OPRI
Study protocol

Study protocol

ICARUS: Inhaled Corticosteroid And Real life Unlicensed Spacer use – stage 2

Studying the adverse events in real-life unlicensed and licensed use of inhaled corticosteroids with spacers in patients with asthma in the United Kingdom

Date:
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TITLE	ICARUS: Stage 2
Subtitle	Examining the real-life unlicensed and licensed use of inhaled corticosteroids with spacers in patients with asthma in the United Kingdom
Protocol version number	1.3
Medicinal product	Clenil (beclomethasone dipropionate)
Medical device	Aerochamber, Volumatic spacers
Marketing authorisation holder	Clenil: Chiesi Limited 333 Styal Road Manchester M22 5LG
Study aims and objectives	The aim of this study is to compare matched patients that are treated with non-extrafine beclomethasone dipropionate with a Volumatic® spacer against patients that are treated with non-extrafine beclomethasone dipropionate with an Aerochamber® spacer. As a subquestion, patients prescribed Aerochamber® and Volumatic® who step down their inhaled corticosteroids will be compared in terms of baseline asthma exacerbations and SABA usage
Country of study	UK
Author	OPRI 5a Coles Lane Oakington Cambridge CB24 3BA United Kingdom

1.0 Contents

2.0 Tables

3.0 Background

Asthma is considered a heterogeneous obstructive lung disease caused by an inappropriate inflammatory reaction in the airways. Increased mucus production and bronchospasm can lead to exacerbations and significant mortality. Narrowed airways can result in reduced quality of everyday living – the Royal College of Physicians three questions surveys whether asthma is controlled by asking the patient whether they have nocturnal disturbances, whether asthma limits activity, and whether they suffer from any daytime symptoms. Treatment of asthma is centered around the use of inhaled corticosteroids, which are recommended in all but the mildest patients with asthma[1]. The latest GINA guidelines recommend patients who require their reliever more than once a fortnight be prescribed inhaled corticosteroids[1]. Reducing the inflammatory response not only helps control the disease, prevents exacerbations and reduces the daily symptoms, but also might help to reduce any chronic changes that occur as a result of long term inflammation.

However, the use of corticosteroids can cause significant side effects, especially when prescribed to young children or when higher doses are required. Inhaled corticosteroids are dispensed at significantly lower doses than oral corticosteroids, significantly reducing the risk of glucocorticoid side effects compared to oral therapy [2](Table 1).

System Class	Adverse Reaction	Frequency
Infections	Oral thrush	Very common
Immune system	Rash, urticarial, pruritus, erythema	Uncommon
	Oedema	Very Rare
Endocrine	Adrenal suppression, bone density reduction, growth retardation	Very Rare
Psychiatric disorders	Psychomotor hyperactivity, sleep disorder, depression, anxiety, behavioural disorders	Unknown
Nervous system disorders	Headache	Unknown
Eye disorders	Cataracts, glaucoma	Very Rare
Thoracic disorders	Hoarseness, throat irritation	Common
	Cough, bronchospasm, wheezing, dyspnoea	Very rare
Gastrointestinal	Nausea	Unknown

Table 1: Side effects of non-extrafine beclomethasone dipropionate listed by system [3]

Unlike oral therapy, the use of inhaled corticosteroids requires a meaningful delivery of the drug to the lungs, which requires good adherence and a proper inhaler technique from the

patient. Up to 80% of the inhaled drug ends up impacting in the oropharynx and being systemically absorbed, even when good technique is used. Accordingly, spacer devices are suggested to improve drug delivery to the lungs[4].

Spacer devices are an extension add-on device that allows the aerosol from metered dose inhalers to expand and slow down. This effect changes the actuation spray into a fine mist, allowing more time for the evaporation of the propellant, so a larger proportion of the particles can be inhaled. A fine mist is less likely to impact the oropharynx and reach the target of the lungs. Spacers also help to coordinate the breathing between actuation and breath. The use of bronchodilators and spacers is on par to that of nebulisers in terms of effectiveness [5]. The improved drug delivery from using a spacer in conjunction with a pMDI can help reduce the amount of inhaled corticosteroid required.

The use of spacers is recommended by NICE for patients aged under 16 with the following guidance [4]:

Inhaler devices for children under 5 years with chronic asthma (August 2000)

A child's needs and likelihood of good compliance should govern the choice of inhaler and spacer device; only then should cost be considered.

- corticosteroid and bronchodilator therapy should be delivered by pressurised metered-dose inhaler and spacer device, with a facemask if necessary;

Inhaler devices for children 5–15 years with chronic asthma (March 2002)

A child's needs, ability to develop and maintain effective technique, and likelihood of good compliance should govern the choice of inhaler device; only then should cost be considered.

- corticosteroid therapy should be routinely delivered by a pressurised metered-dose inhaler and spacer device;
- for other inhaled drugs, particularly bronchodilators, a wider range of devices should be considered;
- children and their carers should be trained in the use of the chosen device; suitability of the device should be reviewed at least annually. Inhaler technique and compliance should be monitored.

Figure 1: NICE guidance for spacer use in children

Spacers are also advised for patients who have problems with co-ordinating actuation since they are simpler to use. They are also advised to be used in adult patients using high doses of inhaled corticosteroids (cut off defined as 500 µg fluticasone/1000 µg beclomethasone

dipropionate equivalent or higher)[6]. Finally, elderly patients, those with false teeth or mouth/lip structural damage, or those unable to coordinate activation with respiration are suitable candidates for an spacer.

There are several brands of spacers that fit different inhalers as shown in Table 2:

MDI	Able spacer	Aerochamber Plus	Optichamber	Pocket Chamber	Volumatic
Beclomethasone Dipropionate (Clenil Modulite)	a	a	a	a	✓
Beclomethasone Dipropionate HFA	a	✓	a	a	×
Fluticasone propionate	a	✓	a	a	✓
Ciclesonide	a	✓	a	a	×
Beclomethasone/ formoterol	a	✓	a	a	×
Fluticasone propionate / formoterol	a	✓	a	a	×
Fluticasone propionate / salmeterol	a	✓	a	a	✓

Table 2: Spacer and suitable MDI devices

a = fits spacer but not licensed for use ✓ = licensed for use × = does not fit spacer

The license for non-extrafine beclomethasone dipropionate (Clenil Modulite) with the Volumatic spacer, but it has also been shown to be prescribed off-license for Aerochamber, in previous unpublished research from OPRI (formerly Research in Real Life). There is a concern that the use of some spacers may result in a greater number of adverse events; larger spacers such as the Volumatic® spacer have been shown to feature a lower deposition of drug on the filters compared to the use of smaller spacers and thus less more effective distribution [2].

In real-life practice, the effectiveness of any device combination depends on the willingness and ability of the patient to use it[7]. Patients may not use the spacers correctly in a number of ways as described in Table 3:

Errors with spacer devices
Placement of inhaler in the wrong end of the spacer
Failure to exhale slowly
Failure to shake inhaler well
Waiting too long before inhaling
Pressing too many times on the MDI
Rapid inhalation

Exhaling into device
Inadequate breath hold

Table 3: Spacer errors [7]

In addition, primary care physicians who prescribe spacers may not adhere to prescription guidelines given that their patients may be unwilling to carry or use the devices.

In stage 1 of this study, a significant number of patients prescribed spacers and non-extra-fine beclomethasone dipropionate off license were found. Stage 2 will focus on comparing the adverse events between non-extra-fine beclomethasone dipropionate prescribed using the Volumatic® spacer and the Aerochamber® spacer.

For this study, database outcomes and patient questionnaires will be examined. Asthma questionnaires have been used in quality of life reviews[8], randomised controlled trials[9] and have been an essential component for improving asthma care in the United Kingdom [10].

Patient-reported side effects will provide a unique perspective to disease outcomes compared to database Read codes, where bruising for example is seldom reported. An extract of the adult and child questionnaire is shown below (Figure 2 and Figure 3).

Do you experience any of these side effects from your preventer inhaler? Please tick yes or no for each one

	Yes	*No*		*Yes*	*No*
Continual sore mouth/throat	☐	☐	Hoarse voice	☐	☐
Oral Thrush	☐	☐	Abnormal Weight Gain	☐	☐
Bruising	☐	☐	Cough	☐	☐

Figure 2: British Lung Foundation asthma questionnaire extract for adults

Does your child experience any of the following side effects from their preventer inhaler?
Please tick **Yes** or **No** for each one

	Yes	No		Yes	No
Continual sore mouth or throat	☐	☐	Hoarse voice	☐	☐
Oral thrush	☐	☐	Abnormal weight gain	☐	☐
Bruising	☐	☐	Cough	☐	☐

Figure 3: British Lung Foundation asthma questionnaire extract for children

4.0 Study aims and objectives

4.1 Study aims

The aim of this study is to characterise the adverse events in patients with asthma treated with non-extra fine beclomethasone dipropionate with Volumatic® spacer or Aerochamber® spacer.

In addition, as an additional question, the study will also attempt to explore whether

Aerochamber patients experience increased efficacy leading to their daily dose of non-EF beclomethasone being changed (stepped down or titrated down) compared to Volumatic users.

4.2 Study objectives

4.2.1 Primary objective

Non-inferiority of non-extrafine beclomethasone dipropionate with Aerochamber® spacer compared to non-extrafine beclomethasone dipropionate with Volumatic® spacer, in terms of the rate of patient-reported outcomes listed on the British Lung Foundation Questionnaire, ie the incidence of oral thrush or hoarseness.

4.2.2 Secondary objective

Comparison of database outcomes for non-extrafine beclomethasone dipropionate with Volumatic® spacer and non-extrafine beclomethasone dipropionate with Aerochamber® spacer in terms of Read codes for adverse reactions to beclomethasone dipropionate over a three-year period.

4.2.3 Exploratory objective

Patients who step down their prescribed dose of non-extra fine beclomethasone dipropionate with Volumatic® and Aerochamber® will be compared in terms of baseline exacerbation rate and SABA usage.

4.3 Sub-analysis

1) To split the primary and secondary objectives by patients under 16 years of age and patients 16–65 years of age at the time of the index date.
2) To split the primary and secondary objectives by patients prescribed high dose (≥1000 µg of beclomethasone dipropionate and low dose <1000 µg beclomethasone dipropionate).

5.0 Study design

5.1 Products studied

The medicinal product is non extra fine beclomethasone which provides 50, 100, 200 and 250 µg beclomethasone diproprionate per actuation in a pressurised MDI device.[11]
The devices studied include the Volumatic® and Aerochamber® spacer devices.

5.2 Study design (questionnaire outcomes)

A longitudinal study to compare patient-reported side effects for asthma patients prescribed non extra fine beclomethasone with Volumatic® spacer or Aerochamber® spacer (Figure 4). The index date of the study is the date of administration of the BLF Questionnaire. This study design will also be used to explore patients who step down at the index date with Volumatic and Aerochamber spacers. This exploratory objective will explore the baseline year (ie: year before index) in terms of comparative efficacy. If required (due to insufficient patients) an additional study design will be incorporated which will consider date of step down as index date (instead of date of BLF questionnaire).

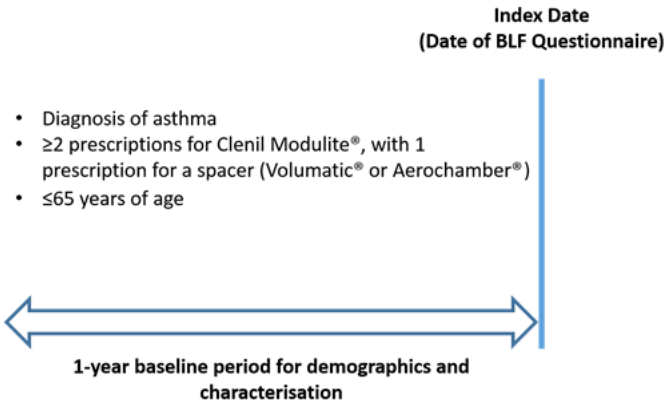

Figure 4: Study Design (questionnaire outcomes)

5.3 Sub analysis

1. Characterisation of patients in terms of demographics, baseline variables and patient-reported outcomes (BLF Questionnaire) by age group (<16, 16–65, all ages, >65 as an exploratory group)
2. Characterisation of patients in terms of demographics, baseline variables and adverse events by prescription for high daily ICS dose (>500 µg fluticasone equivalence/1000 µg beclomethasone dipropionate) defined as ≥1 prescription for 1000 µg beclomethasone dipropionate during the baseline period
3. Characterisation of patients in terms of demographics, baseline variables and patient-reported outcomes (BLF Questionnaire) by high daily ICS dose (>500

µg fluticasone equivalence/1000 µg beclomethasone dipropionate) calculated as an average daily ICS dose* during the baseline period

5.4 Study design (database outcomes)

This is a historical database study composed of a 1-year baseline period for demographics, characterisation and matching. The index date is the date of prescription of a spacer (Volumatic® or Aerochamber®), with a 3-year outcome period for detection of adverse events. Patients will require 4 years' continuous practice data.

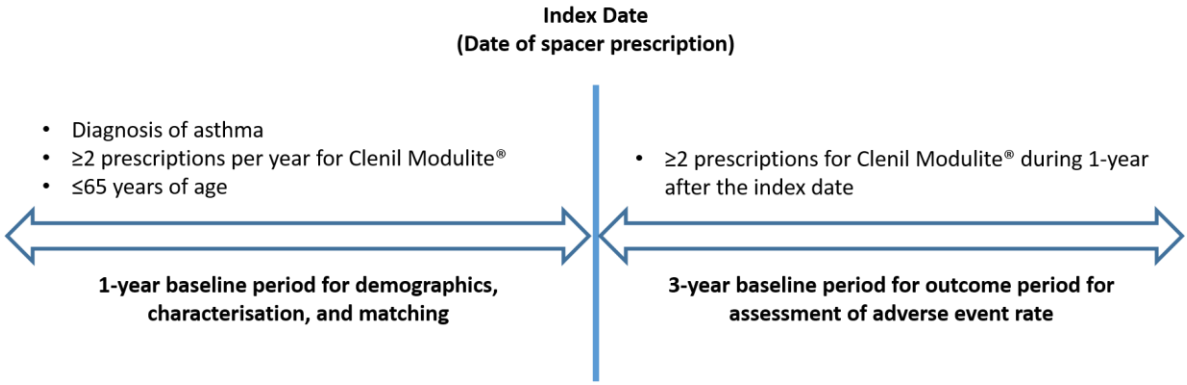

Figure 5: Study Design (database outcomes) extractions from 2005 onwards

5.5 Sub analysis

1. Characterisation of patients in terms of demographics, baseline variables and adverse events by age group (<16, 16–65, all ages, >65 as an exploratory group)
2. Characterisation of patients in terms of demographics, baseline variables and adverse events by prescription for high daily ICS dose (>500 µg fluticasone equivalence/1000 µg beclomethasone dipropionate) defined as ≥1 prescription for 1000 µg beclomethasone dipropionate during the baseline period
3. Characterisation of patients in terms of demographics, baseline variables and adverse events by high daily ICS dose (>500 µg fluticasone equivalence/1000 µg beclomethasone dipropionate) calculated as an average daily ICS dose† during the baseline period

* Average daily ICS dose will be calculated as: ∑(((Count of inhalers * doses in pack) / baseline period) * mcg strength)
† Average daily ICS dose will be calculated as: ∑(((Count of inhalers * doses in pack) / baseline period) * mcg strength)

6.0 Study Population

6.1 Inclusion and exclusion criteria (questionnaire outcomes)

Inclusion criteria
Diagnosis for asthma (confirmed by diagnostic Read code)
Age ≤65 years at index date for main outcomes, all ages for exploratory
Two years of continuous practice data comprising 2-year data prior to questionnaire
Asthma questionnaire returned
Prescription of Aerochamber® or Volumatic® spacer prior to the questionnaire
≥2 separate prescriptions of non extrafine beclomethasone in the baseline year prior to the index date
Exclusion criteria
Received multiple types of ICS or FDC ICS/LABA during the baseline period or at the index date
Prescribed both Aerochamber and Volumatic spacers

Table 6: Inclusion and exclusion criteria for questionnaire outcomes

6.2 Inclusion and exclusion criteria (database outcomes)

Inclusion criteria
Diagnosis for asthma (confirmed by diagnostic Read code)
Age ≤65 years at index date for main outcomes, all ages for exploratory
4-years of continuous practice data comprising 1-year baseline data and 3-year outcome data
≥2 separate prescriptions of the beclomethasone pMDI in outcome year after index prescription date
Stepped down ICS in outcome period
Spacer prescription (Aerochamber or Volumatic)
Exclusion criteria
Received multiple types of ICS or FDC ICS/LABA during the baseline period, at the index date or during the outcome period
Prescribed both Aerochamber and Volumatic spacers

Table 7: Inclusion and exclusion criteria for database outcomes

6.3 Data source

The study will use patient data from the Optimum Patient Care Research Database (OPCRD).[12] The study team work with anonymous data removed of any patient identifiable

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

The OPCRD currently comprises longitudinal medical records for over 2.5 million patients from over 550 primary care practices across the UK. The OPCRD contains two types of data: (1) routinely recorded clinical data and (2) questionnaire responses from over 55,700 patients with respiratory conditions. The OPC questionnaires are a compilation of validated questions covering symptoms, disease control, triggers, side effects, quality of life, and unique adherence measures. OPCRD is the only database in the UK that complements routinely recorded disease coding and prescribing information with patient-reported outcomes. The OPCRD also links with nationwide practice prescribing data to enable targeted delivery of dataset needs.

A unique dataset is provided for each study with only the variables necessary to inform the study objectives included. Only studies that evaluate risk-benefit profiles of treatment options will report adverse events of treatments, ensuring confidentiality of data at all stages. The study will be performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices. The database has received a favourable opinion from the Health Research Authority for clinical research use (REC reference: 15/EM/0150). Governance is provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG, http://www.effectivenessevaluation.org/) to govern the standard of research conducted on internationally recognised databases. All research using OPCRD will be registered on established study databases such as the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP, http://www.encepp.eu/).

7.0 Study variables and study outcomes

Refer to Appendices for detailed variable and outcome definitions, and mock tables of demographic and baseline variables and outcome results.

7.1 Demographic and baseline variables for patient questionnaire outcomes

- Gender (male/female)

- Age of patient (years, at index date)
- Body Mass Index (BMI, at time nearest index date, calculated from height and weight data if available, otherwise taken from practice-recorded BMI value, detailed definition in Appendix 1)
- Smoking status (identified by Read code, closest to index date)
- SABA daily dose calculated 1 year prior to index date*
- Percentage predicted peak flow (closest to index date)
- Total cumulative ICS dose
- Spacer type
- Total cumulative non-extrafine beclomethasone dipropionate therapy
- Duration of ICS therapy
- Number of exacerbations (ATS/ERS 2015 consensus definition†) from 1 year prior to index date
- Number of oral corticosteroid prescriptions from 1 year prior to index date
- Number of antibiotic prescriptions for lower respiratory tract infections from 1 year prior to index date
- History of comorbidities related to asthma:
    - Pneumonia (Read code diagnosis from 1 year prior to the index date)
    - Diabetes (Read code diagnosis and/or antidiabetic drugs ever prior to the index date)
    - Ischaemic heart disease (Read code diagnosis before one year prior to the index date)
    - Rhinitis (Read code diagnosis, including chronic and allergic rhinitis and prescriptions for nasal steroids between one year prior to index date)
    - Eczema (Read code diagnosis between one year prior to index date)
    - Osteoporosis (Read code diagnosis between one year prior to the index date)
    - Charlson Comorbidity Index (based on Read code diagnoses between one year prior to index date, detailed definition in Appendix 1)

7.2 Demographics and baseline variables for database outcomes

- Gender (male/female)

* Calculated as average number of puffs per day over the year multiplied by strength (in µg);
i.e. $\frac{Number\ of\ inhalers * doses\ per\ inhaler}{365} * strength$

† See appendix 1 for definitions

- Age of patient (years, at index date)
- Body Mass Index (BMI, at time nearest index date, calculated from height and weight data if available, otherwise taken from practice-recorded BMI value, detailed definition in Appendix 1)
- Smoking status (identified by Read code, closest to index date)
- SABA daily dose calculated in baseline prior to index date*
- Percentage predicted peak flow (peak flow predicted, closest to index date)
- Total cumulative ICS dose
- Total cumulative non-extrafine beclomethasone dipropionate therapy
- Duration of ICS therapy
- Number of exacerbations (ATS/ERS 2015 consensus definition†) prior to index date
- Number of oral corticosteroid prescriptions prior to index date
- Number of antibiotic prescriptions for lower respiratory tract infections prior to index date
- History of comorbidities related to asthma:
    - Pneumonia (Read code diagnosis in the year prior to the index date)
    - Diabetes (Read code diagnosis and/or antidiabetic drugs ever prior to the index date)
    - Ischaemic heart disease (Read code diagnosis prior to the index date)
    - Rhinitis (Read code diagnosis, including chronic and allergic rhinitis and prescriptions for nasal steroids prior to index date)
    - Eczema (Read code diagnosis prior to index date)
    - Osteoporosis (Read code diagnosis prior to the index date)
    - Charlson Comorbidity Index (based on Read code diagnoses in the year prior to index date, detailed definition in Appendix 1)

7.3 Questionnaire outcomes

Total and individual questionnaire related outcomes for

1) Continual sore mouth or throat
2) Oral thrush
3) Hoarse voice

* Calculated as average number of puffs per day over the year multiplied by strength (in µg);
† See appendix 1 for definitions
i.e. $\frac{Number\ of\ inhalers * doses\ per\ inhaler}{365} * strength$

4) Bruising
5) Abnormal weight gain
6) Cough

As an exploratory outcome, the prescribed ICS dose at index dose will be considered to create the subgroups of step down patients for the Volumatic and Aerochamber spacers.

7.4 Database outcomes

Total and individual database outcomes including Read code diagnosis for

1) Oral thrush
2) Rash
3) Oedema/swelling
4) Adrenal suppression diagnosis
5) Osteoporosis/osteopenia
6) Anxiety/depression
7) Cataracts
8) Glaucoma

7.5 Step down outcomes

1) Number of severe exacerbations in baseline year
2) Daily average SABA category in baseline year

8.0 Statistical analysis

8.1 Software used and power calculation

The dataset will be analysed using SPSS version 23, SAS version 9.3, Stata SE version 14 (StataCorp, College Station, TX) and Microsoft Office EXCEL 2013, as appropriate.
The study was powered using the occurrence of oral thrush as the representative adverse event. The occurrence of adverse events is 34% based on the oropharyngeal side effects in users of ICS in a real life setting reported in the literature[13].

The minimum study numbers are based on the following assumption:

When the sample sizes in the groups are 293 and 147, a two-group large-sample normal approximation test of proportions with a one-sided 0.025 significance level will have 80% power to reject the null hypothesis that the test and the standard are not equivalent (the difference in proportions, pT - pS, is 0.130 or farther from zero in the same direction) in favor of the alternative hypothesis that the proportions in the two groups are equivalent, assuming that the expected difference in proportions is 0.000 and the proportion in the standard group is 0.300.

8.2 Baseline characterisation

Data preparation and exploratory analysis will include the investigation of potential outliers and missing data for all variables. Plots will be produced for all explanatory and outcome variables. For variables measured on the interval or ratio scale, these will include:

- Frequency plots to illustrate the distribution of the variable and whether categorisation may be necessary (for example, if heavily skewed)
- Box plots to illustrate the location and spread of the variable and identify potential outliers

For categorical variables, bar plots will be produced to illustrate distributions and highlight differences between exposure groups.

Skewed data will be transformed or categorised, as appropriate.

8.2.1 Summary statistics

Summary statistics will be produced for all baseline and outcome variables, as a complete dataset, by treatment group and for sub-groups. For variables measured on the interval or ratio scale, these will include:

- Sample size (n)
- Percentage non-missing
- Mean
- Standard Deviation (SD)
- Median
- Inter-quartile range (IQR – 25th and 75th percentiles)

For categorical variables, the summary statistics will include:

- Sample size (n)
- Count and percentage by category

Variables measured on the interval/ratio scale will be compared using a t-test (normal distribution) or Mann-Whitney U test (non-parametric). Categorical variables will be compared using a chi-square test. The statistical significance for all tests will be set at $p<0.05$.

8.3 Matching

Initially, baseline data will be compared between unmatched cohorts. Exact matching for categorical variables and coarsened exact matching for numeric variables will be used to match patients using 1:1 nearest neighbour matching, without replacement. Matching variables such as demographic data, disease co-morbidity and indicators of disease severity will be considered for selection using a combination of baseline data analysis and predictive modelling of the baseline data in relation to the primary outcome variable (independently of treatment group).

If patient numbers allow, patients will be matched on sub groups for age (under 16s and 16-65 year olds) and high/low average ICS dose (1000 µg non-extrafine beclomethasone dipropionate or more/under 1000 µg non-extrafine beclomethasone dipropionate). For the sub-question of step down patients, matching will be implemented if the numbers are sufficient.

8.4 Analysis of study outcomes

8.4.1 Primary analysis: Questionnaire based adverse events

Adverse events as total and individual events in the questionnaires will be compared using a conditional Poisson regression model. The model will use empirical standard errors and adjustments will be made for potential baseline confounders.
The adjusted rate ratio with 95% confidence interval will be reported.

Non-inferiority in patient reported adverse events (oral thrush OR hoarseness) will be achieved if the proportion of Clenil/Aerochamber is no more than 13% higher (based on the upper boundary of the 95% confidence interval) than the proportion of patients on Clenil/Volumatic.[14]

8.4.2 Secondary analysis – database outcomes

The total number of adverse events as listed in the Summary of Product characteristics in the outcome period will be compared between treatment groups compared using a conditional

Poisson regression model. The model will use empirical standard errors and adjustments will be made for potential baseline confounders.

The adjusted rate ratio with 95% confidence interval will be reported.

Exploratory analysis – The exacerbation rate and separately the daily SABA dosage for patients during the baseline year who step down ICS at the index date treated with an Aerochamber spacer will be compared to patients prescribed a Volumatic spacer and compared with a Wilcoxon ranked test.

9.0 Regulatory and ethical compliance

This study was designed and shall be implemented and reported in accordance with the criteria of the “European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study” and follows the ENCePP Code of Conduct (EMA 2014).

10.0 Data dissemination

Initial results will be presented in poster and/or oral format at appropriate thoracic conferences.

11.0 Advisory group

A steering committee has not been currently selected for this study.

12.0 Research team

Research Organisation:

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Senior data analyst: Derek Skinner (derek@optimumpatientcare.org)

Study sponsor:

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Matthias Ochel

13.0 Timelines

Table 8: Project timelines

Action	Timeline	Dates
Protocol development	3 weeks	(post phase 1 delivered Summer 2016)
Chiesi sign off	2 weeks	27th October 2016
ADEPT application		27th October 2016
OPC to obtain BLF Questionnaires	18 weeks	16th May 2016
Data extraction	1 week	10th November 2016
Cohort analysis	3 weeks	30th November 2016
Initial/baseline report	3 weeks	24th December 2016
Baseline Chiesi review	1 week	1th January 2017
Sub-analysis	3 weeks	31st January 2017
Final report writing (PowerPoint and Word report)	3 weeks	28th February 2017
Chiesi review	1 week	10th March 2017

14.0 References

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15.0 APPENDIX

15.1 Appendix 1: Definitions

15.1.1 Body Mass Index (BMI)

The BMI is a representative measure of body weight based on the weight and height of the subject. It is defined as the weight (in kg) divided by the square of the height (in m) and is measured in kg/m^2. BMI will be categorised as follows: underweight (< 18.5), normal BMI (18.5 - 24.99), overweight (25-29.99), obese (≥30).

15.1.2 Asthma exacerbation (ATS/ERS consensus definition 2015)

Where an exacerbation is defined as an occurrence* of:

1. Asthma-related†: Unscheduled hospital admission / A&E attendance; OR
2. An acute‡ course of oral steroids; OR
3. Antibiotics prescribed with lower respiratory consultation§.

15.1.3 Comorbidities – Charlson Comorbidity Index (CCI)

The CCI was developed in the US in 1987 as a method of classifying prognostic comorbidity in longitudinal studies.[15] It predicts the one-year mortality for a patient who may have a range of comorbid conditions such as heart disease, AIDS or cancer. Each condition is assigned a "weight" depending on the risk of dying associated with the condition; scores are then summed to give a total score predicting mortality.

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*Where ≥1 oral steroid course / hospitalisation / antibiotics prescription occur within 2 weeks of each other, these events will be considered to be the result of the same exacerbation (and will only be counted once).

†**Asthma-related Hospitalisations:** consist of either a definite Asthma Emergency Attendance or a definite COPD Hospital Admission; OR a generic hospitalisation read code which has been recorded on the same day as a **Lower Respiratory Consultation**§§ (see below; (a) – (c) only and excluding where the only lower respiratory code recorded on that day was for a lung function test).

‡ Acute oral steroid use associated with asthma exacerbation treatment will be defined as:

- all courses that are definitely not maintenance therapy, and/or
- all courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed), and/or
- all courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions.

where "maintenance therapy" is defined as: daily dosing instructions of <=10mg Prednisolone or prescriptions for 1mg or 2.5mg Prednisolone tablets where daily dosing instructions are not available.

§ **Lower Respiratory Consultations -** consist of the following:

a) Lower Respiratory read codes (including Asthma, COPD and LRTI read codes);
b) Asthma/COPD review codes excl. any monitoring letter codes;
c) Lung function and/or asthma monitoring
d) Any additional respiratory examinations, referrals, chest x-rays, or events.

The weights were revised and updated (for example, mortality due to HIV has fallen) by Dr Foster Intelligence (DFI) in their HSMR Methodology documentation[16] and calibrated using UK data (due to differences in coding practice and hospital patient population characteristics from the US), using ICD-10 codes. As a result:

- DFI have expanded the coding definition of some conditions;
- Only secondary diagnoses (DIAG02-DIAG14) are now considered;
- There is greater variation in weights between conditions and the Charlson Index (the sum of the weights) can be treated as a continuous variable (limited to the range 0-50) for the purposes of risk adjustment.

The weights, codes and conditions used in this study are summarised in the table below.

Table 9: Co-morbid conditions and scores used in the Charlson Co-morbidity Index (CCI)

Condition	Condition name	ICD-10 codes	Weight
1	Acute myocardial infarction	I21, I22, I23, I252, I258	5
2	Cerebral vascular accident	G450, G451, G452, G454, G458, G459, G46, I60-I69	11
3	Congestive heart failure	I50	13
4	Connective tissue disorder	M05, M060, M063, M069, M32, M332, M34, M353	4
5	Dementia	F00, F01, F02, F03, F051	14
6	Diabetes	E101, E105, E106, E108, E109, E111, E115, E116, E118, E119, E131, E131, E136, E138, E139, E141, E145, E146, E148, E149	3
7	Liver disease	K702, K703, K717, K73, K74	8
8	Peptic ulcer	K25, K26, K27, K28	9
9	Peripheral vascular disease	I71, I739, I790, R02, Z958, Z959	6
10	Pulmonary disease	J40-J47, J60-J67	4
11	Cancer	C00-C76, C80-C97	8
12	Diabetes complications	E102, E103, E104, E107, E112, E113, E114, E117, E132, E133, E134, E137, E142, E143, E144, E147	-1
13	Paraplegia	G041, G81, G820, G821, G822	1
14	Renal disease	I12, I13, N01, N03, N052-N056, N072-N074, N18, N19, N25	10
15	Metastatic cancer	C77, C78, C79	14
16	Severe liver disease	K721, K729, K766, K767	18
17	HIV	B20, B21, B22, B23, B24	2

15.2 Appendix 2: Mock baseline results tables

15.2.1 Primary analysis

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X
Continual sore mouth	x	x-x	x	X
Oral thrush	x	x-x	x	X
Bruising	x	x-x	x	X
Hoarse Voice	x	x-x	x	X
Abnormal weight gain	x	x (x)	x (x)	X
Cough	x	x (x)	x (x)	X

Table 10: Total patient questionnaire reported adverse events

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X
Continual sore mouth	x	x-x	x	X
Oral thrush	x	x-x	x	X
Bruising	x	x-x	x	X
Hoarse Voice	x	x-x	x	X
Abnormal weight gain	x	x (x)	x (x)	X
Cough	x	x (x)	x (x)	X

Table 11: Patient questionnaire reported outcomes for patients <16

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X
Continual sore mouth	x	x-x	x	X
Oral thrush	x	x-x	x	X
Bruising	x	x-x	x	X
Hoarse Voice	x	x-x	x	X
Abnormal weight gain	x	x (x)	x (x)	X
Cough	x	x (x)	x (x)	X

Table 12: Patient questionnaire reported outcomes for patients aged 16-65

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X
Continual sore mouth	x	x-x	x	X
Oral thrush	x	x-x	x	X
Bruising	x	x-x	x	X
Hoarse Voice	x	x-x	x	X
Abnormal weight gain	x	x (x)	x (x)	X
Cough	x	x (x)	x (x)	X

Table 13: Patient questionnaire reported outcomes for patients prescribed <1000 µg non extra fine beclomethasone

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value

Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X
Continual sore mouth	x	x-x	x	X
Oral thrush	x	x-x	x	X
Bruising	x	x-x	x	X
Hoarse Voice	x	x-x	x	X
Abnormal weight gain	x	x (x)	x (x)	X
Cough	x	x (x)	x (x)	X

Table 14: Patient questionnaire reported outcomes for patients prescribed >1000 µg non-extrafine beclomethasone

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X
Continual sore mouth	x	x-x	x	X
Oral thrush	x	x-x	x	X
Bruising	x	x-x	x	X
Hoarse Voice	x	x-x	x	X
Abnormal weight gain	x	x (x)	x (x)	X
Cough	x	x (x)	x (x)	X

Table 15: Patient questionnaire reported outcomes for patients prescribed <1000 µg non-extrafine beclomethasone aged <16

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X

Continual sore mouth	x	x-x	x	X
Oral thrush	x	x-x	x	X
Bruising	x	x-x	x	X
Hoarse Voice	x	x-x	x	X
Abnormal weight gain	x	x (x)	x (x)	X
Cough	x	x (x)	x (x)	X

Table 16: Patient questionnaire with <1000 µg beclomethasone and aged 16-65

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X
Continual sore mouth	x	x-x	x	X
Oral thrush	x	x-x	x	X
Bruising	x	x-x	x	X
Hoarse Voice	x	x-x	x	X
Abnormal weight gain	x	x (x)	x (x)	X
Cough	x	x (x)	x (x)	X

Table 17: Patient questionnaire with >1000 µg beclomethasone and aged <16

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X
Continual sore mouth	x	x-x	x	X

Oral thrush	x	x-x	x	X
Bruising	x	x-x	x	X
Hoarse Voice	x	x-x	x	X
Abnormal weight gain	x	x (x)	x (x)	X
Cough	x	x (x)	x (x)	X

Table 18: Patient questionnaire with >1000 µg beclomethasone and aged 16-65

15.2.2 Database adverse events

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of database adverse events, n (%)	x (x)	x (x)	x (x)	X
Rash	x	x-x	x	X
Oral thrush	x	x-x	x	X
Adrenal suppression	x	x-x	x	X
Osteoporosis	x	x-x	x	X
Anxiety/depression	x	x (x)	x (x)	X
Cataracts	x	x (x)	x (x)	X
Glaucoma	x	x (x)	x (x)	x

Table 19: Total patient questionnaire reported adverse events

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X
Rash	x	x-x	x	X

Oral thrush	x	x-x	x	X
Adrenal suppression	x	x-x	x	X
Osteoporosis	x	x-x	x	X
Anxiety/depression	x	x (x)	x (x)	X
Cataracts	x	x (x)	x (x)	X
Glaucoma	x	x (x)	x (x)	x

Table 20: Patient questionnaire reported outcomes for patients <16

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X
Rash	x	x-x	x	X
Oral thrush	x	x-x	x	X
Adrenal suppression	x	x-x	x	X
Osteoporosis	x	x-x	x	X
Anxiety/depression	x	x (x)	x (x)	X
Cataracts	x	x (x)	x (x)	X
Glaucoma	x	x (x)	x (x)	x

Table 21: Patient questionnaire reported outcomes for patients aged 16-65

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X

Rash	x	x-x	x	X
Oral thrush	x	x-x	x	X
Adrenal suppression	x	x-x	x	X
Osteoporosis	x	x-x	x	X
Anxiety/depression	x	x (x)	x (x)	X
Cataracts	x	x (x)	x (x)	X
Glaucoma	x	x (x)	x (x)	x

Table 22: Patient questionnaire reported outcomes for patients prescribed <1000 µg non extra fine beclomethasone

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X
Rash	x	x-x	x	X
Oral thrush	x	x-x	x	X
Adrenal suppression	x	x-x	x	X
Osteoporosis	x	x-x	x	X
Anxiety/depression	x	x (x)	x (x)	X
Cataracts	x	x (x)	x (x)	X
Glaucoma	x	x (x)	x (x)	x

Table 23: Patient questionnaire reported outcomes for patients prescribed >1000 µg non-extrafine beclomethasone

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X

Rash	x	x-x	x	X
Oral thrush	x	x-x	x	X
Adrenal suppression	x	x-x	x	X
Osteoporosis	x	x-x	x	X
Anxiety/depression	x	x (x)	x (x)	X
Cataracts	x	x (x)	x (x)	X
Glaucoma	x	x (x)	x (x)	x

Table 24: Patient questionnaire reported outcomes for patients prescribed <1000 µg non-extrafine beclomethasone aged <16

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X
Rash	x	x-x	x	X
Oral thrush	x	x-x	x	X
Adrenal suppression	x	x-x	x	X
Osteoporosis	x	x-x	x	X
Anxiety/depression	x	x (x)	x (x)	X
Cataracts	x	x (x)	x (x)	X
Glaucoma	x	x (x)	x (x)	x

Table 25: Patient questionnaire with <1000 µg beclomethasone and aged 16-65

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value

Total number of patient reported adverse events, n (%)	x (x)	x (x)	x (x)	X
Continual sore mouth	x	x-x	x	X
Oral thrush	x	x-x	x	X
Bruising	x	x-x	x	X
Hoarse Voice	x	x-x	x	X
Abnormal weight gain	x	x (x)	x (x)	X
Cough	x	x (x)	x (x)	X

Table 26: Patient questionnaire with >1000 µg beclomethasone and aged <16

	Aerochamber®	Volumatic®	95% Confidence Interval	p-value
Total number of database adverse events, n (%)	x (x)	x (x)	x (x)	X
Rash	x	x-x	x	X
Oral thrush	x	x-x	x	X
Adrenal suppression	x	x-x	x	X
Osteoporosis	x	x-x	x	X
Anxiety/depression	x	x (x)	x (x)	X
Cataracts	x	x (x)	x (x)	X
Glaucoma	x	x (x)	x (x)	x

Table 27: Patient questionnaire with >1000 µg beclomethasone and aged 16-65

Table 28: Summary statistic of baseline variables overall

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Age (years)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Gender, n (%)	Male	x (x)	x (x)	x (x)
	Female	x (x)	x (x)	x (x)
BMI (kg/m^2)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
BMI (categorised), n (%)	Underweight	x (x)	x (x)	x (x)
	Normal	x (x)	x (x)	x (x)
	Overweight	x (x)	x (x)	x (x)
	Obese	x (x)	x (x)	x (x)
Smoking status, n (%)	Current smoker	x (x)	x (x)	x (x)
	Ex-smoker	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose (categorised), n (%)	Low	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
FEV_1/FVC ratio	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Exacerbation count	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Oral corticosteroids prescriptions	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Antibiotic prescriptions for LRTI	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
% Predicted Peak Flow	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Table 29: Summary statistics for diagnoses of co-morbidities at baseline

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Pneumonia	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Diabetes	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Ischaemic heart disease	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Rhinitis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Eczema	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Osteoporosis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Charlson comorbidity index, n (%)	0	x (x)	x (x)	x (x)
	1-4	x (x)	x (x)	x (x)
	5+	x (x)	x (x)	x (x)

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Age (years)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Gender, n (%)	Male	x (x)	x (x)	x (x)
	Female	x (x)	x (x)	x (x)
BMI (kg/m^2)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
BMI (categorised), n (%)	Underweight	x (x)	x (x)	x (x)
	Normal	x (x)	x (x)	x (x)
	Overweight	x (x)	x (x)	x (x)
	Obese	x (x)	x (x)	x (x)
Smoking status, n (%)	Current smoker	x (x)	x (x)	x (x)
	Ex-smoker	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose (categorised), n (%)	Low	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
FEV_1/FVC ratio	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Exacerbation count	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)

	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Oral corticosteroids prescriptions	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Antibiotic prescriptions for LRTI	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
% Predicted Peak Flow	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Table 30: Summary statistics for <16 age group

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Pneumonia	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Diabetes	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Ischaemic heart disease	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Rhinitis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Eczema	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Osteoporosis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Charlson comorbidity index, n (%)	0	x (x)	x (x)	x (x)
	1-4	x (x)	x (x)	x (x)
	5+	x (x)	x (x)	x (x)

Table 31: Summary statistics for comorbidities in <16 age group

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Age (years)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Gender, n (%)	Male	x (x)	x (x)	x (x)
	Female	x (x)	x (x)	x (x)
BMI (kg/m^2)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
BMI (categorised), n (%)	Underweight	x (x)	x (x)	x (x)
	Normal	x (x)	x (x)	x (x)
	Overweight	x (x)	x (x)	x (x)
	Obese	x (x)	x (x)	x (x)
Smoking status, n (%)	Current smoker	x (x)	x (x)	x (x)
	Ex-smoker	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose (categorised), n (%)	Low	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
FEV_1/FVC ratio	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Exacerbation count	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Oral corticosteroids prescriptions	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Antibiotic prescriptions for LRTI	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
% Predicted Peak Flow	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Table 32: Summary statistics for mean <1000µg beclomethasone per day

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Pneumonia	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Diabetes	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Ischaemic heart disease	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Rhinitis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Eczema	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Osteoporosis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Charlson comorbidity index, n (%)	0	x (x)	x (x)	x (x)
	1-4	x (x)	x (x)	x (x)
	5+	x (x)	x (x)	x (x)

Table 33: Summary statistics for mean ICS <1000µg dose per day

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Age (years)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Gender, n (%)	Male	x (x)	x (x)	x (x)
	Female	x (x)	x (x)	x (x)
BMI (kg/m^2)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
BMI (categorised), n (%)	Underweight	x (x)	x (x)	x (x)
	Normal	x (x)	x (x)	x (x)
	Overweight	x (x)	x (x)	x (x)
	Obese	x (x)	x (x)	x (x)
Smoking status, n (%)	Current smoker	x (x)	x (x)	x (x)
	Ex-smoker	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose (categorised), n (%)	Low	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
FEV_1/FVC ratio	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Exacerbation count	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Oral corticosteroid	N (% non-missing)	x (x)	x (x)	x (x)

s prescriptions	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Antibiotic prescriptions for LRTI	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
% Predicted Peak Flow	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Table 34: Summary statistics for 16-65 year olds

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Pneumonia	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Diabetes	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Ischaemic heart disease	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Rhinitis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Eczema	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Osteoporosis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Charlson comorbidity index, n (%)	0	x (x)	x (x)	x (x)
	1-4	x (x)	x (x)	x (x)
	5+	x (x)	x (x)	x (x)

Table 35: Summary co-morbidities for 16-65 year olds

	Volumatic®	Aerochamber®	p-value

	Total (%)	**x (x)**	**x (x)**	**x (x)**
Age (years)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Gender, n (%)	Male	x (x)	x (x)	x (x)
	Female	x (x)	x (x)	x (x)
BMI (kg/m^2)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
BMI (categorised), n (%)	Underweight	x (x)	x (x)	x (x)
	Normal	x (x)	x (x)	x (x)
	Overweight	x (x)	x (x)	x (x)
	Obese	x (x)	x (x)	x (x)
Smoking status, n (%)	Current smoker	x (x)	x (x)	x (x)
	Ex-smoker	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose (categorised), n (%)	Low	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
FEV_1/FVC ratio	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Exacerbation count	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Oral corticosteroid	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)

s prescriptions	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Antibiotic prescriptions for LRTI	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
% Predicted Peak Flow	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Table 36: Summary statistics for mean dose of 1000+ µg beclomethasone

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Pneumonia	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Diabetes	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Ischaemic heart disease	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Rhinitis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Eczema	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Osteoporosis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Charlson comorbidity index, n (%)	0	x (x)	x (x)	x (x)
	1-4	x (x)	x (x)	x (x)
	5+	x (x)	x (x)	x (x)

Table 37: Summary statistics for mean dose (1000+µg of beclomethasone)

	Volumatic®	Aerochamber®	p-value
Total (%)	**x (x)**	**x (x)**	**x (x)**

Age (years)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Gender, n (%)	Male	x (x)	x (x)	x (x)
	Female	x (x)	x (x)	x (x)
BMI (kg/m^2)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
BMI (categorised), n (%)	Underweight	x (x)	x (x)	x (x)
	Normal	x (x)	x (x)	x (x)
	Overweight	x (x)	x (x)	x (x)
	Obese	x (x)	x (x)	x (x)
Smoking status, n (%)	Current smoker	x (x)	x (x)	x (x)
	Ex-smoker	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose (categorised), n (%)	Low	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
FEV_1/FVC ratio	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Exacerbation count	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Oral corticosteroids prescriptions	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Antibiotic prescriptions for LRTI	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
% Predicted Peak Flow	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Table 38: Summary statistics for <16 and high dose ICS

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Pneumonia	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Diabetes	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Ischaemic heart disease	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Rhinitis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Eczema	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Osteoporosis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Charlson comorbidity index, n (%)	0	x (x)	x (x)	x (x)
	1-4	x (x)	x (x)	x (x)
	5+	x (x)	x (x)	x (x)

Table 39: Summary statistics for <16 and high dose ICS

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Age (years)	N (% non-missing)	x (x)	x (x)	x (x)

	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Gender, n (%)	Male	x (x)	x (x)	x (x)
	Female	x (x)	x (x)	x (x)
BMI (kg/m^2)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
BMI (categorised), n (%)	Underweight	x (x)	x (x)	x (x)
	Normal	x (x)	x (x)	x (x)
	Overweight	x (x)	x (x)	x (x)
	Obese	x (x)	x (x)	x (x)
Smoking status, n (%)	Current smoker	x (x)	x (x)	x (x)
	Ex-smoker	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose (categorised), n (%)	Low	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
FEV_1/FVC ratio	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Exacerbation count	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Oral corticosteroids prescriptions	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Antibiotic prescriptions for LRTI	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)

	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
% Predicted Peak Flow	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Table 40: Summary statistics <16 and low dose ICS

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Pneumonia	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Diabetes	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Ischaemic heart disease	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Rhinitis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Eczema	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Osteoporosis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Charlson comorbidity index, n (%)	0	x (x)	x (x)	x (x)
	1-4	x (x)	x (x)	x (x)
	5+	x (x)	x (x)	x (x)

Table 41: Summary co-morbidities for <16 and low dose ICS

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Age (years)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Gender, n (%)	Male	x (x)	x (x)	x (x)
	Female	x (x)	x (x)	x (x)
BMI (kg/m^2)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
BMI (categorised), n (%)	Underweight	x (x)	x (x)	x (x)
	Normal	x (x)	x (x)	x (x)
	Overweight	x (x)	x (x)	x (x)
	Obese	x (x)	x (x)	x (x)
Smoking status, n (%)	Current smoker	x (x)	x (x)	x (x)
	Ex-smoker	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose (categorised), n (%)	Low	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
FEV_1/FVC ratio	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Exacerbation count	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Oral corticosteroids prescriptions	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Antibiotic prescriptions for LRTI	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

% Predicted Peak Flow	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Table 42: Summary statistics 16-65 and low dose ICS

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Pneumonia	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Diabetes	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Ischaemic heart disease	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Rhinitis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Eczema	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Osteoporosis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Charlson comorbidity index, n (%)	0	x (x)	x (x)	x (x)
	1-4	x (x)	x (x)	x (x)
	5+	x (x)	x (x)	x (x)

Table 43: Summary co-morbidities 16-65 and low dose ICS

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Age (years)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Gender, n (%)	Male	x (x)	x (x)	x (x)

	Female	x (x)	x (x)	x (x)
BMI (kg/m^2)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
BMI (categorised), n (%)	Underweight	x (x)	x (x)	x (x)
	Normal	x (x)	x (x)	x (x)
	Overweight	x (x)	x (x)	x (x)
	Obese	x (x)	x (x)	x (x)
Smoking status, n (%)	Current smoker	x (x)	x (x)	x (x)
	Ex-smoker	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose (categorised), n (%)	Low	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
FEV_1/FVC ratio	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Exacerbation count	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Oral corticosteroids prescriptions	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Antibiotic prescriptions for LRTI	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
% Predicted Peak Flow	N (% non-missing)	x (x)	x (x)	x (x)

	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Table 44: Summary statistics 16-65 and high dose ICS

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Pneumonia	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Diabetes	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Ischaemic heart disease	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Rhinitis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Eczema	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Osteoporosis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Charlson comorbidity index, n (%)	0	x (x)	x (x)	x (x)
	1-4	x (x)	x (x)	x (x)
	5+	x (x)	x (x)	x (x)

Table 45: Summary statistics for comorbidities 16-65 and low dose ICS

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Age (years)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Gender, n (%)	Male	x (x)	x (x)	x (x)
	Female	x (x)	x (x)	x (x)
BMI (kg/m^2)	N (% non-missing)	x (x)	x (x)	x (x)

	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
BMI (categorised), n (%)	Underweight	x (x)	x (x)	x (x)
	Normal	x (x)	x (x)	x (x)
	Overweight	x (x)	x (x)	x (x)
	Obese	x (x)	x (x)	x (x)
Smoking status, n (%)	Current smoker	x (x)	x (x)	x (x)
	Ex-smoker	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose (categorised), n (%)	Low	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
FEV_1/FVC ratio	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Exacerbation count	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Oral corticosteroids prescriptions	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Antibiotic prescriptions for LRTI	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
% Predicted Peak Flow	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Table 46: Summary statistics 65+

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Pneumonia	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Diabetes	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Ischaemic heart disease	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Rhinitis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Eczema	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Osteoporosis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Charlson comorbidity index, n (%)	0	x (x)	x (x)	x (x)
	1-4	x (x)	x (x)	x (x)
	5+	x (x)	x (x)	x (x)

Table 47: Summary statistics for >65 age group

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Age (years)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Gender, n (%)	Male	x (x)	x (x)	x (x)
	Female	x (x)	x (x)	x (x)
BMI (kg/m^2)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

BMI (categorised), n (%)	Underweight	x (x)	x (x)	x (x)
	Normal	x (x)	x (x)	x (x)
	Overweight	x (x)	x (x)	x (x)
	Obese	x (x)	x (x)	x (x)
Smoking status, n (%)	Current smoker	x (x)	x (x)	x (x)
	Ex-smoker	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose (categorised), n (%)	Low	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
FEV_1/FVC ratio	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Exacerbation count	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Oral corticosteroids prescriptions	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Antibiotic prescriptions for LRTI	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
% Predicted Peak Flow	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Table 48: Summary statistics for 65+ and low dose ICS

	Volumatic®	Aerochamber®	p-value

		Total (%)	**x (x)**	**x (x)**	**x (x)**
Pneumonia	N (% non-missing)	x (x)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Diabetes	N (% non-missing)	x (x)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Ischaemic heart disease	N (% non-missing)	x (x)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Rhinitis	N (% non-missing)	x (x)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Eczema	N (% non-missing)	x (x)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Osteoporosis	N (% non-missing)	x (x)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Charlson comorbidity index, n (%)	0	x (x)	x (x)	x (x)	x (x)
	1-4	x (x)	x (x)	x (x)	x (x)
	5+	x (x)	x (x)	x (x)	x (x)

Table 49: Summary co-morbidities for 65+ and low dose ICS

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Age (years)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Gender, n (%)	Male	x (x)	x (x)	x (x)
	Female	x (x)	x (x)	x (x)
BMI (kg/m^2)	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
BMI (categorised), n (%)	Underweight	x (x)	x (x)	x (x)
	Normal	x (x)	x (x)	x (x)

	Overweight	x (x)	x (x)	x (x)
	Obese	x (x)	x (x)	x (x)
Smoking status, n (%)	Current smoker	x (x)	x (x)	x (x)
	Ex-smoker	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose (categorised), n (%)	Low	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
FEV_1/FVC ratio	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Exacerbation count	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Oral corticosteroids prescriptions	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Antibiotic prescriptions for LRTI	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
% Predicted Peak Flow	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)

Table 50: Summary statistics for 65+ and high dose ICS

		Volumatic®	Aerochamber®	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**
Pneumonia	N (% non-missing)	x (x)	x (x)	x (x)

	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Diabetes	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Ischaemic heart disease	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Rhinitis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Eczema	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Osteoporosis	N (% non-missing)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)
Charlson comorbidity index, n (%)	0	x (x)	x (x)	x (x)
	1-4	x (x)	x (x)	x (x)
	5+	x (x)	x (x)	x (x)

Table 51: Summary statistics for 65+ age group and high dose ICS

		Step down Volumatic®	Non step down Volumatic	Step down Aerochamber®	Non step down Aerochamber	p-value
	Total (%)	**x (x)**	**x (x)**	**x (x)**	**x (x)**	**x (x)**
Age (years)	N (% non-missing)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Gender, n (%)	Male	x (x)	x (x)	x (x)	x (x)	x (x)
	Female	x (x)	x (x)	x (x)	x (x)	x (x)
BMI (kg/m^2)	N (% non-missing)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
BMI (categorised), n (%)	Underweight	x (x)	x (x)	x (x)	x (x)	x (x)
	Normal	x (x)	x (x)	x (x)	x (x)	x (x)
	Overweight	x (x)	x (x)	x (x)	x (x)	x (x)

	Obese	x (x)	x (x)	x (x)	x (x)	x (x)
Smoking status, n (%)	Current smoker	x (x)	x (x)	x (x)	x (x)	x (x)
	Ex-smoker	x (x)	x (x)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose	N (% non-missing)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Average SABA daily dose (categorised), n (%)	Low	x (x)	x (x)	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)	x (x)	x (x)
	Medium	x (x)	x (x)	x (x)	x (x)	x (x)
	High	x (x)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
FEV_1/FVC ratio	N (% non-missing)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Exacerbation count	N (% non-missing)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Oral corticosteroids prescriptions	N (% non-missing)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Antibiotic prescriptions for LRTI	N (% non-missing)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
% Predicted Peak Flow	N (% non-missing)	x (x)	x (x)	x (x)	x (x)	x (x)
	Mean (SD)	x (x)	x (x)	x (x)	x (x)	x (x)
	Median (IQR)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)

Table 50: additional subanalysis