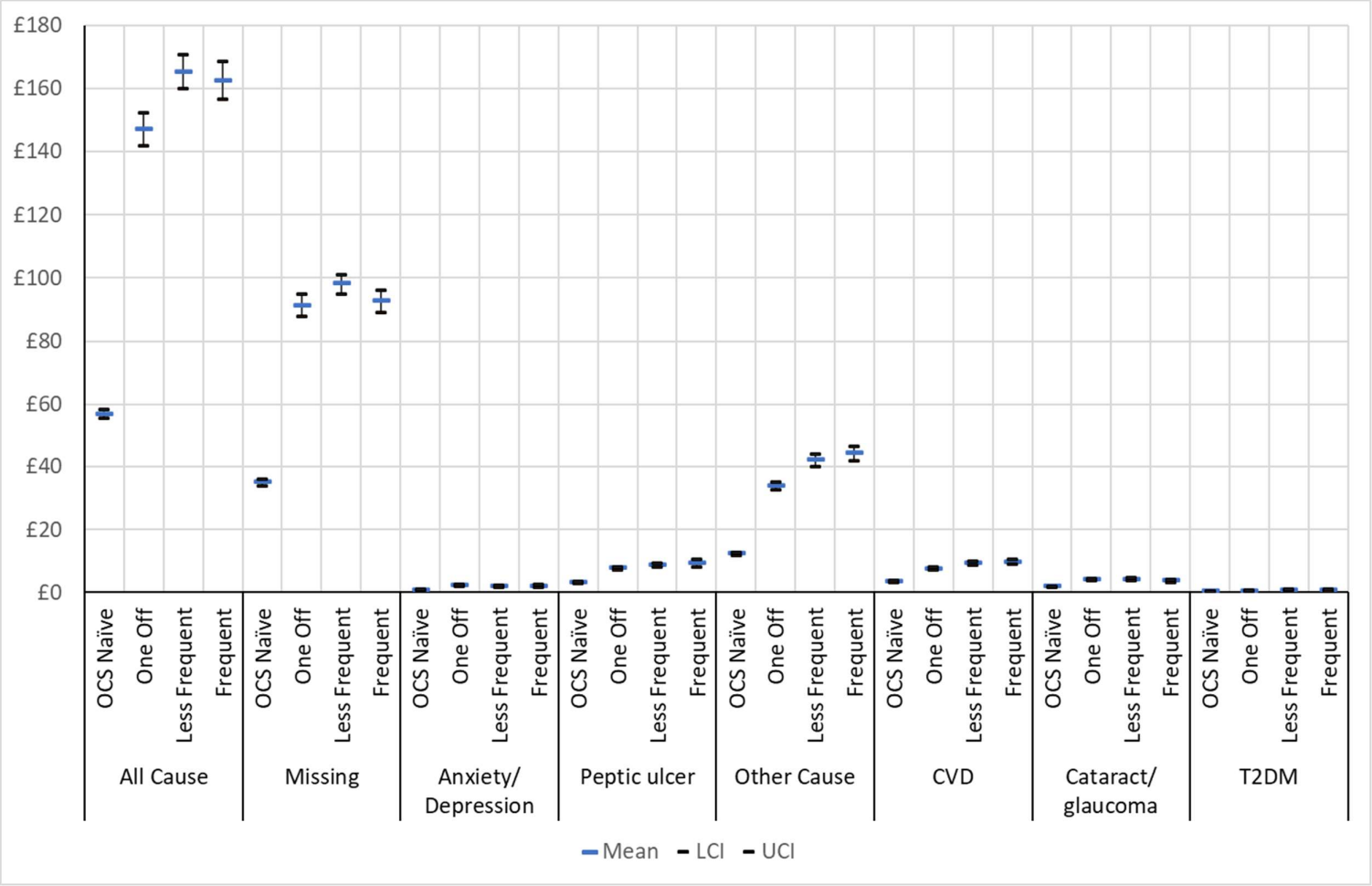


Figure 38 Comparison of the annualized cause-specific per-patient healthcare costs for A&E attendances by OCS use patterns. “Other causes” refer to causes that were non-missing and not any of anxiety / depression, peptic ulcer, cardiovascular disease, cataract / glaucoma, type 2 diabetes mellitus.

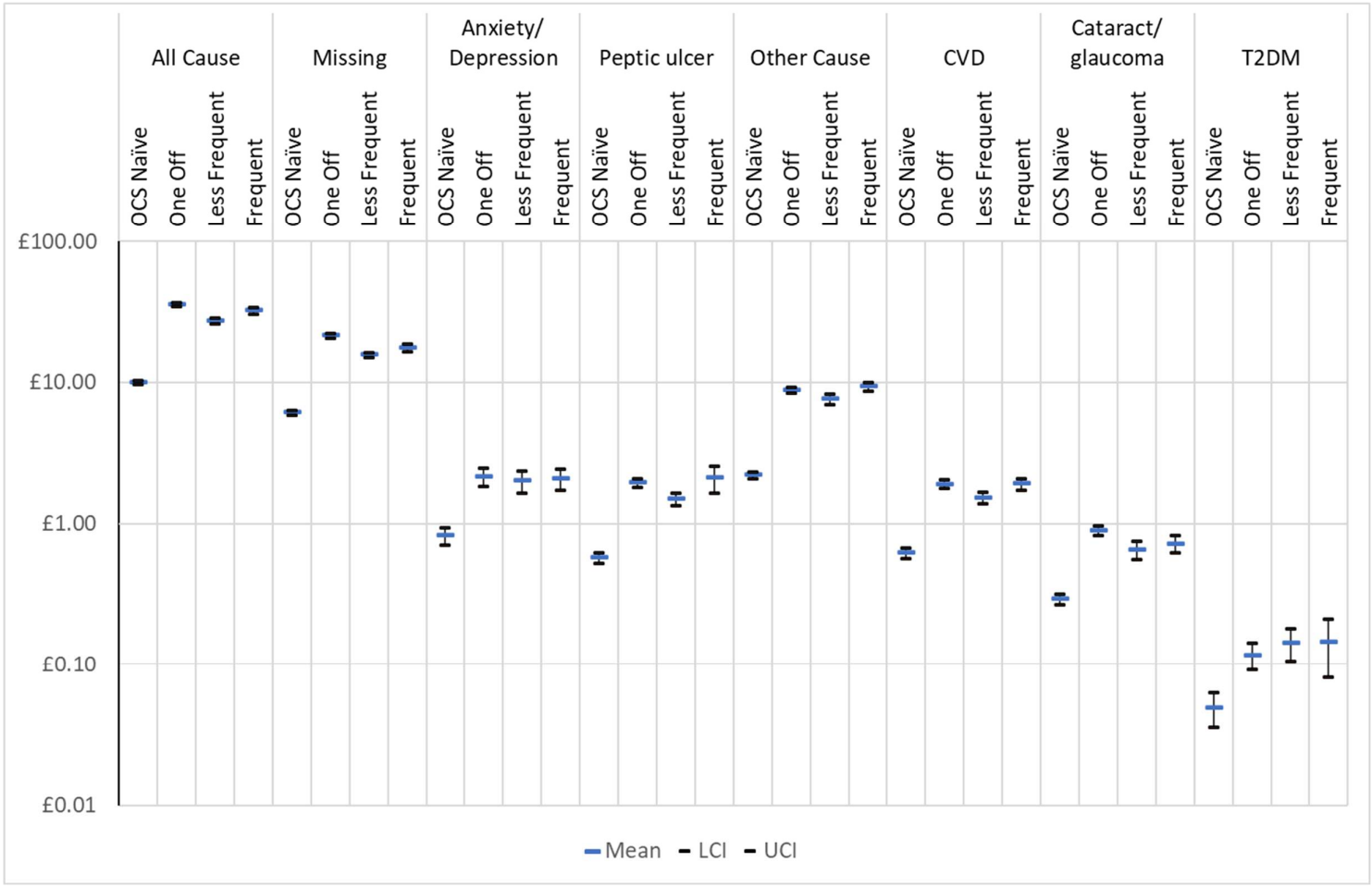


Table 64 Comparison of cause-specific per-patient healthcare costs for outpatient attendances by OCS use patterns.

Outpatients		OCS	95% CI		OCS Naïve	95% CI		One Off	95% CI		Less Frequent	95% CI		Frequent	95% CI	
All Cause	Total Cost	£199,323,856			£82,377,136			£87,942,648			£58,885,920			£52,495,288		
	Patients	158,431			66,492			72,336			46,051			40,044		
	£ per patient	£1,337	£1,303	£1,370	£552	£538	£566	£1,173	£1,114	£1,232	£1,441	£1,396	£1,485	£1,578	£1,528	£1,627
Outpatients		OCS	95% CI		OCS Naïve	95% CI		One Off	95% CI		Less Frequent			Frequent	95% CI	
Other	Total Cost	£91,575,904			£38,139,120			£42,506,504			£26,467,560			£22,601,836		
	Patients	39,788			18,152			19,795			11,184			8,809		
	£ per patient	£614	£598	£630	£256	£249	£262	£567	£538	£596	£648	£627	£668	£679	£656	£702
T2DM	Total Cost	£21,651,570			£9,591,345			£8,964,405			£6,651,855			£6,035,310		
	Patients	19,700			8,303			8,807			5,748			5,145		
	£ per patient	£145	£140	£150	£64	£61	£67	£120	£112	£127	£163	£153	£173	£181	£172	£190
Osteo-porosis	Total Cost	£18,532,935			£8,051,940			£8,344,755			£5,565,240			£4,622,940		
	Patients	21,124			9,099			10,107			6,146			4,871		
	£ per patient	£124	£121	£127	£54	£52	£56	£111	£106	£116	£136	£131	£141	£139	£133	£145
Cardio-vascular	Total Cost	£16,015,860			£6,572,610			£6,787,800			£4,739,850			£4,488,210		
	Patients	18,126			7,448			7,925			5,381			4,820		
	£ per patient	£107	£104	£111	£44	£42	£46	£91	£85	£96	£116	£111	£121	£135	£128	£141
Cataract/ glaucoma	Total Cost	£11,805,750			£5,581,035			£4,974,480			£3,604,230			£3,227,040		
	Patients	12,418			5,678			5,529			3,637			3,252		
	£ per patient	£79	£76	£82	£37	£36	£39	£66	£62	£71	£88	£83	£93	£97	£91	£103
Hyperten-sion	Total Cost	£12,308,085			£4,821,795			£5,115,690			£3,672,810			£3,519,585		
	Patients	15,355			6,063			6,599			4,552			4,204		
	£ per patient	£83	£80	£85	£32	£31	£34	£68	£64	£72	£90	£85	£95	£106	£100	£111
Potential Pneumonia	Total Cost	£11,448,675			£3,365,820			£4,429,890			£3,391,065			£3,627,720		
	Patients	14,069			4,749			5,812			4,200			4,057		
	£ per patient	£77	£74	£79	£23	£21	£24	£59	£55	£63	£83	£78	£88	£109	£103	£115
Peptic ulcer	Total Cost	£9,440,685			£3,570,615			£3,912,705			£2,818,395			£2,709,585		
	Patients	13,477			5,211			5,769			3,975			3,733		
	£ per patient	£63	£61	£66	£24	£23	£25	£52	£48	£56	£69	£65	£73	£81	£77	£86
Anxiety/ Depression	Total Cost	£5,259,870			£1,858,680			£2,472,660			£1,494,720			£1,292,490		
	Patients	3,466			1,342			1,629			967			870		
	£ per patient	£35	£33	£38	£12	£11	£14	£33	£29	£37	£37	£31	£42	£39	£33	£44
Renal	Total Cost	£1,284,525			£824,175			£433,755			£480,195			£370,575		
	Patients	908			447			364			261			283		
	£ per patient	£9	£6	£11	£6	£4	£7	£6	£4	£7	£12	£5	£18	£11	£7	£15

Figure 39 Comparison of cause-specific per-patient healthcare costs for outpatient attendances by OCS use patterns. “Other” refers to causes that were non-missing and not any of anxiety / depression, peptic ulcer, cardiovascular disease, cataract / glaucoma, type 2 diabetes mellitus.

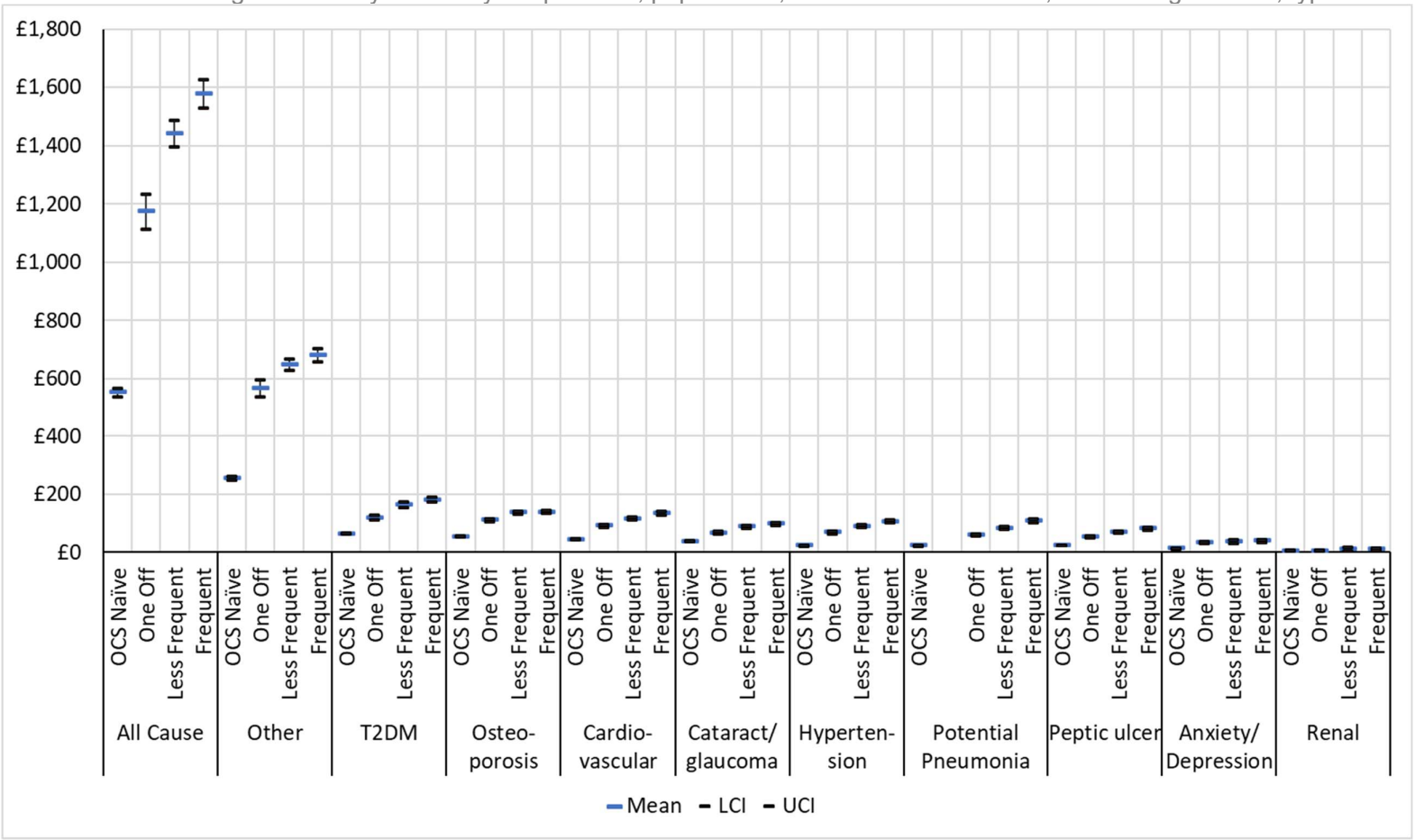
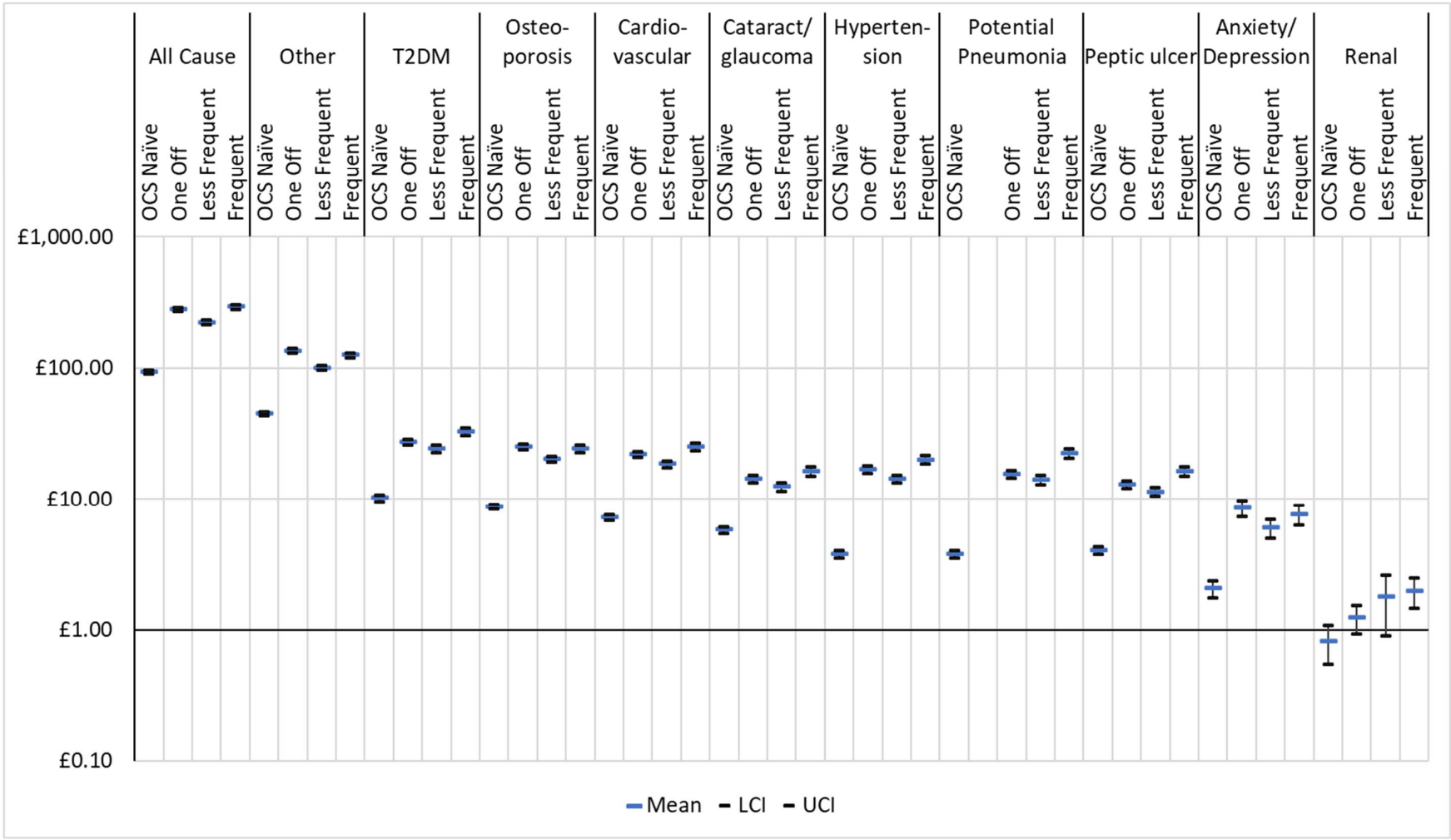


Figure 40 Comparison of the annualized cause-specific per-patient healthcare costs for outpatient attendances by OCS use patterns. “Other” refers to causes that were non-missing and not any of anxiety / depression, peptic ulcer, cardiovascular disease, cataract / glaucoma, type 2 diabetes mellitus.



7.4.4 Objective 4

Patients with more frequent OCS use patterns had higher cumulative OCS doses (Table 65).

Table 65 Comparison of the median cumulative OCS dosage between OCS use pattern categories.

OCS Dose by Sequence Cass

	OCS Sequence Categories		
	One Off	**Less Frequent**	**Frequent**
Median OCS Dose	150mg	420mg	940mg

Compared to the non-OCS group, patients with higher cumulative OCS dose generally had higher unadjusted and adjusted incidence rates of adverse events (Table 66 and Figure 41 [adjusted estimates]), with particularly strong effects observed for sleep apnoea, depression/anxiety, and pneumonia.

Table 66 Incidence rate ratios (IRRs) for each category of cumulative OCS doses for each adverse event, compared against the non-OCS group and adjusted for age, gender, smoking status, and BMI.

Adverse Group	Group	Crude IRR	LCI	UCI	Adjusted IRR [1]	LCI	UCI
T2 Diabetes	Reference Group	1			1		
	>0 to <0.5 g	1.30	1.29	1.30	1.34	1.31	1.37
	0.5 to <1.0 g	1.60	1.57	1.62	1.64	1.60	1.69
	1.0 to <2.5 g	1.74	1.71	1.78	1.87	1.82	1.92
	2.5 to <5 g	1.86	1.77	1.94	2.11	2.02	2.21
	5 to <10 g	2.10	1.93	2.26	2.26	2.12	2.42
	≥10 g	2.32	2.05	2.57	2.65	2.44	2.88
Cataracts	Reference Group	1			1		
	>0 to <0.5 g	0.97	0.96	0.98	1.50	1.47	1.53
	0.5 to <1.0 g	1.27	1.24	1.29	1.46	1.42	1.49
	1.0 to <2.5 g	1.43	1.39	1.46	1.50	1.47	1.54
	2.5 to <5 g	1.60	1.51	1.68	1.51	1.45	1.57
	5 to <10 g	1.82	1.66	1.98	1.40	1.32	1.49
	≥10 g	2.22	1.94	2.48	1.75	1.62	1.88
Cardiovascular	Reference Group	1			1		
	>0 to <0.5 g	1.08	1.08	1.09	1.24	1.21	1.27
	0.5 to <1.0 g	1.38	1.35	1.41	1.43	1.38	1.48
	1.0 to <2.5 g	1.53	1.49	1.57	1.57	1.52	1.63
	2.5 to <5 g	1.60	1.51	1.69	1.61	1.53	1.70
	5 to <10 g	1.57	1.41	1.72	1.61	1.48	1.74

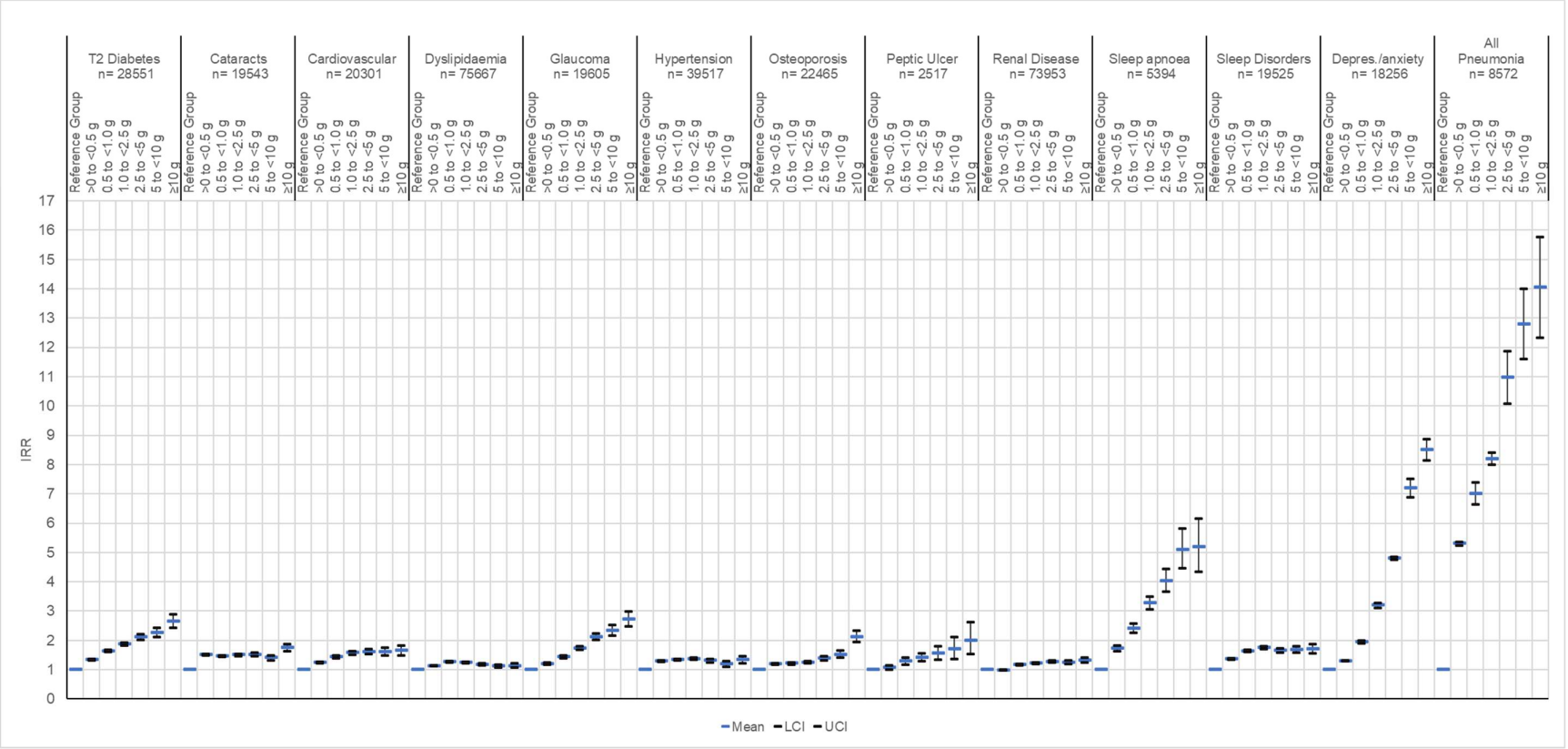
	≥10 g	1.86	1.60	2.10	1.65	1.48	1.84
Dyslipidaemia	Reference Group	1			1		
	>0 to <0.5 g	1.16	1.16	1.16	1.13	1.11	1.14
	0.5 to <1.0 g	1.20	1.18	1.21	1.27	1.25	1.29
	1.0 to <2.5 g	1.08	1.06	1.10	1.23	1.21	1.26
	2.5 to <5 g	0.97	0.93	1.00	1.18	1.15	1.22
	5 to <10 g	0.93	0.87	0.99	1.12	1.07	1.17
	≥10 g	1.00	0.91	1.10	1.13	1.06	1.21
Glaucoma	Reference Group	1			1		
	>0 to <0.5 g	1.20	1.19	1.21	1.20	1.17	1.24
	0.5 to <1.0 g	1.41	1.38	1.44	1.43	1.38	1.48
	1.0 to <2.5 g	1.67	1.63	1.71	1.73	1.67	1.79
	2.5 to <5 g	1.97	1.87	2.07	2.12	2.02	2.23
	5 to <10 g	2.35	2.15	2.54	2.34	2.17	2.52
	≥10 g	2.49	2.18	2.80	2.71	2.47	2.98
Hypertension	Reference Group	1			1		
	>0 to <0.5 g	1.06	1.05	1.06	1.30	1.28	1.33
	0.5 to <1.0 g	1.22	1.21	1.24	1.34	1.30	1.38
	1.0 to <2.5 g	1.22	1.19	1.24	1.37	1.33	1.41
	2.5 to <5 g	1.21	1.15	1.26	1.31	1.25	1.37
	5 to <10 g	1.26	1.16	1.36	1.19	1.11	1.28
	≥10 g	1.15	1.01	1.29	1.33	1.21	1.46
Osteoporosis	Reference Group	1			1		
	>0 to <0.5 g	0.93	0.93	0.94	1.19	1.17	1.22
	0.5 to <1.0 g	1.28	1.25	1.30	1.21	1.17	1.25
	1.0 to <2.5 g	1.60	1.57	1.63	1.25	1.21	1.29
	2.5 to <5 g	2.11	2.02	2.19	1.39	1.32	1.47
	5 to <10 g	2.51	2.35	2.67	1.52	1.40	1.65
	≥10 g	3.40	3.14	3.65	2.12	1.93	2.33
Peptic Ulcer	Reference Group	1			1		
	>0 to <0.5 g	1.00	1.00	1.00	1.07	1.00	1.15
	0.5 to <1.0 g	1.30	1.22	1.37	1.29	1.18	1.41
	1.0 to <2.5 g	1.27	1.17	1.37	1.42	1.29	1.56
	2.5 to <5 g	1.18	0.96	1.38	1.55	1.34	1.81
	5 to <10 g	1.61	1.16	2.02	1.69	1.35	2.12
	≥10 g	1.37	0.74	1.96	2.00	1.53	2.63
Renal Disease	Reference Group	1			1		
	>0 to <0.5 g	1.06	1.05	1.06	0.98	0.97	1.00
	0.5 to <1.0 g	1.22	1.20	1.23	1.17	1.15	1.19
	1.0 to <2.5 g	1.24	1.22	1.25	1.23	1.20	1.25
	2.5 to <5 g	1.26	1.22	1.30	1.27	1.23	1.31
	5 to <10 g	1.28	1.21	1.35	1.25	1.20	1.31
	≥10 g	1.38	1.26	1.49	1.32	1.24	1.40

Sleep apnoea	Reference Group	1			1		
	>0 to <0.5 g	1.92	1.91	1.93	1.73	1.63	1.83
	0.5 to <1.0 g	2.52	2.44	2.59	2.41	2.25	2.58
	1.0 to <2.5 g	2.94	2.83	3.05	3.27	3.05	3.50
	2.5 to <5 g	3.55	3.23	3.85	4.03	3.66	4.45
	5 to <10 g	3.85	3.23	4.44	5.09	4.46	5.81
	≥10 g	4.52	3.49	5.50	5.18	4.35	6.17
Sleep Disorders	Reference Group	1			1		
	>0 to <0.5 g	1.07	1.06	1.08	1.37	1.35	1.40
	0.5 to <1.0 g	1.64	1.62	1.67	1.64	1.60	1.68
	1.0 to <2.5 g	2.08	2.05	2.11	1.76	1.71	1.80
	2.5 to <5 g	2.29	2.22	2.37	1.66	1.58	1.73
	5 to <10 g	2.52	2.38	2.66	1.69	1.58	1.81
	≥10 g	2.47	2.27	2.66	1.71	1.56	1.88
Depression/anxiety	Reference Group	1			1		
	>0 to <0.5 g	1.22	1.21	1.24	1.30	1.29	1.32
	0.5 to <1.0 g	1.90	1.82	1.97	1.95	1.90	2.00
	1.0 to <2.5 g	3.12	3.00	3.23	3.20	3.11	3.29
	2.5 to <5 g	4.76	4.44	5.06	4.80	4.74	4.86
	5 to <10 g	6.92	6.30	7.50	7.20	6.88	7.52
	≥10 g	8.20	7.16	9.17	8.50	8.14	8.86
All Pneumonia	Reference Group	1			1		
	>0 to <0.5 g	5.21	5.24	5.17	5.30	5.24	5.36
	0.5 to <1.0 g	6.68	6.63	6.73	7.01	6.63	7.39
	1.0 to <2.5 g	8.09	7.99	8.19	8.20	7.99	8.41
	2.5 to <5 g	10.50	10.07	10.91	10.97	10.07	11.87
	5 to <10 g	12.57	11.59	13.50	12.80	11.59	14.01
	≥10 g	14.04	12.33	15.66	14.05	12.33	15.77

IRR, incidence rate ratio. LCI, lower confidence interval. UCI, upper confidence interval.

[1] Adjusted for age, gender, smoking status, and BMI.

Figure 41 Adjusted incidence rate ratios for each category of cumulative OCS doses for each adverse event, compared against the non-OCS group and adjusted for age, gender, smoking status, and BMI.



8 Summary and Discussion

8.1 Summary

Making use of a historical UK cohort of 952,334 patients with over 8 years of median follow-up, this study achieved the following:

1. Developing an algorithm to classify patients by intermittent OCS use patterns using electronic health records;
2. Demonstrating that even intermittent OCS use in patients with relatively mild and moderate asthma was associated with significantly higher risks of adverse events;
3. Demonstrating that intermittent OCS use was associated with increased healthcare resources utilization; and
4. Demonstrating that patients with more frequent OCS use patterns had higher cumulative OCS doses which were associated with higher risks of adverse events.

8.2 Algorithmic classification of OCS use patterns

Various measures of asthma severity and control exist. While GINA treatment steps are frequently used for this purpose,[39] they only capture maintenance therapy and thus reflect longer-term asthmatic control, and intermittent medications prescribed for acute flare-ups are not captured. We showed that even in patients with mild asthma on early steps of GINA treatment, it is not uncommon to have had frequent intermittent OCS use at some point. This echoes the findings by Tran et al who found, using US data, that that most patients on high- and low-dose OCS/SCS had mild asthma (52.5% and 58.3% GINA Steps 1 and 2, respectively), contrasting only 23.2% and 29.8% with severe asthma (GINA Steps 4–5).[40] This reflects that patients who may be perceived to be stable in the long run may still have clinically active disease with frequent acute flare-ups requiring intermittent medications. This probably reflects the fluctuating nature of inflammation in asthma, thus suggesting that long-term stabilization and suppression of inflammation as a potential means via which even-related intermittent OCS use may be reduced. Additionally, this shows that maintenance therapy does not truly reflect disease severity and stability, which highlights the importance of accurately classifying intermittent OCS use, which would better reflect disease stability.

The current study thus represents an effort to systematically classify intermittent OCS use, which, to the best of our knowledge, is the first of its kind. Our approach contrasts previous studies, which have mostly relied on aggregate measures such as cumulative OCS dose which neglects the temporal patterns of OCS use.[25] Aside from adding much-needed

granularity to prescription analysis in asthmatic patients, our approach is likely widely applicable, as medication prescription records are much more readily available in electronic health record systems than spirometry results, blood tests and clinical history. Our novel algorithmic classification is therefore a practical, realistic, and accurate approach to prescription pattern analysis.

8.3 Association between intermittent OCS use and adverse events

While it is well established that long-term OCS use is associated with increased risks of adverse events which were positively correlated to cumulative dose,[41] previous studies have combined maintenance and intermittent OCS use without isolated analysis of the latter, which has caused confusion and uncertainty over the risks associated specifically with intermittent OCS use.[9–11,41] This study therefore analysed the risks associated with intermittent OCS use specifically, demonstrating that intermittent OCS use was associated with increased risk of adverse events, with increasing frequency being associated with higher risks regardless of age and prior asthmatic medication usages. Importantly, even infrequent intermittent OCS users had increased risks of adverse events. This complemented prior studies that showed associations between long-term high-dose OCS use and AEs in severe asthma.[42,43] Our findings also echoed previous studies which showed that even short bursts of OCS/SCS can be associated with AEs, and each OCS/SCS prescription results in a cumulative burden, regardless of the dose and duration.[24]

These results validated the algorithmic classification of OCS use patterns developed in Objective 1. In addition, we provided new insights into the many risks associated with OCS use, which must be re-considered when balancing the risks and benefits of OCS use in clinical practice. Our results provide strong arguments against routine use of intermittent OCS and have direct implications in clinical practice. In eligible patients, steroid-sparing agents such as biologics may be useful to optimize asthmatic control while avoiding the risks associated with OCS use. This is an emerging area of research and some agents, such as tezepelumab, have been shown to be efficacious in recent trials.[44] In others, research for strategies to mitigate or even eliminate OCS use, or better implementation of such strategies, remain much needed.[45]

8.4 Increased healthcare resources utilization with intermittent OCS use

Whilst higher OCS use has been shown to be associated with higher healthcare resources utilization, previous studies have focused on long-term OCS use without specific analysis of

intermittent OCS use.[23,26,35] In this study, we showed that OCS use was likewise associated with increased healthcare costs in all areas, including admission episodes, consultations, and prescriptions. Specifically, more frequent OCS use patterns were generally associated with significantly higher healthcare costs, which was consistent with the aforementioned association between more frequent OCS use patterns and adverse events. Nonetheless, patients with one-off OCS use were observed to have higher HRU than those in the less frequent OCS use category. The exact reasons underlying such observation was not immediately apparent, but may be related to unobserved confounders (e.g. willingness to remain on long-term medications), amongst other possibilities.

9 Limitation(s)

This study has several limitations. First, the classification algorithm in objective 1 was designed with a focus on specificity (i.e. ensuring that captured patients were intermittent OCS users) instead of sensitivity (i.e. ensuring that all intermittent OCS users were captured). Some intermittent OCS users may therefore have been mis-classified. Vice versa, though less likely, some long-term OCS users may have been mis-classified as well.

Second, whilst the OCS use pattern classification was used as a surrogate of OCS exposure, true adherence to OCS was not measured. Some studies have shown that patients with severe asthma may have low adherence to maintenance OCS, although such analyses have not been conducted for intermittent OCS.[46] Such studies are nonetheless difficult and would need to be prospective in nature. Currently, serum cortisol/prednisolone assays are the main stay of adherence assessment aside from questionnaires. FeNO has been explored as a potential marker of adherence as well.[47]

Third, patients with prior occurrence of outcome events were excluded from the analyses. This may have excluded recurrent events, which would be relevant for some acute events e.g. pneumonia and peptic ulcers. This study therefore may have selected for patients who are at relatively low risks of the outcomes.

Fourth, due to the nature of the data source, individual patients' records could not be adjudicated. This may have resulted in higher proportion of patients with missing data. The number of inhalers prescribed may also have been underestimated, as the number of prescriptions were used as a surrogate for the number of inhalers prescribed for some patients without accounting for the possibility of multiple inhalers being prescribed in a single

prescription. Nonetheless, the data input was performed by the treating healthcare team, and none of the investigators were involved or authorized to edit the entries. The database has been used in other peer-reviewed publications as well.[48,49]

Lastly, inherent to the observational design of this study, residual and unobserved confounders may exist and bias the results, which may include the disease severity and indications for OCS use, possibly constituting bias by indication.

10 Conclusion

Making use of a historical UK cohort of 476,167 patients with active asthma registered at GP practices, this study devised a classification algorithm which systematically classified patterns of intermittent OCS use into one-off, less frequent, and frequent OCS use. Over a median follow-up period of over eight years, OCS users had significantly higher risks of adverse events than 1:1 gender-matched non-OCS-user controls, with frequent OCS users, as classified using the above algorithm, generally showing higher risks of adverse events than one-off and less frequent users. In contrast, there were no associations between the risks of adverse events and OCS use patterns as classified by annualized OCS dose. OCS users also incurred significantly higher healthcare costs than non-users, with frequent OCS users generally incurring the highest costs.

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14 Appendices

14.1 Appendix 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

14.2 Appendix 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				

14.3 Appendix 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
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
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
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
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
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
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
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
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 foure , 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
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

14.4 Appendix 4: Asthma Read Codes

read_code	read_term
173A.	Exercise-induced asthma
H3120	Chronic asthmatic bronchitis
H33..	Asthma
H330.	(Hay fever with asthma) or (extrinsic asthma without status asthmaticus)
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
Xa0lZ	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

14.5 Appendix 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
c51B.	FENOTEROL + IPRATROPIUM BROMIDE breath act inh 100micrograms + 40micrograms/actuation
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
x02qI	SALAMOL inh 100micrograms/actuation
x02uD	VENTOLIN ACCUHALER 200micrograms/actuation

14.6 Appendix 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
c51B.	FENOTEROL + IPRATROPIUM BROMIDE breath act inh 100micrograms + 40micrograms/actuation
c51C.	IPRATROPIUM BROMIDE + SALBUTAMOL inh 20mcg + 100mcg
c51D.	COMBIVENT inh 20mcg + 100mcg
c51E.	COMBIVENT UDVs neb soln 2.5ml
c51F.	IPRATROPIUM BROMIDE + SALBUTAMOL unit dose neb soln 500micrograms + 2.5mg/2.5ml
c51H.	SALBUTAMOL + IPRATROPIUM BROMIDE unit dose neb soln 2.5mg + 500micrograms/2.5ml
c51i.	DUOVENT inh 40micrograms + 100micrograms/actuation
c51v.	DUOVENT UDVs neb soln
c51w.	IPRATROPIUM BROMIDE + SALBUTAMOL unit dose neb soln 500micrograms + 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

14.7 Appendix 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. FLUTICASONE inh 50micrograms/actuation
c65I. FLUTICASONE inh 50micrograms/actuation
c65J. FLUTICASONE inh 250micrograms/actuation
c65K. FLIXOTIDE inh 250micrograms/actuation
c65L. FLIXOTIDE disc 500micrograms
c65M. FLIXOTIDE disc 500micrograms
c65N. FLUTICASONE disc 500micrograms
c65O. FLUTICASONE disc 500micrograms
c65P. FLUTICASONE breath act pwdr inh 50micrograms/inhalation
c65Q. FLUTICASONE breath act pwdr inh 100micrograms/inhalation
c65R. FLIXOTIDE ACCUHALER 250micrograms/inhalation
c65S. FLUTICASONE breath act pwdr inh 500micrograms/inhalation
c65T. FLIXOTIDE ACCUHALER 50micrograms/inhalation
c65U. FLIXOTIDE ACCUHALER 100micrograms/inhalation
c65V. FLIXOTIDE ACCUHALER 250micrograms/inhalation
c65W. FLIXOTIDE ACCUHALER 500micrograms/inhalation
c65b. FLUTICASONE cfc free inh 125micrograms/actuation
c65c. FLUTICASONE cfc free inh 250micrograms/actuation
c65d. FLIXOTIDE EVOHALER 125micrograms/actuation
c65e. FLIXOTIDE EVOHALER 250micrograms/actuation
c65f. FLUTICASONE cfc free inh 50micrograms/actuation
c65g. FLUTICASONE 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 pwdr 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 pwdr inh 250micrograms/actuation
c66G. BECLOMETASONE breath act pwdr inh 400micrograms/actuation

c66H.	BECLOMETASONE breath act pwdr inh 200micrograms/actuation
c66I.	PULVINAL BECLOMETASONE DIPROPIONATE breath act pwdr 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

14.8 Appendix 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

14.9 Appendix 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
c333.	Spiriva Respimat Solution For Inhalation 2.5 micrograms/puff 60 puffs
c33x.	Spiriva Respimat Solution For Inhalation 2.5 micrograms/puff 60 puffs
c33y.	SPIRIVA inh pdr caps+dev 18 micrograms
c33z.	SPIRIVA inh caps 18 micrograms
c341.	EKLIRA GENUAIR inhalation powder 322micrograms
c342.	Aclidinium Bromide Dry Powder Inhaler 375 micrograms/dose
c351.	Incruse Ellipta 55micrograms/dose dry powder inhaler
c352.	UMECLIDINIUM 55micrograms/dose dry powder inhaler

o323.	SEEBRI BREEZHALER 44micrograms inhalation capsules
o324.	GLYCOPYRRONIUM 44micrograms inhalation capsules
x05gG	SPIRIVA inh pdr cap (refill) 18 micrograms

14.10 Appendix 10: LABA/LAMA Read Codes

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

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

14.12 Appendix 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
c41b.	PHYLLOCONTIN CONTINUS forte tabs 350mg
c41c.	PHYLLOCONTIN CONTINUS paed tab 100mg
c41d.	AMINOPHYLLINE SR tablets 225mg [IVAX]

c41f.	AMINOPHYLLINE HYDRATE mr tab 350mg
c41g.	AMINOPHYLLINE mr tab 100mg
c41h.	AMNIVENT sr tab 225mg
c41k.	AMINOPHYLLINE inj 25mg/ml [CELLTECH]
c41m.	AMINOPHYLLINE HYDRATE mr tab 225mg
c421.	CHOLEDYL tabs 100mg
c422.	CHOLEDYL tabs 200mg
c423.	CHOLEDYL syrp 62.5mg/5ml
c42w.	CHOLINE THEOPHYLLINATE tabs 100mg
c42x.	CHOLINE THEOPHYLLINATE tabs 200mg
c431.	BIOPHYLLINE syrp 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
x02lT	NUELIN tabs 125mg
x02tm	UNIPHYLLIN CONTINUS tabs 200mg

14.13 Appendix 13: ICS/LABA/LAMA Snowmed codes

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

14.14 Appendix 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
fe3r.	DEXAMETHASONE 500micrograms/5mL solution
fe3s.	DEXAMETHASONE 2mg/5mL sugar free 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..	PREDNISONE
fe71.	*PREDNISONE 1mg tablets
fe72.	*PREDNISONE 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.	PREDNISONE 5mg m/r tablets
fe7y.	PREDNISONE 2mg m/r tablets
fe7z.	PREDNISONE 1mg m/r tablets
x00yP	Oral prednisolone
x01Mh	Oral dexamethasone
x01Na	Oral hydrocortisone
x01Nb	Oral methylprednisolone

14.15 Appendix 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

14.16 Appendix 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

14.17 Appendix 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

14.18 Appendix 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

14.19 Appendix 19: Polymyalgia rheumatica Read codes

Code	Terms
N20..	Polymyalgia
N20..	Polymyalgia rheumatica
N200.	Giant cell arteritis with polymyalgia rheumatica

14.20 Appendix 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	

14.21 Appendix 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

14.22 Appendix 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

14.23 Appendix 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
B2230	Malignant neoplasm of middle lobe 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
B224z	Malignant neoplasm of lower lobe, bronchus or lung 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
B242.	Malignant neoplasm of anterior 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
B26..	Malignant neoplasm, overlapping lesion of 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
B8124	Carcinoma in situ of lower lobe bronchus and 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
XE1vc	Malignant neoplasm of bronchus or lung 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
XaEJe	Squamous cell carcinoma of bronchus in left lower 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
XaEJi	Squamous cell carcinoma of bronchus in right upper 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

14.24 Appendix 24: Rheumatoid arthritis Read codes

Read Code	Read Term
N040.	Rheumatoid arthritis
X701h	Seropositive rheumatoid arthritis
XaBMO	Seropositive errosive 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

14.25 Appendix 25: Temporal arteritis Read codes

Code	Terms
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

14.26 Appendix 26: Height, weight, BMI Read Codes

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

14.27 Appendix 27: Blood Eosinophil Count Read codes

Read code	Read term
42K..	Eosinophil count
42K1.	Eosinophil count normal
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
X00l1	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
Y80lD	Eosinophil
Ya14p	EP-Acute eosinophil pneumonia
Yaeib	Percentage eosinophil count
YakcK	Eosinophil count - observation

14.28 Appendix 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
XaIxQ	FEV1 before bronchodilation
XaIxR	FEV1 after bronchodilation
XaIxU	FEV1 pre steroids
XaIxV	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
XaPpI	Forced vital capacity before bronchodilation
XaVx3	Percentage predicted FEV1 after bronchodilation

14.29 Appendix 29: Peak Expiratory Flow Read codes

Read code	Read term
339..	Respiratory flow rates

Read code	Read term
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

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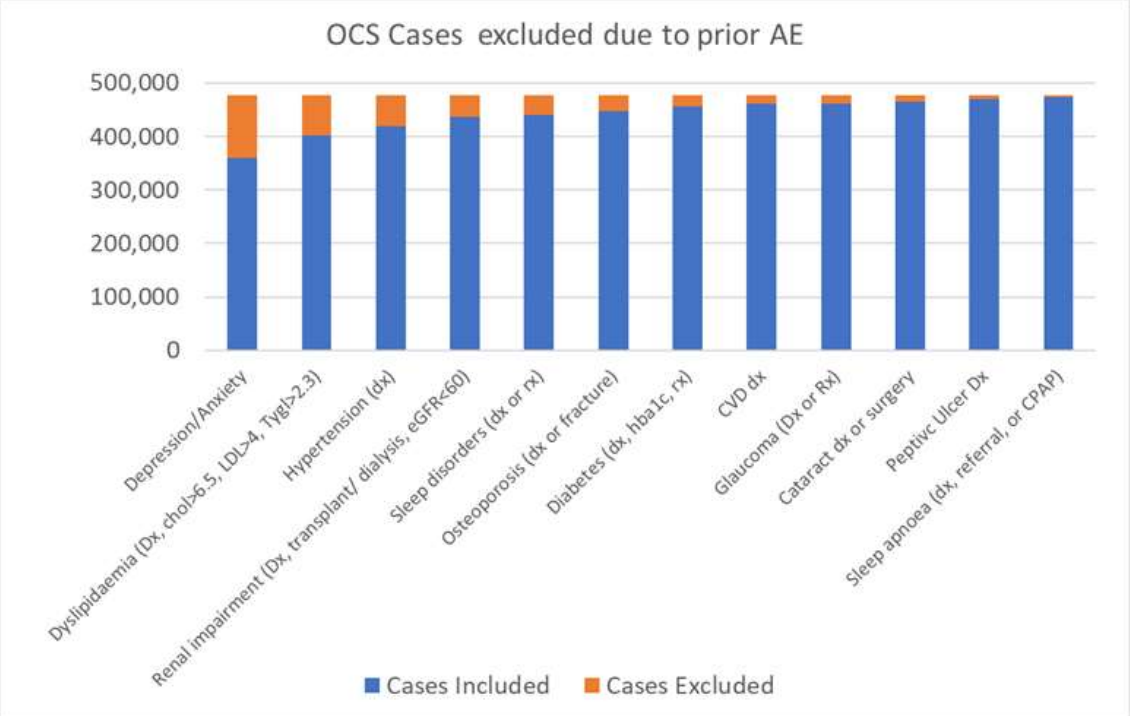
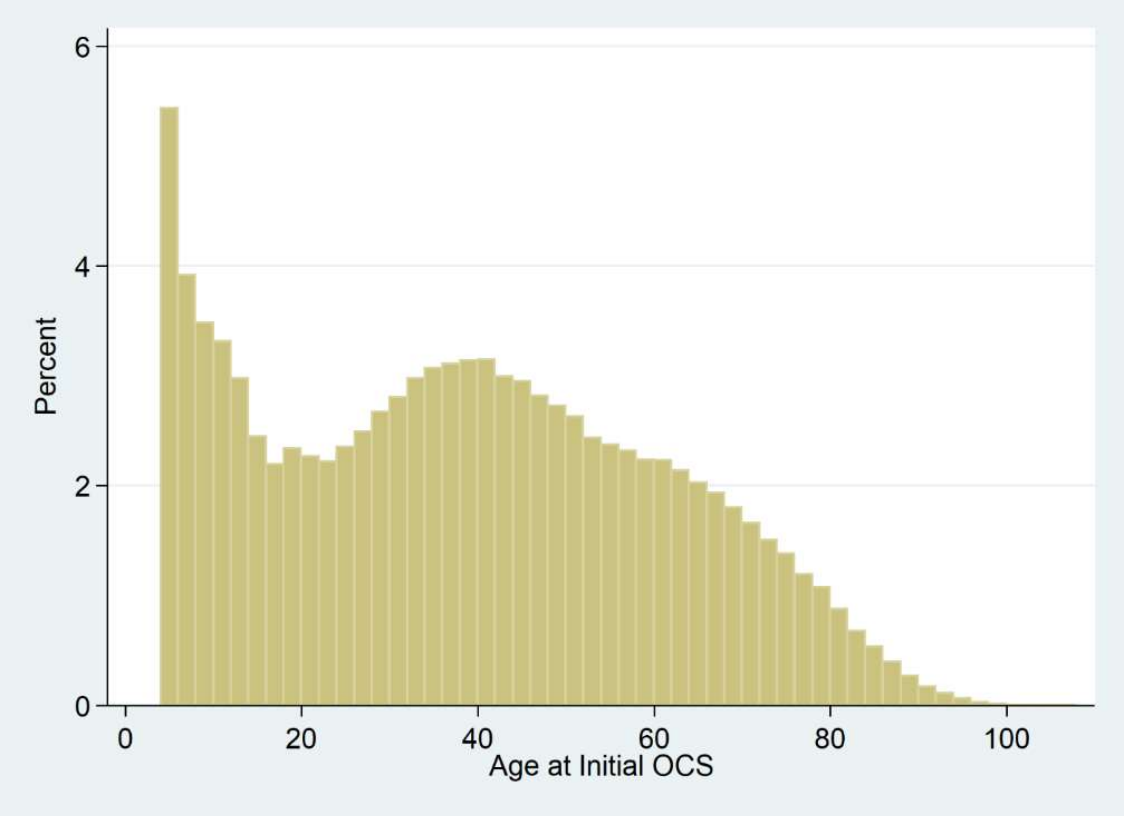
17 Supplemental Figures

Supplemental Figure 1. Distribution of OCS cases excluded due to prior adverse events.



Supplemental Figure 2. Bimodal distribution of age at initial OCS.



18 Supplemental Tables

Supplemental Table 1. Comparison of body-mass index (BMI) by OCS use pattern categories.

BMI nearest to Initial OCS

	OCS Sequence Categories									
	No OCS		OCS		One Off		Less Frequent		Frequent	
Underweight (%)	23,904	7.1%	35,998	9.4%	15,159	10.1%	10,257	9.9%	10,553	8.1%
Normal (%)	144,517	42.9%	138,469	36.0%	56,728	37.6%	37,665	36.4%	44,061	33.8%
Overweight (%)	102,328	30.3%	109,042	28.4%	42,521	28.2%	28,899	28.0%	37,612	28.9%
Obese (%)	66,473	19.7%	100,995	26.3%	36,410	24.1%	26,529	25.7%	38,048	29.2%
Unknow (%)	138,946		91,710		47,601		24,057		20,038	
	476,167		476,167		198,420		127,419		150,326	

Supplemental Table 2. Comparison of smoking status by OCS use pattern categories.

Smoking Status prior to Initial OCS

	OCS Sequence Categories									
	No OCS		OCS		One Off		Less Frequent		Frequent	
Never (%)	135,708	42.3%	141,231	44.1%	60,915	19.0%	37,512	11.7%	42,813	13.4%
Current (%)	117,089	36.5%	131,851	41.1%	53,514	16.7%	34,951	10.9%	43,384	13.5%
Ex (%)	67,711	21.1%	84,377	26.3%	33,950	10.6%	21,075	6.6%	29,359	9.2%
Unknown (%)	155,659		118,708		50,042		33,881		34,755	
	476,167		476,167		198,420		127,419		150,326	

Supplemental Table 3. Comparison of height by OCS use pattern categories.

Height nearest to Initial OCS					
			OCS Sequence Categories		
	No OCS	OCS	One Off	Less Frequent	Frequent
IQR (25%)	1.59	1.57	1.57	1.56	1.57
Median	1.65	1.65	1.65	1.64	1.64
IQR (75%)	1.74	1.73	1.74	1.73	1.72

Supplemental Table 4. Maximum eosinophil readings of patients stratified by OCS use pattern categories.

Maximum Eosinophil reading within 2 years of Initial OCS*								
			OCS Sequence Categories					
	OCS		One Off		Less Frequent		Frequent	
0 - 150	18,797	18.9%	7,236	20.4%	4,809	18.3%	6,752	17.8%
150 - 300	29,583	29.7%	10,796	30.4%	7,832	29.8%	10,955	29.0%
300 - 450	27,276	27.4%	9,693	27.3%	7,183	27.4%	10,400	27.5%
450+	23,950	24.0%	7,809	22.0%	6,415	24.4%	9,726	25.7%
Missing	376,561		162,886		101,180		112,493	
	476,167		198,420		127,419		150,326	

* without any exacerbation within 14 days

Supplemental Table 5. RCP readings of patients stratified by OCS use pattern categories.

Nearest RCP reading within 2 years of Initial OCS								
			OCS Sequence Categories					
	OCS		One Off		Less Frequent		Frequent	
Well Controlled	92,410	34.0%	42,558	42.3%	24,901	32.0%	24,951	26.9%
Poor Control	178,999	66.0%	58,105	57.7%	52,953	68.0%	67,941	73.1%
Missing	204,758		97,757		49,565		57,434	
	476,167		198,420		127,419		150,326	

Supplemental Table 6. Percentage predicted PEF of patients stratified by OCS use pattern categories.

Percent Predicted PEF nearest prior to Initial OCS								
			OCS Sequence Categories					
	OCS		One Off		Less Frequent		Frequent	
0 - < 0.5	13,452	7.7%	4,739	6.7%	3,654	7.6%	5,060	9.0%
0.5 - < 0.8	69,991	40.0%	27,772	39.2%	19,054	39.6%	23,165	41.4%
0.8 < 10	91,496	52.3%	38,293	54.1%	25,421	52.8%	27,782	49.6%
Missing	301,228		127,617		79,290		94,319	
	476,167		198,421		48,129		150,326	

Supplemental Table 7. Age of patients stratified by SABA use categories and OCS use pattern categories.

Age at initial OCS Prescription								
	OCS Sequence Categories							
	OCS		One Off		Less Frequent		Frequent	
0 SABAs	41	(22-59)	36	(17-56)	40	(21-58)	48	(31-63)
1 - < 3	35	(17-51)	31	(14-48)	34	(15-50)	41	(24-57)
3 - < 12	38	(18-56)	36	(16-54)	36	(17-54)	42	(24-60)
12 - < 90	45	(29-63)	46	(29-65)	42	(27-60)	46	(30-63)

Supplemental Table 8. Sex of patients stratified by SABA use categories and OCS use pattern categories.

Gender: % Female								
	OCS Sequence Categories							
	OCS		One Off		Less Frequent		Frequent	
0 SABAs	63,454	56.0%	23,459	52.4%	17,668	57.0%	22,326	59.5%
1 - < 3	120,197	56.3%	50,619	52.3%	31,765	57.1%	37,813	61.8%
3 - < 12	73,356	55.0%	26,311	51.1%	20,217	55.2%	26,828	59.4%
12 - < 90	8,078	50.3%	2,479	46.0%	2,103	50.4%	3,496	53.8%
	265,085	55.7%	102,868	51.8%	71,753	56.3%	90,463	60.2%

Supplemental Table 9. Body mass index distribution of patients stratified by SABA use categories and OCS use pattern categories.

Number of SABAs prior to Initial OCS by BMI									
				OCS Sequence Categories					
		OCS (n)	%	One Off (n)	%	Less Frequent (n)	%	Frequent (n)	%
0 SABAs	Underweight	5,663	6.6%	2,402	7.6%	1,527	6.7%	1,734	5.7%
	Normal	31,003	36.4%	12,257	38.5%	8,469	37.1%	10,277	33.6%
	Overweight	26,142	30.7%	9,584	30.1%	6,981	30.6%	9,577	31.4%
	Obese	22,374	26.3%	7,555	23.8%	5,862	25.7%	8,957	29.3%
	Unknown	28,080		12,970		8,148		6,962	
		113,262		44,768		30,987		37,507	
1 - < 3	Underweight	18,361	10.5%	8,281	11.2%	5,216	11.3%	4,864	9.0%
	Normal	63,331	36.4%	28,365	38.3%	16,849	36.6%	18,117	33.6%
	Overweight	47,856	27.5%	20,228	27.3%	12,497	27.1%	15,131	28.1%
	Obese	44,549	25.6%	17,207	23.2%	11,514	25.0%	15,828	29.3%
	Unknown	39,497		22,670		9,584		7,243	
		213,594		96,751		55,660		61,183	
3 - < 12	Underweight	11,192	10.1%	4,237	10.5%	3,325	10.8%	3,630	9.1%
	Normal	39,427	35.4%	14,639	36.2%	11,115	36.0%	13,673	34.2%
	Overweight	31,056	27.9%	11,432	28.2%	8,391	27.2%	11,233	28.1%
	Obese	29,649	26.6%	10,165	25.1%	8,003	26.0%	11,481	28.7%
	Unknown	21,931		11,046		5,768		5,117	
		133,255		51,519		36,602		45,134	
12 - < 90	Underweight	765	5.5%	243	5.4%	195	5.4%	327	5.7%
	Normal	4,699	33.9%	1,469	32.9%	1,238	34.3%	1,992	34.5%
	Overweight	3,977	28.7%	1,277	28.6%	1,027	28.4%	1,673	28.9%
	Obese	4,414	31.9%	1,475	33.0%	1,150	31.9%	1,789	30.9%
	Unknown	2,201		920		560		721	
		16,056		5,384		4,170		6,502	

Supplemental Table 10. Smoking status of patients stratified by SABA use categories and OCS use pattern categories.

% Patients by OCS use, Smoking and Age

				OCS Sequence Categories					
		OCS (n)	**%**	**One Off** (n)	**%**	**Less Frequent** (n)	**%**	**Frequent** (n)	**%**
0 SABAs	Never	31,114	39.6%	12,328	40.6%	8,611	40.7%	10,175	37.6%
	Current	29,209	37.2%	11,036	36.4%	8,036	38.0%	10,137	37.5%
	Ex	18,219	23.2%	6,970	23.0%	4,517	21.3%	6,732	24.9%
	Unknown	34,720		14,434		9,823		10,463	
		113,262		44,768		30,987		37,507	
1 - < 3	Never	65,811	41.3%	30,903	43.0%	16,828	41.7%	18,080	38.5%
	Current	56,831	35.7%	25,132	35.0%	14,596	36.1%	17,103	36.4%
	Ex	36,560	23.0%	15,762	22.0%	8,975	22.2%	11,823	25.2%
	Unknown	54,392		24,954		15,261		14,177	
		213,594		96,751		55,660		61,183	
3 - < 12	Never	40,735	38.4%	16,506	39.8%	11,131	39.2%	13,098	36.3%
	Current	39,090	36.9%	15,047	36.3%	10,544	37.1%	13,499	37.5%
	Ex	26,132	24.7%	9,954	24.0%	6,737	23.7%	9,441	26.2%
	Unknown	27,298		10,012		8,190		9,096	
		133,255		51,519		36,602		45,134	
12 - < 90	Never	3,581	26.0%	1,182	24.9%	942	26.5%	1,457	26.6%
	Current	6,715	48.7%	2,294	48.4%	1,771	49.7%	2,650	48.4%
	Ex	3,483	25.3%	1,265	26.7%	848	23.8%	1,370	25.0%
	Unknown	2,277		643		609		1,025	
		16,056		5,384		4,170		6,502	

Supplemental Table 11. Prior GINA treatment steps of patients stratified by SABA use categories and OCS use pattern categories.

Respiratory Regimen (Gina Step) prior to Initial OCS by SABA use

				OCS Sequence Categories					
		OCS (n)	**%**	**One Off** (n)	**%**	**Less Frequent** (n)	**%**	**Frequent** (n)	**%**
0 SABAs	**No Athma Medication**	65,624	57.9%	25,034	55.9%	17,704	57.1%	22,886	61.0%
	Step 1 (ICS PRN/SABA alone)	1,827	1.6%	868	1.9%	520	1.7%	439	1.2%
	Step 2 (Daily Low Dose ICS)	23,780	21.0%	10,063	22.5%	6,812	22.0%	6,905	18.4%
	Step 3 (Low ICS/LABA or Med ICS)	14,801	13.1%	6,118	13.7%	4,048	13.1%	4,635	12.4%
	Step 4 (Med ICS/LABA or High ICS)	6,050	5.3%	2,291	5.1%	1,623	5.2%	2,136	5.7%
	Step 5 (High ICS/LABA +)	1,178	1.0%	392	0.9%	280	0.9%	506	1.3%
		113,260		44,766		30,987		37,507	
1 - < 3	**No Athma Medication**								
	Step 1 (ICS PRN/SABA alone)	95,034	44.5%	43,810	45.3%	24,334	43.7%	26,890	44.0%
	Step 2 (Daily Low Dose ICS)	68,434	32.0%	31,379	32.4%	18,379	33.0%	18,676	30.5%
	Step 3 (Low ICS/LABA or Med ICS)	33,276	15.6%	14,999	15.5%	8,709	15.6%	9,568	15.6%
	Step 4 (Med ICS/LABA or High ICS)	14,021	6.6%	5,705	5.9%	3,560	6.4%	4,756	7.8%
	Step 5 (High ICS/LABA +)	2,829	1.3%	858	0.9%	678	1.2%	1,293	2.1%
		213,594		96,751		55,660		61,183	
3 - < 12	**No Athma Medication**								
	Step 1 (ICS PRN/SABA alone)	20,931	15.7%	8,279	16.1%	5,661	15.5%	6,991	15.5%
	Step 2 (Daily Low Dose ICS)	54,539	40.9%	21,465	41.7%	15,623	42.7%	17,451	38.7%
	Step 3 (Low ICS/LABA or Med ICS)	35,073	26.3%	13,773	26.7%	9,466	25.9%	11,834	26.2%
	Step 4 (Med ICS/LABA or High ICS)	18,310	13.7%	6,671	12.9%	4,805	13.1%	6,834	15.1%
	Step 5 (High ICS/LABA +)	4,402	3.3%	1,331	2.6%	1,047	2.9%	2,024	4.5%
		133,255		51,519		36,602		45,134	
12 - < 90	**No Athma Medication**								
	Step 1 (ICS PRN/SABA alone)	1,895	11.8%	645	12.0%	456	10.9%	794	12.2%
	Step 2 (Daily Low Dose ICS)	5,403	33.7%	1,861	34.6%	1,516	36.4%	2,026	31.2%
	Step 3 (Low ICS/LABA or Med ICS)	4,604	28.7%	1,591	29.6%	1,194	28.6%	1,819	28.0%
	Step 4 (Med ICS/LABA or High ICS)	3,138	19.5%	1,002	18.6%	779	18.7%	1,357	20.9%
	Step 5 (High ICS/LABA +)	1,016	6.3%	285	5.3%	225	5.4%	506	7.8%
		16,056		5,384		4,170		6,502	

Supplemental Table 12. Prior ICS prescriptions of patients stratified by SABA use categories and OCS use pattern categories.

ICS Use prior to Initial OCS by SABA use

		OCS Sequence Categories							
		OCS (n)	**%**	**One Off** (n)	**%**	**Less Frequent** (n)	**%**	**Frequent** (n)	**%**
0 SABAs	**0**	69,448	61.3%	26,536	59.3%	18,743	60.5%	24,169	64.4%
	1 - < 7	38,179	33.7%	16,107	36.0%	10,710	34.6%	11,362	30.3%
	7 - < 13	4,858	4.3%	1,834	4.1%	1,334	4.3%	1,690	4.5%
	13 - < 25	755	0.7%	284	0.6%	195	0.6%	276	0.7%
	25 - < 105	20	0.0%	5	0.0%	5	0.0%	10	0.0%
		113,260		44,766		30,987		37,507	
1 - < 3	**0**	96,861	45.3%	44,406	45.9%	24,774	44.5%	27,681	45.2%
	1 - < 7	110,881	51.9%	50,005	51.7%	29,405	52.8%	31,471	51.4%
	7 - < 13	5,221	2.4%	2,093	2.2%	1,335	2.4%	1,793	2.9%
	13 - < 25	625	0.3%	246	0.3%	143	0.3%	236	0.4%
	25 - < 105	6	0.0%	1	0.0%	3	0.0%	2	0.0%
		213,594		96,751		55,660		61,183	
3 - < 12	**0**	22,636	17.0%	8,726	16.9%	6,120	16.7%	7,790	17.3%
	1 - < 7	88,090	66.1%	34,466	66.9%	24,726	67.6%	28,898	64.0%
	7 - < 13	20,701	15.5%	7,672	14.9%	5,318	14.5%	7,711	17.1%
	13 - < 25	1,801	1.4%	650	1.3%	427	1.2%	724	1.6%
	25 - < 105	27	0.0%	5	0.0%	11	0.0%	11	0.0%
		133,255		51,519		36,602		45,134	
12 - < 90	**0**	2,195	13.7%	735	13.7%	540	12.9%	920	14.1%
	1 - < 7	5,237	32.6%	1,693	31.4%	1,434	34.4%	2,110	32.5%
	7 - < 13	5,140	32.0%	1,668	31.0%	1,371	32.9%	2,101	32.3%
	13 - < 25	3,372	21.0%	1,256	23.3%	807	19.4%	1,309	20.1%
	25 - < 105	112	0.7%	32	0.6%	18	0.4%	62	1.0%
		16,056		5,384		4,170		6,502	

Supplemental Table 13. Sex distribution of patients stratified by ICS use categories.

Gender: % Female

	OCS Sequence Categories							
	OCS		**One Off**		**Less Frequent**		**Frequent**	
0	104,917	39.6%	41,085	39.9%	27,981	39.0%	35,851	39.6%
1 - < 7	136,001	51.3%	53,435	51.9%	37,511	52.3%	45,055	49.8%
7 - < 13	20,396	7.7%	7,025	6.8%	5,355	7.5%	8,016	8.9%
13 - < 25	3,686	1.4%	1,305	1.3%	889	1.2%	1,492	1.6%
25 - < 105	82	0.0%	16	0.0%	17	0.0%	49	0.1%
	265,082		102,866		71,753		90,463	

Supplemental Table 14. Body mass index categories of patients stratified by ICS use categories.

BMI by ICSs prior to Initial OCS

				OCS Sequence Categories					
		OCS (n)	**%**	**One Off** (n)	**%**	**Less Frequent** (n)	**%**	**Frequent** (n)	**%**
0 ICSs	Underweight	13,975	9.3%	5,941	9.9%	3,878	9.8%	4,156	8.0%
	Normal	53,396	35.4%	22,507	37.6%	14,129	35.7%	16,760	32.4%
	Overweight	43,266	28.6%	16,923	28.3%	11,253	28.5%	15,090	29.2%
	Obese	40,411	26.8%	14,479	24.2%	10,275	26.0%	15,657	30.3%
	Unknown	40,093		20,554		10,642		8,897	
		191,141		80,404		50,177		60,560	
1 - < 7 ICSs	Underweight	19,870	10.1%	8,448	10.8%	5,805	10.7%	5,617	8.7%
	Normal	73,211	37.2%	30,095	38.6%	20,430	37.6%	22,686	35.2%
	Overweight	54,605	27.8%	21,499	27.6%	14,821	27.3%	18,285	28.4%
	Obese	48,987	24.9%	17,828	22.9%	13,326	24.5%	17,833	27.7%
	Unknown	45,715		24,402		11,893		9,420	
		242,388		102,272		66,275		73,841	
7 - < 13 ICSs	Underweight	1,865	6.0%	678	6.2%	511	6.4%	676	5.7%
	Normal	10,042	32.6%	3,516	32.0%	2,667	33.2%	3,859	32.6%
	Overweight	9,426	30.6%	3,463	31.5%	2,409	30.0%	3,554	30.0%
	Obese	9,503	30.8%	3,326	30.3%	2,438	30.4%	3,739	31.6%
	Unknown	5,084		2,284		1,333		1,467	
		35,920		13,267		9,358		13,295	
13 - < 25 ICSs	Underweight	256	4.4%	92	4.4%	66	4.8%	98	4.3%
	Normal	1,764	30.6%	602	29.0%	435	31.4%	727	31.6%
	Overweight	1,695	29.4%	625	30.1%	405	29.2%	665	29.0%
	Obese	2,044	35.5%	758	36.5%	479	34.6%	807	35.1%
	Unknown	794		359		187		248	
		6,553		2,436		1,572		2,545	
25 - < 105 ICSs	Underweight	15	10.6%	4	11.1%	3	9.4%	8	10.8%
	Normal	47	33.1%	10	27.8%	10	31.3%	27	36.5%
	Overweight	39	27.5%	11	30.6%	8	25.0%	20	27.0%
	Obese	41	28.9%	11	30.6%	11	34.4%	19	25.7%
	Unknown	23		7		5		11	
		165		43		37		85	

Supplemental Table 15. Smoking statuses of patients stratified by ICS use categories.

% Patients by ICS use, Smoking and OCS

				OCS Sequence Categories					
		OCS (n)	**%**	**One Off** (n)	**%**	**Less Frequent** (n)	**%**	**Frequent** (n)	**%**
0 ICSs	Never	51,798	38.2%	22,504	39.9%	13,434	39.0%	15,860	35.6%
	Current	52,373	38.7%	21,278	37.7%	13,595	39.5%	17,500	39.2%
	Ex	31,252	23.1%	12,614	22.4%	7,410	21.5%	11,228	25.2%
	Unknown	55,718		24,008		15,738		15,972	
		191,141		80,404		50,177		60,560	
1 - < 7	Never	77,216	41.8%	33,833	43.4%	20,902	42.1%	22,481	39.3%
	Current	65,603	35.5%	27,093	34.7%	17,781	35.8%	20,729	36.2%
	Ex	42,071	22.8%	17,088	21.9%	10,989	22.1%	13,994	24.5%
	Unknown	57,498		24,258		16,603		16,637	
		242,388		102,272		66,275		73,841	
7 - < 13	Never	10,603	34.1%	3,967	33.9%	2,815	35.2%	3,821	33.5%
	Current	11,301	36.3%	4,225	36.1%	2,919	36.5%	4,157	36.4%
	Ex	9,226	29.6%	3,521	30.1%	2,261	28.3%	3,444	30.2%
	Unknown	4,790		1,554		1,363		1,873	
		35,920		13,267		9,358		13,295	
13 - < 25	Never	1,593	27.0%	606	27.3%	353	25.2%	634	27.7%
	Current	2,499	42.3%	889	40.1%	639	45.6%	971	42.4%
	Ex	1,814	30.7%	723	32.6%	408	29.1%	683	29.9%
	Unknown	647		218		172		257	
		6,553		2,436		1,572		2,545	
25 - < 105	Never	31	23.7%	9	23.7%	8	26.7%	14	22.2%
	Current	69	52.7%	24	63.2%	13	43.3%	32	50.8%
	Ex	31	23.7%	5	13.2%	9	30.0%	17	27.0%
	Unknown	34		5		7		22	
		165		43		37		85	

Supplemental Table 16. Prior GINA treatment steps of patients stratified by ICS use categories.

Respiratory Regimen (Gina Step) prior to Initial OCS by ICS use

				OCS Sequence Categories					
		OCS (n)	%	**One Off** (n)	%	**Less Frequent** (n)	%	**Frequent** (n)	%
O ICS	**No Athma Medication**	65,612	34.3%	25,025	31.1%	17,701	35.3%	22,886	37.8%
	Step 1 (ICS PRN/SABA alone)	119,189	62.4%	53,358	66.4%	30,843	61.5%	34,988	57.8%
	Step 2 (Daily Low Dose ICS)	3,777	2.0%	1,238	1.5%	1,014	2.0%	1,525	2.5%
	Step 3 (Low ICS/LABA or Med ICS)	2,556	1.3%	782	1.0%	618	1.2%	1,156	1.9%
	Step 4 (Med ICS/LABA or High ICS	7	0.0%	1	0.0%	1	0.0%	5	0.0%
	Step 5 (High ICS/LABA +)	0	0.0%		0.0%		0.0%		0.0%
		191,141		80,404		50,177		60,560	
1 - < 7	**Step 1** (ICS PRN/SABA alone)	474	0.2%	231	0.2%	125	0.2%	118	0.2%
	Step 2 (Daily Low Dose ICS)	135,503	55.9%	58,630	57.3%	37,809	57.0%	39,064	52.9%
	Step 3 (Low ICS/LABA or Med ICS)	70,080	28.9%	29,949	29.3%	18,899	28.5%	21,232	28.8%
	Step 4 (Med ICS/LABA or High ICS	30,224	12.5%	11,612	11.4%	7,967	12.0%	10,645	14.4%
	Step 5 (High ICS/LABA +)	6,106	2.5%	1,849	1.8%	1,475	2.2%	2,782	3.8%
		242,387		102,271		66,275		73,841	
7 - < 13	**Step 1** (ICS PRN/SABA alone)	32	0.1%	21	0.2%	6	0.1%	5	0.0%
	Step 2 (Daily Low Dose ICS)	11,228	31.3%	4,285	32.3%	3,066	32.8%	3,877	29.2%
	Step 3 (Low ICS/LABA or Med ICS)	12,835	35.7%	4,888	36.8%	3,325	35.5%	4,622	34.8%
	Step 4 (Med ICS/LABA or High ICS	9,175	25.5%	3,249	24.5%	2,359	25.2%	3,567	26.8%
	Step 5 (High ICS/LABA +)	2,650	7.4%	824	6.2%	602	6.4%	1,224	9.2%
		35,920		13,267		9,358		13,295	
13 - < 25	**Step 1** (ICS PRN/SABA alone)	5	0.1%	2	0.1%	0	0.0%	3	0.1%
	Step 2 (Daily Low Dose ICS)	1,591	24.3%	604	24.8%	427	27.2%	560	22.0%
	Step 3 (Low ICS/LABA or Med ICS)	2,235	34.1%	846	34.7%	563	35.8%	826	32.5%
	Step 4 (Med ICS/LABA or High ICS	2,065	31.5%	795	32.6%	430	27.4%	840	33.0%
	Step 5 (High ICS/LABA +)	657	10.0%	189	7.8%	152	9.7%	316	12.4%
		6,553		2,436		1,572		2,545	
25 - < 105	**Step 1** (ICS PRN/SABA alone)	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Step 2 (Daily Low Dose ICS)	57	34.5%	11	25.6%	14	37.8%	32	37.6%
	Step 3 (Low ICS/LABA or Med ICS)	48	29.1%	16	37.2%	12	32.4%	20	23.5%
	Step 4 (Med ICS/LABA or High ICS	48	29.1%	12	27.9%	10	27.0%	26	30.6%
	Step 5 (High ICS/LABA +)	12	7.3%	4	9.3%	1	2.7%	7	8.2%
		165		43		37		85	

Supplemental Table 17. Prior SABA use categories of patients stratified by ICS use categories.

SABA Use prior to Initial OCS by ICS use

				OCS Sequence Categories					
		OCS (n)	**%**	**One Off** (n)	**%**	**Less Frequent** (n)	**%**	**Frequent** (n)	**%**
0 ICS	0 SABAs	69,449	36.3%	26,537	33.0%	18,743	37.4%	24,169	39.9%
	1 - < 3	96,861	50.7%	44,406	55.2%	24,774	49.4%	27,681	45.7%
	3 - < 12	22,636	11.8%	8,726	10.9%	6,120	12.2%	7,790	12.9%
	12 - < 90	2,195	1.1%	735	0.9%	540	1.1%	920	1.5%
		191,141		80,404		50,177		60,560	
1 - < 7	0 SABAs	38,180	15.8%	16,108	15.8%	10,710	16.2%	11,362	15.4%
	1 - < 3	110,881	45.7%	50,005	48.9%	29,405	44.4%	31,471	42.6%
	3 - < 12	88,090	36.3%	34,466	33.7%	24,726	37.3%	28,898	39.1%
	12 - < 90	5,237	2.2%	1,693	1.7%	1,434	2.2%	2,110	2.9%
		242,388		102,272		66,275		73,841	
7 - < 13	0 SABAs	4,858	13.5%	1,834	13.8%	1,334	14.3%	1,690	12.7%
	1 - < 3	5,221	14.5%	2,093	15.8%	1,335	14.3%	1,793	13.5%
	3 - < 12	20,701	57.6%	7,672	57.8%	5,318	56.8%	7,711	58.0%
	12 - < 90	5,140	14.3%	1,668	12.6%	1,371	14.7%	2,101	15.8%
		35,920		13,267		9,358		13,295	
13 - < 25	0 SABAs	755	11.5%	284	11.7%	195	12.4%	276	10.8%
	1 - < 3	625	9.5%	246	10.1%	143	9.1%	236	9.3%
	3 - < 12	1,801	27.5%	650	26.7%	427	27.2%	724	28.4%
	12 - < 90	3,372	51.5%	1,256	51.6%	807	51.3%	1,309	51.4%
		6,553		2,436		1,572		2,545	
25 - < 105	0 SABAs	20	12.1%	5	11.6%	5	13.5%	10	11.8%
	1 - < 3	6	3.6%	1	2.3%	3	8.1%	2	2.4%
	3 - < 12	27	16.4%	5	11.6%	11	29.7%	11	12.9%
	12 - < 90	112	67.9%	32	74.4%	18	48.6%	62	72.9%
		165		43		37		85	

Supplemental Table 18. Sex of patients stratified by age categories.

Gender: % Female

			OCS Sequence Categories					
	OCS		One Off		Less Frequent		Frequent	
3 <12	29,227	37.9%	13,441	37.9%	8,382	37.1%	7,404	38.8%
12 <18	16,722	46.1%	8,137	42.1%	4,634	48.7%	3,951	53.3%
18 <65	176,247	60.2%	65,958	55.8%	48,194	61.3%	62,095	64.7%
65 <110	42,889	61.3%	15,333	60.3%	10,543	62.9%	17,013	61.2%
Total	265,085		102,869		71,753		90,463	

Supplemental Table 19. Body mass index categories of patients stratified by age categories.

BMI prior to Initial OCS by Age

		OCS Sequence Categories							
		OCS (n)	%	One Off (n)	%	Less Frequent (n)	%	Frequent (n)	%
3 <12	Underweight	24,996	57.8%	9,939	58.4%	7,557	56.6%	7,500	58.1%
	Normal	14,326	33.1%	5,542	32.6%	4,527	33.9%	4,257	33.0%
	Overweight	2,626	6.1%	1,015	6.0%	820	6.1%	791	6.1%
	Obese	1,320	3.1%	514	3.0%	438	3.3%	368	2.8%
	Unknown	33,863		18,468		9,226		6,169	
		77,131		35,478		22,568		19,085	
12 <18	Underweight	4,617	22.6%	2,439	25.1%	1,167	20.6%	1,011	19.8%
	Normal	11,028	53.9%	5,154	53.0%	3,073	54.3%	2,801	54.9%
	Overweight	3,053	14.9%	1,361	14.0%	874	15.5%	818	16.0%
	Obese	1,776	8.7%	763	7.9%	541	9.6%	472	9.3%
	Unknown	15,788		9,619		3,863		2,306	
		36,262		19,336		9,518		7,408	
18 <65	Underweight	5,307	2.0%	2,362	2.3%	1,333	1.9%	1,612	1.8%
	Normal	94,355	36.4%	39,115	38.4%	25,661	36.8%	29,579	33.6%
	Overweight	80,378	31.0%	31,862	31.3%	21,572	31.0%	26,944	30.6%
	Obese	79,527	30.6%	28,504	28.0%	21,113	30.3%	29,910	34.0%
	Unknown	33,211		16,320		8,893		7,998	
		292,778		118,163		78,572		96,043	
65 <110	Underweight	1,061	1.7%	423	1.9%	206	1.4%	432	1.8%
	Normal	18,751	30.7%	6,919	31.1%	4,410	30.0%	7,422	30.6%
	Overweight	22,974	37.6%	8,283	37.2%	5,630	38.3%	9,061	37.4%
	Obese	18,363	30.0%	6,621	29.8%	4,437	30.2%	7,305	30.2%
	Unknown	8,847		3,199		2,078		3,570	
		69,996		25,445		16,761		27,790	

Supplemental Table 20. Smoking statuses of patients stratified by age categories.

% Patients by OCS use, Smoking and Age

				OCS Sequence Categories					
		OCS (n)	**%**	**One Off** (n)	**%**	**Less Frequent** (n)	**%**	**Frequent** (n)	**%**
3 <12	Never	11,873	78.9%	5,709	80.2%	3,323	78.2%	2,841	77.3%
	Current	2,995	19.9%	1,332	18.7%	868	20.4%	795	21.6%
	Ex	181	1.2%	79	1.1%	61	1.4%	41	1.1%
	Unknown	62,082		28,358		18,316		15,408	
		77,131		35,478		22,568		19,085	
12 <18	Never	12,303	67.3%	6,935	69.3%	2,989	65.3%	2,379	64.2%
	Current	5,427	29.7%	2,813	28.1%	1,448	31.6%	1,166	31.5%
	Ex	562	3.1%	257	2.6%	143	3.1%	162	4.4%
	Unknown	17,970		9,331		4,938		3,701	
		36,262		19,336		9,518		7,408	
18 <65	Never	96,066	36.7%	40,608	37.6%	26,068	37.4%	29,390	35.0%
	Current	106,875	40.8%	43,354	40.1%	28,514	40.9%	35,007	41.7%
	Ex	58,729	22.4%	24,076	22.3%	15,085	21.7%	19,568	23.3%
	Unknown	31,108		10,125		8,905		12,078	
		292,778		118,163		78,572		96,043	
65 <110	Never	20,999	33.6%	7,667	33.0%	5,132	34.1%	8,200	33.9%
	Current	16,548	26.5%	6,010	25.9%	4,117	27.4%	6,421	26.5%
	Ex	24,922	39.9%	9,539	41.1%	5,788	38.5%	9,595	39.6%
	Unknown	7,527		2,229		1,724		3,574	
		69,996		25,445		16,761		27,790	

Supplemental Table 21. Prior GINA treatment steps of patients stratified by age categories.

Respiratory Regimen (Gina Step) prior to Initial OCS by Age

				OCS Sequence Categories					
		OCS (n)	**%**	**One Off** (n)	**%**	**Less Frequent** (n)	**%**	**Frequent** (n)	**%**
3 <12	**No Athma Medication**	9,437	12.2%	4,262	12.0%	2,797	12.4%	2,378	12.5%
	Step 1 (ICS PRN/SABA alone)	22,532	29.2%	10,640	30.0%	6,542	29.0%	5,350	28.0%
	Step 2 (Daily Low Dose ICS)	24,155	31.3%	10,920	30.8%	7,242	32.1%	5,993	31.4%
	Step 3 (Low ICS/LABA or Med ICS)	14,317	18.6%	6,807	19.2%	4,103	18.2%	3,407	17.9%
	Step 4 (Med ICS/LABA or High ICS)	6,104	7.9%	2,672	7.5%	1,720	7.6%	1,712	9.0%
	Step 5 (High ICS/LABA +)	586	0.8%	177	0.5%	164	0.7%	245	1.3%
		77,131		35,478		22,568		19,085	
12 <18	**No Athma Medication**	3,648	10.1%	1,932	10.0%	972	10.2%	744	10.0%
	Step 1 (ICS PRN/SABA alone)	8,982	24.8%	5,170	26.7%	2,263	23.8%	1,549	20.9%
	Step 2 (Daily Low Dose ICS)	15,796	43.6%	8,413	43.5%	4,243	44.6%	3,140	42.4%
	Step 3 (Low ICS/LABA or Med ICS)	5,482	15.1%	2,787	14.4%	1,424	15.0%	1,271	17.2%
	Step 4 (Med ICS/LABA or High ICS)	2,137	5.9%	957	4.9%	555	5.8%	625	8.4%
	Step 5 (High ICS/LABA +)	217	0.6%	77	0.4%	61	0.6%	79	1.1%
		36,262		19,336		9,518		7,408	
18 <65	**No Athma Medication**	41,006	14.0%	14,964	12.7%	11,217	14.3%	14,825	15.4%
	Step 1 (ICS PRN/SABA alone)	74,021	25.3%	32,511	27.5%	18,911	24.1%	22,599	23.5%
	Step 2 (Daily Low Dose ICS)	92,775	31.7%	38,202	32.3%	25,983	33.1%	28,590	29.8%
	Step 3 (Low ICS/LABA or Med ICS)	53,174	18.2%	21,351	18.1%	14,314	18.2%	17,509	18.2%
	Step 4 (Med ICS/LABA or High ICS)	25,393	8.7%	9,207	7.8%	6,641	8.5%	9,545	9.9%
	Step 5 (High ICS/LABA +)	6,409	2.2%	1,928	1.6%	1,506	1.9%	2,975	3.1%
		292,778		118,163		78,572		96,043	
65 <110	**No Athma Medication**	11,534	16.5%	3,877	15.2%	2,718	16.2%	4,939	17.8%
	Step 1 (ICS PRN/SABA alone)	14,152	20.2%	5,281	20.8%	3,255	19.4%	5,616	20.2%
	Step 2 (Daily Low Dose ICS)	19,430	27.8%	7,233	28.4%	4,862	29.0%	7,335	26.4%
	Step 3 (Low ICS/LABA or Med ICS)	14,782	21.1%	5,537	21.8%	3,576	21.3%	5,669	20.4%
	Step 4 (Med ICS/LABA or High ICS)	7,885	11.3%	2,833	11.1%	1,851	11.0%	3,201	11.5%
	Step 5 (High ICS/LABA +)	2,213	3.2%	684	2.7%	499	3.0%	1,030	3.7%
		69,996		25,445		16,761		27,790	

Supplemental Table 22. Prior ICS use category of patients stratified by age categories.

Number of ICS prior to Initial OCS by Age

				OCS Sequence Categories					
		OCS (n)	**%**	**One Off** (n)	**%**	**Less Frequent** (n)	**%**	**Frequent** (n)	**%**
3 <12	0 ICS	32,965	42.7%	15,244	43.0%	9,645	42.7%	8,076	42.3%
	1 - <7 ICS	40,845	53.0%	18,947	53.4%	11,967	53.0%	9,931	52.0%
	7 - <13 ICS	3,025	3.9%	1,169	3.3%	884	3.9%	972	5.1%
	13 - <25 ICS	284	0.4%	116	0.3%	70	0.3%	98	0.5%
	25 - <105 ICS	12	0.0%	2	0.0%	2	0.0%	8	0.0%
		77,131		35,478		22,568		19,085	
12 <18	0 ICS	12,915	35.6%	7,219	37.3%	3,321	34.9%	2,375	32.1%
	1 - <7 ICS	21,090	58.2%	11,202	57.9%	5,523	58.0%	4,365	58.9%
	7 - <13 ICS	1,982	5.5%	804	4.2%	601	6.3%	577	7.8%
	13 - <25 ICS	266	0.7%	110	0.6%	69	0.7%	87	1.2%
	25 - <105 ICS	9	0.0%	1	0.0%	4	0.0%	4	0.1%
		36,262		19,336		9,518		7,408	
18 <65	0 ICS	118,056	40.3%	48,249	40.8%	30,916	39.3%	38,891	40.5%
	1 - <7 ICS	150,686	51.5%	61,249	51.8%	41,427	52.7%	48,010	50.0%
	7 - <13 ICS	20,287	6.9%	7,353	6.2%	5,300	6.7%	7,634	7.9%
	13 - <25 ICS	3,643	1.2%	1,280	1.1%	908	1.2%	1,455	1.5%
	25 - <105 ICS	106	0.0%	32	0.0%	21	0.0%	53	0.1%
		292,778		118,163		78,572		96,043	
65 <110	0 ICS	27,205	38.9%	9,692	38.1%	6,295	37.6%	11,218	40.4%
	1 - <7 ICS	29,767	42.5%	10,874	42.7%	7,358	43.9%	11,535	41.5%
	7 - <13 ICS	10,626	15.2%	3,941	15.5%	2,573	15.4%	4,112	14.8%
	13 - <25 ICS	2,360	3.4%	930	3.7%	525	3.1%	905	3.3%
	25 - <105 ICS	38	0.1%	8	0.0%	10	0.1%	20	0.1%
		69,996		25,445		16,761		27,790	

Supplemental Table 23. Prior SABA use category of patients stratified by age categories.

Number of SABAs prior to Initial OCS by Age

				OCS Sequence Categories					
		OCS (n)	**%**	**One Off** (n)	**%**	**Less Frequent** (n)	**%**	**Frequent** (n)	**%**
3 <12	0 SABAs	16,586	21.5%	7,743	21.8%	4,948	21.9%	3,895	20.4%
	1 - <3 SABAs	38,637	50.1%	18,753	52.9%	11,108	49.2%	8,776	46.0%
	3 - <12 SABAs	21,146	27.4%	8,730	24.6%	6,310	28.0%	6,106	32.0%
	12 - <90 SABAs	762	1.0%	252	0.7%	202	0.9%	308	1.6%
		77,131		35,478		22,568		19,085	
12 <18	0 SABAs	6,610	18.2%	3,539	18.3%	1,757	18.5%	1,314	17.7%
	1 - <3 SABAs	17,139	47.3%	9,994	51.7%	4,216	44.3%	2,929	39.5%
	3 - <12 SABAs	11,470	31.6%	5,453	28.2%	3,235	34.0%	2,782	37.6%
	12 - <90 SABAs	1,043	2.9%	350	1.8%	310	3.3%	383	5.2%
		36,262		19,336		9,518		7,408	
18 <65	0 SABAs	69,424	23.7%	26,303	22.3%	19,221	24.5%	23,900	24.9%
	1 - <3 SABAs	133,912	45.7%	58,975	49.9%	34,682	44.1%	40,255	41.9%
	3 - <12 SABAs	78,882	26.9%	29,452	24.9%	21,809	27.8%	27,621	28.8%
	12 - <90 SABAs	10,560	3.6%	3,433	2.9%	2,860	3.6%	4,267	4.4%
		292,778		118,163		78,572		96,043	
65 <110	0 SABAs	20,642	29.5%	7,183	28.2%	5,061	30.2%	8,398	30.2%
	1 - <3 SABAs	23,906	34.2%	9,029	35.5%	5,654	33.7%	9,223	33.2%
	3 - <12 SABAs	21,757	31.1%	7,884	31.0%	5,248	31.3%	8,625	31.0%
	12 - <90 SABAs	3,691	5.3%	1,349	5.3%	798	4.8%	1,544	5.6%
		69,996		25,445		16,761		27,790	

Supplemental Table 24. Age of patients stratified by prior GINA treatment steps.

% Patients by Age and GINA treatment Step

				OCS Sequence Categories					
		OCS		One Off		Less Frequent		Frequent	
No Asthma Rx	3 to < 12	9,417	14.3%	4,255	17.0%	2,790	15.8%	2,372	10.4%
	12 to <18	3,648	5.6%	1,932	7.7%	972	5.5%	744	3.3%
	18 to < 65	41,022	62.5%	14,969	59.8%	11,222	63.4%	14,831	64.8%
	65 to <110	11,538	17.6%	3,879	15.5%	2,720	15.4%	4,939	21.6%
		65,625		25,035		17,704		22,886	
Step 1	3 to < 12	22,504	18.8%	10,622	19.8%	6,537	21.1%	5,345	15.2%
	12 to <18	8,984	7.5%	5,171	9.6%	2,264	7.3%	1,549	4.4%
	18 to < 65	74,041	61.9%	32,524	60.7%	18,914	61.1%	22,603	64.4%
	65 to <110	14,158	11.8%	5,285	9.9%	3,256	10.5%	5,617	16.0%
		119,687		53,602		30,971		35,114	
Step 2	3 to < 12	24,110	15.8%	10,902	16.8%	7,230	17.1%	5,978	13.3%
	12 to <18	15,800	10.4%	8,416	13.0%	4,244	10.0%	3,140	7.0%
	18 to < 65	92,805	61.0%	38,212	59.0%	25,992	61.4%	28,601	63.5%
	65 to <110	19,441	12.8%	7,238	11.2%	4,864	11.5%	7,339	16.3%
		152,156		64,768		42,330		45,058	
Step 3	3 to < 12	14,292	16.3%	6,793	18.6%	4,099	17.5%	3,400	12.2%
	12 to <18	5,482	6.2%	2,787	7.6%	1,424	6.1%	1,271	4.6%
	18 to < 65	53,195	60.6%	21,363	58.6%	14,317	61.1%	17,515	62.9%
	65 to <110	14,786	16.8%	5,539	15.2%	3,577	15.3%	5,670	20.4%
		87,755		36,482		23,417		27,856	
Step 4	3 to < 12	6,097	14.7%	2,669	17.0%	1,719	16.0%	1,709	11.3%
	12 to <18	2,137	5.1%	957	6.1%	555	5.2%	625	4.1%
	18 to < 65	25,400	61.2%	9,210	58.8%	6,642	61.7%	9,548	63.3%
	65 to <110	7,885	19.0%	2,833	18.1%	1,851	17.2%	3,201	21.2%
		41,519		15,669		10,767		15,083	
Step 5	3 to < 12	583	6.2%	174	6.1%	163	7.3%	246	5.7%
	12 to <18	217	2.3%	77	2.7%	61	2.7%	79	1.8%
	18 to < 65	6,410	68.0%	1,929	67.3%	1,507	67.6%	2,974	68.7%
	65 to <110	2,215	23.5%	686	23.9%	499	22.4%	1,030	23.8%
		9,425		2,866		2,230		4,329	

Supplemental Table 25. Sex of patients stratified by prior GINA treatment steps.

Gender: % Female

		OCS Sequence Categories		
	OCS	**One Off**	**Less Frequent**	**Frequent**
No Athma Medication	36,929 56.3%	13,135 52.5%	10,140 57.3%	13,654 59.7%
Step 1 (ICS PRN/SABA alone)	64,882 54.2%	27,084 50.5%	17,038 55.0%	20,760 59.1%
Step 2 (Daily Low Dose ICS)	85,697 56.3%	34,036 52.6%	24,097 56.9%	27,564 61.2%
Step 3 (Low ICS/LABA or Med ICS)	48,534 55.3%	18,810 51.6%	13,068 55.8%	16,656 59.8%
Step 4 (Med ICS/LABA or High ICS)	23,574 56.8%	8,264 52.7%	6,120 56.8%	9,190 60.9%
Step 5 (High ICS/LABA +)	5,469 58.0%	1,540 53.7%	1,290 57.8%	2,639 61.0%
	265,085	102,869	71,753	90,463

Supplemental Table 26. Body mass index of patients stratified by prior GINA treatment steps.

% Patients by OCS use, BMI and GINA treatment Step

				OCS Sequence Categories					
			OCS	One Off		Less Frequent		Frequent	
No Asthma Rx	Underweight	3,589	7.1%	1,456	8.0%	967	7.3%	1,166	6.1%
	Normal	17,713	35.1%	6,881	37.8%	4,730	35.6%	6,102	32.1%
	Overweight	15,395	30.5%	5,422	29.8%	4,043	30.5%	5,930	31.2%
	Obese	13,819	27.4%	4,455	24.5%	3,536	26.6%	5,828	30.6%
	Unknown	15,109		6,821		4,428		3,860	
		65,625		25,035		17,704		22,886	
Step 1	Underweight	9,814	10.3%	4,304	10.7%	2,751	11.0%	2,759	9.1%
	Normal	33,783	35.4%	15,082	37.5%	8,889	35.7%	9,812	32.3%
	Overweight	26,459	27.7%	11,079	27.6%	6,826	27.4%	8,554	28.2%
	Obese	25,374	26.6%	9,706	24.2%	6,438	25.9%	9,230	30.4%
	Unknown	24,257		13,431		6,067		4,759	
		119,687		53,602		30,971		35,114	
Step 2	Underweight	13,807	11.0%	6,045	12.0%	4,037	11.5%	3,725	9.4%
	Normal	47,415	37.9%	19,753	39.2%	13,460	38.2%	14,202	35.9%
	Overweight	34,028	27.2%	13,494	26.8%	9,487	26.9%	11,047	28.0%
	Obese	29,926	23.9%	11,113	22.0%	8,272	23.5%	10,541	26.7%
	Unknown	26,980		14,363		7,074		5,543	
		152,156		64,768		42,330		45,058	
Step 3	Underweight	5,657	8.1%	2,248	8.3%	1,648	8.8%	1,761	7.4%
	Normal	24,781	35.6%	9,836	36.5%	6,794	36.3%	8,151	34.1%
	Overweight	20,475	29.4%	8,057	29.9%	5,336	28.5%	7,082	29.6%
	Obese	18,680	26.8%	6,830	25.3%	4,926	26.3%	6,924	28.9%
	Unknown	18,162		9,511		4,713		3,938	
		87,755		36,482		23,417		27,856	
Step 4	Underweight	2,716	7.8%	990	8.0%	763	8.3%	963	7.2%
	Normal	11,972	34.2%	4,349	34.9%	3,115	34.0%	4,508	33.6%
	Overweight	10,073	28.8%	3,665	29.4%	2,592	28.3%	3,816	28.4%
	Obese	10,273	29.3%	3,443	27.7%	2,689	29.4%	4,141	30.8%
	Unknown	6,485		3,222		1,608		1,655	
		41,519		15,669		10,767		15,083	
Step 5	Underweight	398	4.6%	120	4.6%	97	4.7%	181	4.5%
	Normal	2,796	32.1%	829	31.8%	683	33.2%	1,284	31.8%
	Overweight	2,601	29.9%	804	30.8%	612	29.7%	1,185	29.3%
	Obese	2,914	33.5%	856	32.8%	668	32.4%	1,390	34.4%
	Unknown	716		258		170		288	
		9,425		2,867		2,230		4,328	

Supplemental Table 27. Smoking statuses of patients stratified by prior GINA treatment steps.

% Patients by OCS use, Smoking Status and GINA treatment Step

		OCS Sequence Categories							
		OCS		One Off		Less Frequent		Frequent	
No Asthma Rx	Never	17,714	38.8%	6,727	39.9%	4,860	40.2%	6,127	36.7%
	Current	17,614	38.6%	6,298	37.3%	4,800	39.7%	6,516	39.0%
	Ex	10,335	22.6%	3,839	22.8%	2,439	20.2%	4,057	24.3%
	Unknown	19,962		8,171		5,605		6,186	
		65,625		25,035		17,704		22,886	
Step 1	Never	32,674	38.1%	15,338	40.0%	8,183	38.3%	9,153	35.0%
	Current	33,428	38.9%	14,570	38.0%	8,472	39.7%	10,386	39.7%
	Ex	19,749	23.0%	8,408	21.9%	4,700	22.0%	6,641	25.4%
	Unknown	33,836		15,286		9,616		8,934	
		119,687		53,602		30,971		35,114	
Step 2	Never	48,035	42.1%	21,385	43.6%	13,266	42.7%	13,384	39.4%
	Current	40,934	35.9%	17,209	35.1%	11,217	36.1%	12,508	36.8%
	Ex	25,077	22.0%	10,409	21.2%	6,605	21.2%	8,063	23.7%
	Unknown	38,110		15,765		11,242		11,103	
		152,156		64,768		42,330		45,058	
Step 3	Never	27,370	39.6%	11,796	41.2%	7,221	39.8%	8,353	37.5%
	Current	24,389	35.3%	9,831	34.4%	6,503	35.8%	8,055	36.2%
	Ex	17,296	25.0%	6,991	24.4%	4,436	24.4%	5,869	26.3%
	Unknown	18,700		7,864		5,257		5,579	
		87,755		36,482		23,417		27,856	
Step 4	Never	12,874	37.4%	4,952	38.1%	3,342	37.8%	4,580	36.3%
	Current	12,331	35.8%	4,571	35.2%	3,217	36.4%	4,543	36.0%
	Ex	9,254	26.9%	3,458	26.6%	2,289	25.9%	3,507	27.8%
	Unknown	7,060		2,688		1,919		2,453	
		41,519		15,669		10,767		15,083	
Step 5	Never	2,574	30.6%	721	27.8%	640	32.2%	1,213	31.7%
	Current	3,149	37.5%	1,030	39.7%	738	37.2%	1,381	36.1%
	Ex	2,682	31.9%	846	32.6%	608	30.6%	1,228	32.1%
	Unknown	1,019		269		244		506	
		9,424		2,866		2,230		4,328	

Supplemental Table 28. Prior SABA use category of patients stratified by prior GINA treatment steps.

% Patients by OCS use, GINA step and SABA use

				OCS Sequence Categories					
		OCS		One Off		Less Frequent		Frequent	
No Asthma Rx	0 SABAs	65,624	100.0%	25,034	100.0%	17,704	100.0%	22,886	100.0%
	1 - < 3	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	3 - < 12	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	12 - < 90	0	0.0%	0	0.0%	0	0.0%	0	0.0%
		65,624		25,034		17,704		22,886	
Step 1	0 SABAs	1,827	1.5%	868	1.6%	520	1.7%	439	1.3%
	1 - < 3	95,034	79.4%	43,810	81.7%	24,334	78.6%	26,890	76.6%
	3 - < 12	20,931	17.5%	8,279	15.4%	5,661	18.3%	6,991	19.9%
	12 - < 90	1,895	1.6%	645	1.2%	456	1.5%	794	2.3%
		119,687		53,602		30,971		35,114	
Step 2	0 SABAs	23,780	15.6%	10,063	15.5%	6,812	16.1%	6,905	15.3%
	1 - < 3	68,434	45.0%	31,379	48.4%	18,379	43.4%	18,676	41.4%
	3 - < 12	54,539	35.8%	21,465	33.1%	15,623	36.9%	17,451	38.7%
	12 - < 90	5,403	3.6%	1,861	2.9%	1,516	3.6%	2,026	4.5%
		152,156		64,768		42,330		45,058	
Step 3	0 SABAs	14,802	16.9%	6,119	16.8%	4,048	17.3%	4,635	16.6%
	1 - < 3	33,276	37.9%	14,999	41.1%	8,709	37.2%	9,568	34.3%
	3 - < 12	35,073	40.0%	13,773	37.8%	9,466	40.4%	11,834	42.5%
	12 - < 90	4,604	5.2%	1,591	4.4%	1,194	5.1%	1,819	6.5%
		87,755		36,482		23,417		27,856	
Step 4	0 SABAs	6,050	14.6%	2,291	14.6%	1,623	15.1%	2,136	14.2%
	1 - < 3	14,021	33.8%	5,705	36.4%	3,560	33.1%	4,756	31.5%
	3 - < 12	18,310	44.1%	6,671	42.6%	4,805	44.6%	6,834	45.3%
	12 - < 90	3,138	7.6%	1,002	6.4%	779	7.2%	1,357	9.0%
		41,519		15,669		10,767		15,083	
Step 5	0 SABAs	1,178	12.5%	392	13.7%	280	12.6%	506	11.7%
	1 - < 3	2,829	30.0%	858	29.9%	678	30.4%	1,293	29.9%
	3 - < 12	4,401	46.7%	1,331	46.4%	1,047	47.0%	2,023	46.7%
	12 - < 90	1,016	10.8%	285	9.9%	225	10.1%	506	11.7%
		9,424		2,866		2,230		4,328	

Supplemental Table 29. Prior ICS use category of patients stratified by prior GINA treatment steps.

% Patients by OCS use, GINA Step and ICS use

				OCS Sequence Categories					
		OCS		One Off		Less Frequent		Frequent	
No Asthma Rx	0	65,625	100.0%	25,035	100.0%	17,704	100.0%	22,886	100.0%
	1 - < 7	0	0.0%		0.0%		0.0%		0.0%
	7 - < 13	0	0.0%		0.0%		0.0%		0.0%
	13 - < 25	0	0.0%		0.0%		0.0%		0.0%
	25 - < 105	0	0.0%		0.0%		0.0%		0.0%
		65,625		25,035		17,704		22,886	
Step 1	0	119,189	99.6%	53,358	99.5%	30,843	99.6%	34,988	99.6%
	1 - < 7	461	0.4%	221	0.4%	122	0.4%	118	0.3%
	7 - < 13	32	0.0%	21	0.0%	6	0.0%	5	0.0%
	13 - < 25	5	0.0%	2	0.0%	0	0.0%	3	0.0%
	25 - < 105	0	0.0%	0	0.0%	0	0.0%	0	0.0%
		119,687		53,602		30,971		35,114	
Step 2	0	3,777	2.5%	1,238	1.9%	1,014	2.4%	1,525	3.4%
	1 - < 7	135,503	89.1%	58,630	90.5%	37,809	89.3%	39,064	86.7%
	7 - < 13	11,228	7.4%	4,285	6.6%	3,066	7.2%	3,877	8.6%
	13 - < 25	1,591	1.0%	604	0.9%	427	1.0%	560	1.2%
	25 - < 105	57	0.0%	11	0.0%	14	0.0%	32	0.1%
		152,156		64,768		42,330		45,058	
Step 3	0	2,556	2.9%	782	2.1%	618	2.6%	1,156	4.1%
	1 - < 7	70,081	79.9%	29,950	82.1%	18,899	80.7%	21,232	76.2%
	7 - < 13	12,835	14.6%	4,888	13.4%	3,325	14.2%	4,622	16.6%
	13 - < 25	2,235	2.5%	846	2.3%	563	2.4%	826	3.0%
	25 - < 105	48	0.1%	16	0.0%	12	0.1%	20	0.1%
		87,755		36,482		23,417		27,856	
Step 4	0	7	0.0%	1	0.0%	1	0.0%	5	0.0%
	1 - < 7	30,224	72.8%	11,612	74.1%	7,967	74.0%	10,645	70.6%
	7 - < 13	9,175	22.1%	3,249	20.7%	2,359	21.9%	3,567	23.6%
	13 - < 25	2,065	5.0%	795	5.1%	430	4.0%	840	5.6%
	25 - < 105	48	0.1%	12	0.1%	10	0.1%	26	0.2%
		41,519		15,669		10,767		15,083	
Step 5	0	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	1 - < 7	6,106	64.8%	1,849	64.5%	1,475	66.1%	2,782	64.3%
	7 - < 13	2,649	28.1%	824	28.8%	602	27.0%	1,223	28.3%
	13 - < 25	657	7.0%	189	6.6%	152	6.8%	316	7.3%
	25 - < 105	12	0.1%	4	0.1%	1	0.0%	7	0.2%
		9,424		2,866		2,230		4,328	

Supplemental Table 30. Comparison of all admissions by OCS use patterns with day cases excluded, with stratification for the type of admissions.

Admissions, excluding day cases (spells)

	All Consultations									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate/yr	P value
Non OCS	11,810	36,838	3.12	3.06	3.18	3.45	2	(1-4)	0.32	
OCS	28,343	97,217	3.43	3.36	3.50	5.87	2	(1-4)	0.38	p<0.0001*
Non OCS	11,810	36,838	3.12	3.06	3.18	3.45	2	(1-4)	0.32	
One Off	12,801	39,547	3.09	2.97	3.21	7.14	2	(1-4)	0.39	
Less Frequent	8,193	28,665	3.50	3.41	3.59	4.31	2	(1-4)	0.34	
Frequent	7,349	29,005	3.95	3.84	4.06	4.78	3	(1-5)	0.43	p<0.0001**
	Respiratory as Primary									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	1,929	3,064	1.59	1.52	1.66	1.59	1	(1-2)	0.16	
OCS	8,322	15,971	1.92	1.87	1.97	2.46	1	(1-2)	0.23	p<0.0001*
Non OCS	1,929	3,064	1.59	1.52	1.66	1.59	1	(1-2)	0.16	
One Off	2,979	4,912	1.65	1.59	1.71	1.68	1	(1-2)	0.24	
Less Frequent	2,460	4,699	1.91	1.81	2.01	2.62	1	(1-2)	0.20	
Frequent	2,883	6,360	2.21	2.10	2.31	2.91	1	(1-2)	0.25	p<0.0001**
	Asthma as Primary									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	43	56	1.30	1.08	1.52	0.74	1	(1-1)	0.15	
OCS	2,104	3,158	1.50	1.42	1.58	1.89	1	(1-1)	0.19	p=0.8507*
Non OCS	43	56	1.30	1.08	1.52	0.74	1	(1-1)	0.15	
One Off	719	984	1.37	1.27	1.47	1.33	1	(1-1)	0.23	
Less Frequent	671	975	1.45	1.33	1.57	1.60	1	(1-1)	0.16	
Frequent	714	1,199	1.68	1.50	1.86	2.50	1	(1-1)	0.19	p<0.0001**
	Any Asthma									
	Patients	Episodes	Mean	95% CI		SD	Median	IQR	Rate	P value
Non OCS	711	1,359	1.91	1.75	2.07	2.15	1	(1-2)	0.21	
OCS	16,115	35,181	2.18	2.15	2.22	2.39	1	(1-2)	0.25	p<0.0001*
Non OCS	711	1,359	1.91	1.75	2.07	2.15	1	(1-2)	0.21	
One Off	6,880	13,962	2.03	1.98	2.08	2.28	1	(1-2)	0.28	
Less Frequent	4,940	10,862	2.20	2.14	2.26	2.21	1	(1-3)	0.22	
Frequent	4,295	10,357	2.41	2.33	2.49	2.74	2	(1-3)	0.26	p<0.0001**

* p Values caclulated using Mann-Whitney test

** p values calculated using Chi squared test

Supplemental Table 31. Distribution of patients across OCS use pattern categories, as stratified by annualized OCS dose for the period of OCS prescription.

Dose category by OCS Sequence

	OCS Sequence Categories							
	OCS		One Off		Less Frequent		Frequent	
0 - <250mg	338,106	71.0%	169,736	85.5%	96,758	75.9%	71,612	47.6%
250 - <500mg	74,382	15.6%	24,885	12.5%	18,953	14.9%	30,544	20.3%
500 - <1g	30,097	6.3%	3,593	1.8%	8,743	6.9%	17,761	11.8%
1g +	33,582	7.1%	208	0.1%	2,965	2.3%	30,409	20.2%
	476,167		198,422		127,419		150,326	

Supplemental Table 32. Relationship between annualized OCS dose and study outcomes. All hazard ratios were generated using time-varying multivariable Cox regression analysis adjusting for age, gender, BMI, smnoking, and time-varying OCS prescriptions.

Hazard Ratio - Variable Analysis

Adverse Events	<0.250mg			0.250g-0.499mg			500-999mg			1g+		
	HR	95% CI	95% CI	HR	95% CI	95% CI	HR	95% CI	95% CI	HR	95% CI	95% CI
Any adverse event	1.41	1.40	1.42	1.07	1.06	1.08	1.03	1.01	1.05	1.09	1.07	1.11
Diabetes	1.74	1.71	1.77	1.26	1.22	1.30	1.20	1.13	1.26	1.31	1.25	1.38
Osteoporosis	1.36	1.33	1.38	0.98	0.94	1.02	0.99	0.93	1.06	1.09	1.03	1.16
Hypertension	1.38	1.36	1.40	1.24	1.21	1.28	1.25	1.20	1.31	1.19	1.14	1.25
Glaucoma	1.62	1.59	1.65	1.16	1.11	1.21	1.11	1.04	1.18	1.19	1.12	1.26
Sleep disorders	1.63	1.60	1.65	1.19	1.16	1.23	1.20	1.14	1.26	1.22	1.16	1.28
Sleep apnoea	2.52	2.42	2.63	2.17	2.00	2.34	2.26	2.01	2.55	2.48	2.23	2.77
Depression/Anxiety	1.50	1.48	1.51	1.17	1.15	1.20	1.10	1.06	1.14	1.21	1.17	1.25
Pneumonia	2.46	2.39	2.53	2.08	1.98	2.19	2.20	2.05	2.37	2.07	1.93	2.23
Cataracts	1.50	1.48	1.52	1.56	1.52	1.60	1.65	1.59	1.71	1.61	1.56	1.67
Cardiovascular diseases	1.47	1.44	1.50	1.21	1.16	1.25	1.20	1.14	1.27	1.13	1.07	1.20
Renal disease	1.20	1.19	1.21	0.90	0.88	0.92	0.85	0.82	0.88	0.90	0.88	0.93
Dyslipidaemia	1.30	1.29	1.32	0.93	0.91	0.95	0.82	0.79	0.85	0.83	0.81	0.86
Peptic ulcer	1.39	1.32	1.47	0.88	0.78	0.99	0.93	0.78	1.11	0.93	0.78	1.10
Behavoural Issues	1.11	0.66	1.88	1.20	0.71	2.05	0.00	0.63	1.89	1.21	2.08	2.08