Final report

Real-life effectiveness evaluation of asthma treatment in Korea

Evaluating real-life effectiveness of asthma treatment and inhaler device 'persistence of change' at the Allergy and Clinical Immunology Department at Ajou University Hospital in Korea

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Study aim and objectives	The study aims to characterise asthma treatment and outcomes surrounding the change from DPI to pMDI inhalers for ICS/LABA treatment of patients at the Allergy and Clinical Immunology Department at Ajou University, Korea. The objectives of this study are: • To establish whether patients that changed from a DPI to a pMDI, for FDC ICS/LABA therapy, have non-inferior asthma effectiveness outcomes • To determine whether the proportion of patients who persist with the change of therapy from FDC ICS/LABA DPI to FDC ICS/LABA MDI is ≥70%
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List of abbreviations

AE	Adverse Event
A&E	Accident and Emergency
ATS	American Thoracic Society
BDP	Beclomethasone Dipropionate
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CLR	Conditional Logistic Regression
COPD	Chronic Obstructive Pulmonary Disease
DPI	Dry Powder Inhaler
ED	Emergency Department
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERS	European Respiratory Society
FDC	Fixed Dose Combination
FOR	Formoterol
FP	Fluticasone Propionate
GERD	Gastroesophageal Reflux Disease
GINA	Global Initiative for Asthma
GP	General Practitioner
ICS	Inhaled Corticosteroid
Ig	Immunoglobulin
IHD	Ischaemic Heart Disease
IPD	Index Prescription Date
IQR	Interquartile Range
LABA	Long-Acting Beta2 Agonist
LTRA	Leukotriene Receptor Antagonist
LRTI	Lower Respiratory Tract Infection
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Nonsteroidal Anti-Inflammatory Drug
OAC	Overall Asthma Control
OPRI	Observational and Pragmatic Research Institute
pMDI	Pressurised Metered Dose Inhaler
RAST	Radioallergosorbent Test
RDAC	Risk Domain Asthma Control
REG	Respiratory Effectiveness Group
RiRL	Research in Real Life Limited
RR	Rate Ratio
SABA	Short-Acting $Beta_2$ Agonist
SAMA	Short-acting Muscarinic Agent
SPC	Summary of Product Characteristics

1 Executive summary

1.1 Introduction

Asthma is a chronic inflammatory airway disease with increasing global prevalence and significant morbidity and mortality worldwide[1,2]. In Korea, asthma has an estimated prevalence of 3.9%[1], and was ranked as the fourth most burdensome disease in terms of disability-adjusted life years (DALYs) in 2002[3]. Inhaled therapy to deliver corticosteroids is the mainstay of treatment for patients with asthma; however, incorrect inhaler technique is common among patients and is associated with poor asthma control and reduced adherence[4,5].

Outpatient and medication costs represent the most significant proportion of the total economic cost of asthma in Korea[6]. Pressurised metered-dose inhalers (pMDIs) are cost-effective[7], and, in a real-world observational study, patients prescribed a fixed-dose combination (FDC) inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) delivered via pMDI were found more likely to achieve asthma control and treatment success as compared to those prescribed a dry powder inhaler (DPI)[8]. Furthermore, prescription of mixed inhaler regimes, such as a DPI preventer and pMDI reliever, is associated with increased user error and reduced therapy compliance[9-11]. Change of device for fixed-dose combination (FDC) ICS/LABA therapy from a DPI to a pMDI may therefore improve clinical outcomes through improved inhaler technique and adherence.

Longitudinal, electronic healthcare data for patients treated at specialist asthma care centres enables the assessment of the effects of common asthma treatments in real-life practice. This study therefore aims to assess the uptake and clinical effectiveness of changing from a DPI to a pMDI inhaler for FDC ICS/LABA treatment for patients treated at the Allergy and Clinical Immunology Department at the Ajou University Hospital, Korea.

1.2 Study aims and objectives

This study aims to characterise asthma treatment and outcomes surrounding the change from DPI to pMDI inhalers for FDC ICS/LABA treatment of patients at the Allergy and Clinical Immunology Department at Ajou University, Korea.

The objectives of this study are:

- To establish whether patients that changed from a DPI to a pMDI, for FDC ICS/LABA therapy, have non-inferior asthma effectiveness outcomes

- To determine whether the proportion of patients who persist with the change of therapy from FDC ICS/LABA DPI to FDC ICS/LABA pMDI is ≥70%

1.3 Methods

A historical cohort database study using data extracted from the Electronic Medical Record Database at the Allergy and Clinical Immunology Department at Ajou University Hospital, Korea. The index date was defined as the date at which patients received a first prescription for a FDC ICS/LABA pMDI. Patients with ≥2 separate prescriptions for FDC ICS/LABA DPI during the baseline year were studied. For the exploratory phase (phase 1), baseline and outcome periods of 1 year and 6 months respectively were designed to evaluate the proportion of asthma patients, prescribed ICS/LABA DPI treatment in the baseline period, that continued to collect prescriptions for ICS/LABA pMDI after the initial prescription for change in treatment to a pMDI. Patients changing to ICS/LABA pMDI therapy and those remaining on ICS/LABA DPI treatment were characterised during the baseline year. For the main objective (phase 2), the outcome period was one year. The primary outcome was non-inferiority of asthma effectiveness, namely the proportion of patients who are free from severe exacerbations during the outcome year as compared to the baseline year prior to changing device. Persistence of change was also examined as an exploratory outcome; defined as ≥70% of the population receiving ≥1 prescriptions for FDC ICS/LABA pMDI treatment (post-index date), and no prescription for a FDC ICS/LABA DPI, within 6 months after the initial change in therapy.

1.4 Results

Phase 1 showed that 76% of patients (95% CI (69, 100)) that changed from a FDC ICS/LABA DPI to a FDC ICS/LABA pMDI persisted with the change of inhaler over the 6 months' study period. Although the lower confidence interval was just outside of the pre-defined clinically significant limit of 70%, the point estimate of 76% is above the pre-defined 'change success' limit set *a priori*. Persistence of change over 6 months was similar for patients who changed to either fluticasone/formoterol (Flutiform®) pMDI or beclomethasone/formoterol (Foster®) pMDI, 75% (95%CI 64, 100) and 77% (95%CI 67, 100) of patients respectively. Furthermore, 71% (95%CI 60, 100) of patients switching to fluticasone/formoterol (Flutiform®) pMDI and 77% (95%CI 67, 100) switching to beclomethasone/formoterol (Foster®) received more than 1 prescription for the same inhaler device during the 6 months' study period and no other ICS/LABA prescriptions. There were no statistically significant differences in baseline characteristics between patients that persisted with change from a DPI to a pMDI for FDC

ICS/LABA treatment and those that were non-persistent. A high proportion of patients within the study cohort was determined to have poor asthma control, hence this was deemed an important outcome in phase 2.

In phase 2, a significantly increased proportion of patients that changed to FDC ICS/LABA pMDI, from a DPI, were found to have achieved risk domain (75% vs 58%, p=0.001) and overall asthma control (58% vs 46%, p=0.021) in the year following the change in therapy as compared to the year prior. This significance was driven by patients changing to fluticasone/formoterol (Flutiform®) treatment, and this patient group also had significantly decreased acute respiratory events (p=0.02) over the one-year outcome period. The change from FDC ICS/LABA DPI to FDC ICS/LABA pMDI was associated with a non-inferior proportion of patients experiencing no severe exacerbations as compared to the proportion prior to the change. Patients that received ≥1 fluticasone/formoterol (Flutiform®) pMDI or beclomethasone/formoterol (Foster®) pMDI prescription during the outcome period had statistically significant lower ICS average daily dose (p<0.001) during the year following the change in therapy, as compared to the prior year.

1.5 Conclusion

The change from FDC ICS/LABA DPI to FDC ICS/LABA pMDI was associated with non-inferiority of effectiveness, with regards the proportion of patients experiencing no severe exacerbations as compared to the proportion prior to the change. The year following the switch to FDC ICS/LABA pMDI treatment, was associated with a higher proportion of patients achieving asthma control, decreased acute respiratory events and decreased average ICS daily dose. The proportion of patients with available healthcare records that persisted with a change from a DPI to a pMDI inhaler for FDC ICS/LABA therapy over 6 months was ≥70% (76%, CI (69, 100)).

1 Background

Asthma is a chronic inflammatory airway disease with increasing global prevalence and significant morbidity and mortality worldwide[1,2]. Globally, asthma also imposes substantial economic burden through healthcare resource utilisation and loss of productivity. In Korea, asthma has an estimated prevalence of 3.9%[1], and was ranked as the fourth most burdensome disease in terms of disability-adjusted life years (DALYs) in 2002[3]. An epidemiological study revealed high prevalence of asthma among the elderly (≥65 years) in Korea[12], with older patients (≥50 years) also accounting for the highest per capita cost[6]. Given its rapidly ageing population, the socioeconomic burden posed by asthma in Korea is likely to increase in the future.

The international Global Initiative for Asthma (GINA) and Korean Asthma Guideline recommend inhaled corticosteroids (ICS) and ICS/long-acting β_2-agonist (LABA) combination therapy, dependent upon the treatment step required[13,14]. Inhaler devices currently available for ICS/LABA combination therapy include dry powder inhalers (DPIs) and pressurised metered-dose inhalers (pMDIs). Optimal delivery to the lung requires a different inhalation technique and breathing pattern for each device-type[15]. DPIs are breath-activated, requiring deep and forceful inhalation, while pMDIs require coordination of inhalation with actuation of the inhaler. Incorrect inhaler technique is common among patients and is associated with poor asthma control and reduced adherence[4,5]. Given the different techniques required for optimal drug delivery by a pMDI or a DPI, prescription of mixed inhaler regimes, such as a DPI preventer and pMDI reliever, is associated with increased user errors and adverse effects on therapy compliance[9-11].

A study by Lee *et al.* concluded that outpatient and medication costs were the most significant components of the total economic costs of asthma in Korea[6]. pMDIs are cost-effective[7], and, in a real-world observational study, patients prescribed a fixed-dose combination (FDC) ICS/LABA delivered via pMDI, were found more likely to achieve asthma control and treatment success as compared to those prescribed a DPI[8]. Changing treatment from a DPI to a pMDI may be carried out to reduce drug costs or to individualise asthma therapy according to patient preference[15]. As many asthma patients use a pMDI for reliever treatment, change of device for FDC ICS/LABA combination therapy from a DPI to a pMDI may improve clinical outcomes through improved inhaler technique and adherence.

Longitudinal, electronic healthcare data for patients treated at specialist asthma care centres enables the assessment of the effects of common asthma treatments in real-life practice. The

primary objective of this study will be to assess the uptake and clinical effectiveness of changing from a DPI to a pMDI inhaler for FDC ICS/LABA treatment for asthma patients treated at the Allergy and Clinical Immunology Department at the Ajou University Hospital, Korea. This will be defined as a non-inferior proportion of patients remaining free from severe exacerbations in the year following the change to FDC ICS/LABA pMDI therapy as compared to the year prior.

2 Study aims and objectives

2.1 Study aims

The study aims to characterise asthma treatment and outcomes surrounding the change from DPI to pMDI inhalers for ICS/LABA treatment of patients at the Allergy and Clinical Immunology Department at Ajou University Hospital, Korea.

2.2 Study objectives

The objectives of this study are:

- To establish whether patients that changed from a DPI to a pMDI, for FDC ICS/LABA therapy, have non-inferior asthma effectiveness, in terms of the proportion of patients that remain free from severe exacerbations
- To determine whether the proportion of patients who persist with the change of therapy from FDC ICS/LABA DPI to FDC ICS/LABA MDI is ≥70%

3 Study design

3.1 Products studied

FDC ICS/LABA pMDI and DPI therapies prescribed at the Allergy and Clinical Immunology Department at the Ajou University Hospital were studied.

The pMDI FDC ICS/LABA combinations included beclomethasone diproprionate/formoterol fumarate (Foster®) and fluticasone propionate/formoterol fumarate (Flutiform®). The DPI FDC ICS/LABA combinations included fluticasone propionate/salmeterol xinafoate (Seretide®) and budesonide/formoterol fumarate (Symbicort®).

3.2 Study design

This was a historical cohort database study. Exploratory phase 1 consisted of a 1 year baseline period for characterisation and a 6 months' outcome period, designed to evaluate the proportion of patients, previously prescribed FDC ICS/LABA DPI treatment, that changed to and persisted with FDC ICS/LABA pMDI treatment (figure 1). Persistence of change was considered as ≥70% of the population maintaining their ICS/LABA pMDI, with no prescription of ICS/LABA DPI, during the 6-month outcome period (patients persisting with change).

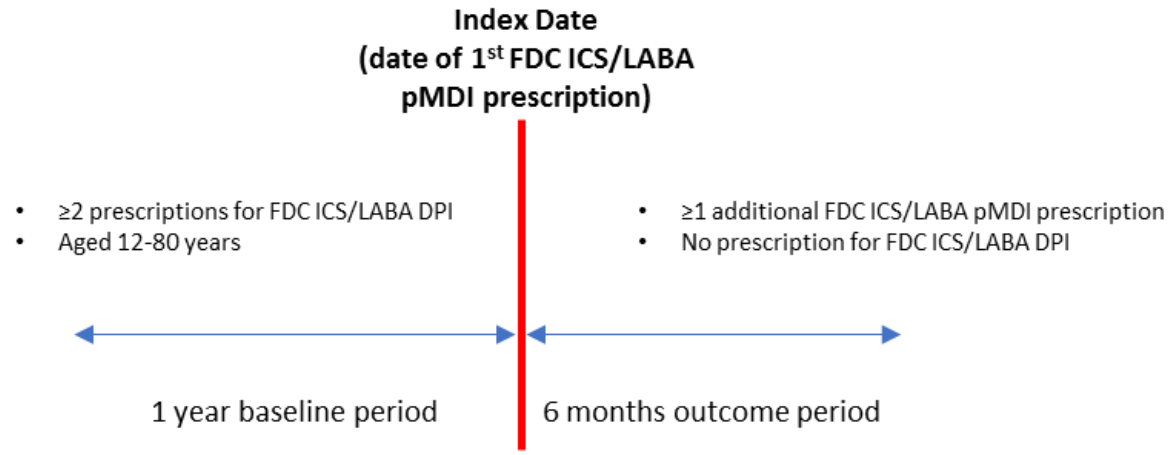

Figure 1: Phase 1 study design

Phase 2 consisted of a 1-year baseline characterisation and a 1-year follow-up of the cohort who received ≥2 separate FDC ICS/LABA pMDI prescriptions, and no prescription for a FDC ICS/LABA DPI during the outcome year. Asthma effectiveness outcomes during the outcome period were compared to those in the baseline year (figure 2).

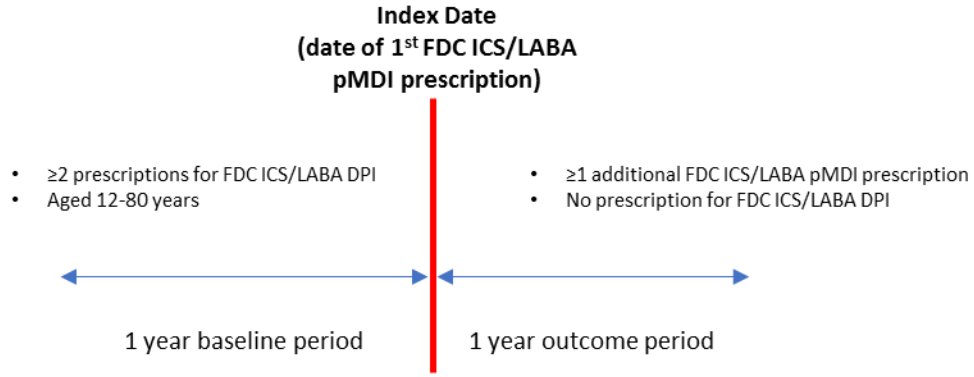

Figure 2: Phase 2 study design

4 Study population

4.1 Inclusion and exclusion criteria

Table 1: Inclusion and exclusion criteria

Inclusion criteria
➢ Aged 12-80 years at date of first prescription for FDC ICS/LABA pMDI ➢ At least 1 year baseline electronic medical records ➢ First prescription of FDC ICS/LABA pMDI is not an inpatient prescription record[1] ➢ Actively treated asthma, defined as ≥2 prescriptions (prescribed on different dates) for FDC ICS/LABA DPI at baseline ➢ Same ICS daily FP equivalent dose category [based on GINA: Low (>100µg & ≤250µg), Medium (>250µg & ≤500µg), High (≥500µg)] at last prescription for FDC ICS/LABA DPI at baseline and prescription of FDC ICS/LABA at index date
Exclusion criteria
➢ Prescription of FDC ICS/LABA pMDI prior to study period ➢ Received maintenance oral corticosteroids[2] during the baseline year ➢ Received multiple FDC ICS/LABA or separate ICS or LABA prescriptions at index date

4.1.1 Phase 1-specific inclusion criteria

Table 2: Phase 1-specific inclusion criteria

Inclusion criteria
➢ ≥1 prescription of FDC ICS/LABA during outcome period ➢ Index date pMDI prescription between 31 Jul 2011 to 31 Jan 2016 (1 year baseline, 6 months outcome)

4.1.2 Phase 2-specific inclusion criteria

Table 3: Phase 2-specific inclusion criteria

Inclusion criteria
➢ ≥ 1 prescription of FDC ICS/LABA pMDI and no prescription of FDC ICS/LABA DPI during outcome period ➢ Index date pMDI prescription between 31 Jul 2011 to 31 Jul 2015 (1 year baseline, 1 year outcome)

[1] Patients are expected to use their own inhalers during inpatient admissions. Therefore, to avoid duplication, inpatient prescriptions of FDC ICS/LABA pMDIs are not considered as first prescriptions.
[2] "Maintenance therapy" is defined as: ≥5 prescriptions of ≤10mg Prednisolone equivalent oral corticosteroids AND no prescription of >10mg Prednisolone equivalent oral corticosteroids during an inpatient admission

4.2 Data source

For this study, data was collected from the Electronic Medical Record Database at the Allergy and Clinical Immunology Department at Ajou University Hospital, Korea. This database contains detailed and extensive longitudinal data of patients with moderate/severe asthma. Data includes diagnostic values (blood eosinophil counts, IgE levels) and drug prescriptions. The data period available for the study was from 31 July 2010 until 31 July 2016.

5 Study variables and study outcomes

5.1 Exposures

Exposures are prescriptions for FDC ICS/LABA DPI and FDC ICS/LABA pMDI.

5.2 Demographic and baseline variables

5.2.1 Demographics (at index date)

- Age (at index date)
- Gender

5.2.2 Comorbidities (1-year baseline and ever)

- Asthma (KCD-6: J45-46, J82)
- COPD (KCD-6: J43-J44)
- Tuberculosis (KCD-6: A15-A16)
- Interstitial lung disease (KCD-6: J84)
- Bronchiectasis (KCD-6: J47)
- Lung cancer (KCD-6: C34)
- Diffuse panbronchiolitis (KCD-6: J21.9)
- Oral thrush (KCD-6: B37)
- Actively treated eczema (KCD-6: L20, L30)
- Gastro-oesophageal reflux disease (GERD) (KCD-6: K21)
- IHD (KCD-6: I20-I25)
- Influenza (KCD-6: J09-J12)
- Other lung disease (KCD-6: J40, J41, J42, J60-J70, J84)
- Nasal polyps (KCD-6: J33)
- Pneumonia (KCD-6: J13-J18)
- Actively treated allergic and non-allergic rhinitis (KCD-6: J30, J31.0)
- Charlson comorbidity index score[3] (CCI) score

[3] Based on the International Classification of Diseases, 10th revision (ICD-10) adapted to Korean Classification of Diseases, 6th revision (KCD-6). Predicts the ten-year mortality for patients with comorbidities, where each comorbidity is assigned a score. Sundararajan, Vijaya et al. "New ICD-10 Version of The Charlson Comorbidity Index Predicted In-Hospital Mortality". *Journal of Clinical Epidemiology* 57.12 (2004): 1288-1294

5.2.3 Disease severity and control (1-year baseline)

- Number of (all/asthma-related[4]) hospitalisations
- Number of (all/asthma-related[4]) hospital outpatient attendances
- Number of (all/asthma-related[4]) emergency attendances
- Number of asthma- related[4] antibiotics[5] without upper respiratory[6] diagnosis
- Asthma- related acute/non-acute courses of oral corticosteroids
- Average SABA inhaler daily dose
- Average SABA nebuliser daily dose
- Average ICS daily dose
- Number of severe asthma exacerbations (section 5.5)
- Number of acute respiratory events (section 5.5)

5.2.4 Medication (1-year baseline)

- FDC ICS/LABA
- Inhaled corticosteroids (ICS)
- Intravenous/Intramuscular corticosteroids (IV/IM CS)
- Short-acting β2 agonist (SABA) inhaler/oral/nebuliser
- Short-acting muscarinic antagonist (SAMA)
- FDC SABA/SAMA
- Long-acting β2 agonist (LABA) inhaler/oral/patch
- Long-acting muscarinic antagonist (LAMA)
- Leukotriene Receptor Antagonist (LTRA)
- Omalizumab
- Theophylline or other methylxanthines
- Cromones
- NSAIDs
- Paracetamol

5.2.5 Clinical measurements (1-year baseline)

- Total IgE
- Blood eosinophils
- Sputum eosinophils

5.3 **Exploratory outcome (Phase 1)**

The outcome of this exploratory study phase was persisting with change, defined as:

- Percentage of ICS/LABA pMDI patients who, at 6 months post-index date, received ≥1 prescriptions of ICS/LABA pMDI (in addition to that issued at their index date prescription) and no prescription for an ICS/LABA DPI over the same period.

[4] Asthma-related: i) primary diagnosis of asthma (J45-J46, J82) OR ii) primary diagnosis of LRTI (J09-J18, J20, J22, J45-46, J82, J96, R06) and secondary diagnosis of asthma OR iii) primary diagnosis of LTRI and previous asthma diagnosis
[5] Antibiotics use associated with asthma exacerbation treatment defined as: antibiotics prescription >7 days
[6] Upper respiratory diagnosis: J01-J06, J30-J39

Persistence of change was claimed if the lower limit of the 95% confidence interval (CI) is ≥70%.

A sub-analysis was performed to assess the number of patients remaining on the same drug and pMDI device:

- A patient prescribed a pMDI at index date was deemed remaining on the same device if, at 6 months post-index date, they received ≥1 prescriptions of the pMDI change drug AND no DPI prescriptions AND no other pMDI prescriptions.

As a further sub-analysis, outcome results were also stratified by the change drug, i.e. the FDC ICS/LABA pMDI at index date.

5.4 Primary outcome (Phase 2)

The primary outcome of this study was a non-inferiority assessment powered on the "no-exacerbation" endpoint:

- Proportion of patients who are prescribed ≥1 FDC ICS/LABA pMDI, in addition to the index date prescription, who have no severe exacerbations within 1 year of changing from a FDC ICS/LABA DPI inhaler device, compared to the baseline year. Non-inferiority was claimed if the lower limit of the 95% CI of the mean difference in patient proportions with no severe exacerbations, outcome - baseline ≥ -0.125

Patients with no severe exacerbations, as defined by the ATS/ERS Task Force 2015, have the absence of the following events:

- Asthma-related[4] hospital admissions AND A&E attendance; AND
- An acute course of oral corticosteroids[7]

5.5 Exploratory effectiveness outcomes (Phase 2)

i. Severe asthma exacerbation rate (ATS/ERS statement definition 2015), defined as an occurrence[8] of the following:
   - Asthma-related[4] hospital admissions OR
   - Asthma-related[4] A&E attendance OR

[7] Acute oral corticosteroid use associated with asthma exacerbation treatment defined as: oral corticosteroid prescription of ≥15mg AND duration greater or equal to 3 days
[8] Where ≥1 oral corticosteroid course / hospital inpatient / hospital outpatient / hospital emergency occurs within 7 days of each other, these events will be considered the result of the same exacerbation (and will only be counted once). Index date exacerbations will be included in the baseline count

- An acute course or oral corticosteroids

ii. Acute respiratory event, defined as an occurrence[3] of the following:

- Asthma-related[1] hospital admissions OR
- Asthma-related[1] A&E attendance OR
- An acute course of oral corticosteroids OR
- Asthma- related[1] antibiotics[5] without upper respiratory diagnosis[6]

iii. Risk domain asthma control (RDAC) defined as absence of:

- Asthma-related[1] hospital admissions AND
- Asthma-related[1] A&E attendance AND
- An acute course of oral corticosteroids AND
- Asthma- related[1] antibiotics[5] without upper respiratory diagnosis[6]

iv. Overall asthma control (OAC)

- RDAC as defined above AND
- ≤200 µg salbutamol/≤500 µg terbutaline average daily dose

v. Treatment stability, defined as:

- RDAC as defined above AND
- No additional or change in therapy as denoted by
  - an increase in ICS dose of ≥50% of that of prescribed at index date AND/OR
  - addition of theophylline or a leukotriene antagonist (LTRA) or LABA

vi. Asthma-related hospitalisation rate, defined as:

- Rate of asthma-related[1] hospital inpatient admissions

vii. Average daily SABA usage:

- Average daily SABA dosage during outcome year (in µg) calculated by

$$\frac{Number\ of\ inhalers * doses\ per\ inhaler}{365} * strength$$

- Categorised as >0 to ≤200, >200 to ≤400, >400 to ≤800, >801 µg daily SABA dosage

viii. Average daily ICS dose

- Average daily ICS (fluticasone equivalent) dosage during outcome year (in µg) calculated by

$$\frac{Number\ of\ inhalers * doses\ per\ inhaler}{365} * strength$$

- Categorised as 0, >0 to ≤250, >250 to ≤500, >500 µg daily ICS dosage (low, medium, high as per GINA guidelines[13])

ix. Incidence of oral thrush:

- Diagnostic code for oral thrush OR
- Prescription of antifungal therapy

6 Statistical analysis

6.1 Software

All statistical analyses were conducted using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistically significant results were defined as $p < 0.05$.

6.2 Sample size calculations

6.2.1 Exploratory outcome: Persistence of change

A previous study conducted by RiRL UK (Mundipharma R03212b-Effectiveness of Flutiform® Stage 2) on the switch success of ICS/LABA DPI to ICS/LABA pMDI was used to inform the following power calculations for the 6-month outcome period. This assumed that changing inhalers is due to cost reasons rather than clinical reasons. It also assumed that the change from a pMDI to a different pMDI had a similar level of satisfaction to the change from a DPI to a pMDI. In reality, a change for clinical reasons is less likely to result in satisfaction, similarly a change to an inhaler that needs radically different technique is less likely to be met with satisfaction[16].

Based on an expected "change-back" probability of approximately 0.20 (20%) among patients changing from existing ICS/LABA DPI to ICS/LABA pMDI at their prescription date, a sample size of 100 patients per change cohort was sufficient to construct a 95% one-sided confidence interval with an upper bound of less than 0.30 (30%) to power the evaluation of ICS/LABA pMDI "persistence of change".

6.2.2 Primary outcome: Non-inferiority of no exacerbations

Non-inferiority of the proportion of patients with no exacerbations was tested between the outcome and the baseline periods within the persistence of change cohort. As such, 163 patients were required based on the following calculation:

When the sample size is 163, a paired McNemar's Chi-square test with a 0.025 one-sided significance level has 90% power to reject the null hypothesis that the proportions are non-inferior (i.e. the difference in proportions of "no exacerbations", outcome-baseline, is 0.125 or farther from zero in the same direction) when the expected difference in proportions is 0, assuming that the proportion of discordant pairs is 0.242 (based on previous RiRL UK research Mundipharma R03212b-Effectiveness of Flutiform® Stage 2).

6.2.3 Primary outcome: Actual data

For 85 patients, a paired McNemar's Chi-square test with a 0.025 one-sided significance level has 73% power to reject the null hypothesis that the proportions are non-inferior (i.e. the difference in proportions of "no exacerbations", outcome-baseline, is 0.125 or farther from zero in the same direction) when the expected difference in proportions is 0, assuming that the proportion of discordant pairs is 0.242 (based on previous RiRL UK research Mundipharma R03212b-Effectiveness of Flutiform® Stage 2).

6.2.4 Multiplicity

Although more than one sample size calculation has been performed, the primary endpoint was non-inferiority of asthma effectiveness, in terms of the proportion of patients that experience no exacerbations. This was the primary focus of the study.

The second power calculation is provided to give an indication of how much data would be needed to demonstrate persistence of change.

The analyses were performed in a hierarchical approach, in that efficacy was only considered with evidence of non-inferiority of asthma effectiveness. The study populations were also different for each phase. Thus, there was no issue of multiple testing.

6.3 **Baseline characterisation**

Summary statistics were produced for all baseline variables. The baseline variables for the two cohorts were compared using the following tests:

- Variables measured on the interval/ratio scale:
  - t-test (normal distribution)
  - Mann-Whitney U test (skewed data)
- Categorical variables:
  - Chi-square test

Results were reported as:

- Variables measured on the interval/ratio scale:
  - Sample size (n) and percentage non-missing
  - Median and inter-quartile range (25th and 75th percentiles)
- Categorical variables:
  - Sample size (n)
  - Count and percentage by category (distribution)

6.4 Analysis of study outcomes

6.4.1 Exploratory outcome: persistence of change

Percentage of ICS/LABA pMDI patients who received ≥1 prescriptions of ICS/LABA pMDI and no ICS/LABA DPI, in addition to that issued at their prescription date, at 6 months was calculated to evaluate ICS/LABA pMDI "persistence of change".

Persistence of change was claimed if the lower confidence interval of percentage of patients persisting on ICS/LABA pMDI ≥70% (clinically significant limit).

Sub-analyses were performed to assess the number of patients remaining on the same drug and pMDI device and outcome results stratified by the change drug.

One-sided 90% confidence intervals for binomial proportions were calculated for all Phase 1 analyses.

6.4.2 Primary outcome: non-inferiority of no exacerbations

Paired difference of binomial proportions with Wald confidence intervals was used to obtain the non-inferiority limit of mean difference in patient proportions with no exacerbations. Non-inferiority was claimed if the lower limit of the 95% CI of the mean difference in patient proportions with no exacerbations, outcome – baseline ≥ -0.125.

Exact McNemar's test with central confidence intervals was used to compare the proportion of patients with "no exacerbations" for within (baseline vs outcome of persistence of change cohort) cohort comparisons.
Wilcoxon signed rank test, exact McNemar's test and marginal homogeneity test were used as appropriate to analyse other effectiveness outcomes.

7 Results

7.1 Phase 1

7.1.1 Patient population

Patients changing from FDC ICS/LABA DPI to pMDI with ≥1 prescription of FDC ICS/LABA pMDI during the 6-month outcome period were investigated in Phase 1.

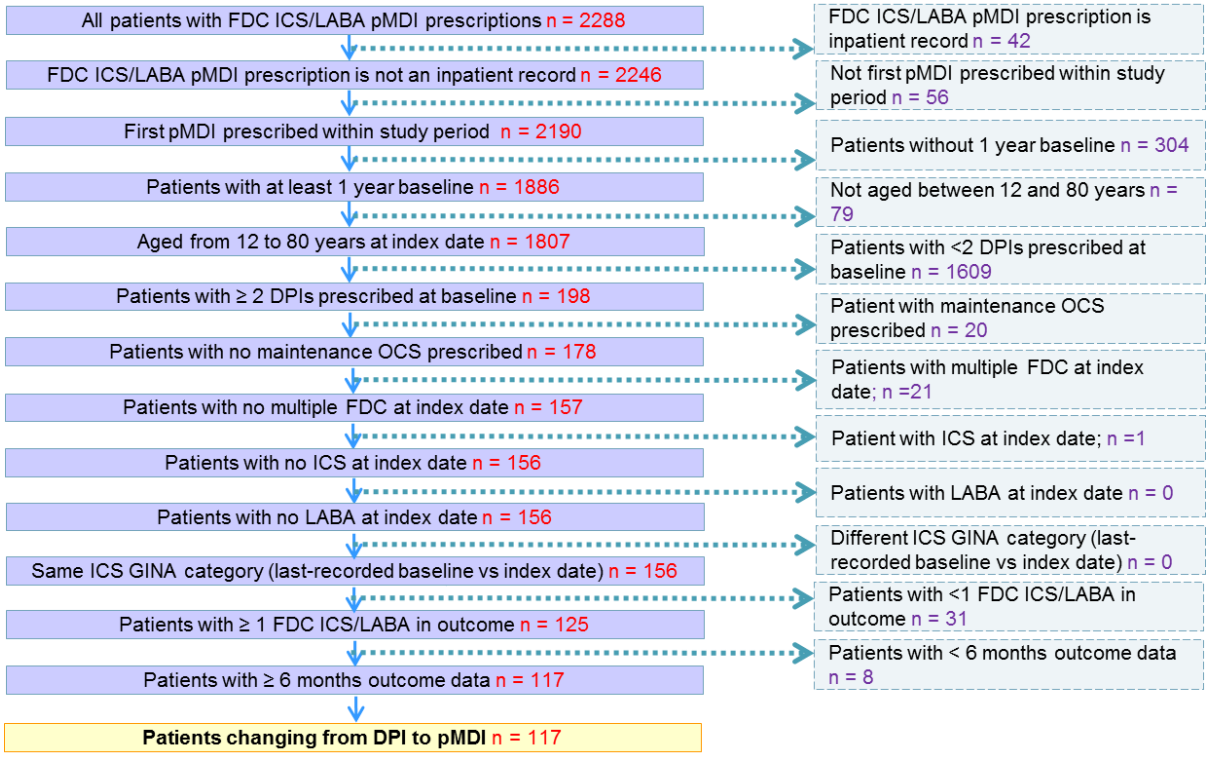

Figure 3: Phase 1 consort diagram

7.1.2 Exploratory outcome: persistence of change

In addition to the FDC ICS/LABA pMDI issued at the index date, 76% (95% CI (69,100)) of patients received ≥1 prescription for FDC ICS/LABA pMDI, and no prescription for FDC ICS/LABA DPI, after 6 months. The lower boundary of the 95% confidence interval was just outside the pre-defined clinically significant limit of 70%.

Table 4: Phase 1 – persistence of change at 6 months

Persistence of change	N	% (one-sided 95% CI)
N not missing	117	100
No	28	23.93 (0.00, 30.96)
Yes	89	76.07 (69.03, 100.00)

7.1.3 Sub-analysis I: persistence of change

At 6 months post-index date, 76.92% patients prescribed beclomethasone/formoterol (Foster®) pMDI and 75.00% patients prescribed fluticasone/formoterol (Flutiform®) pMDI received ≥1 prescriptions of FDC ICS/LABA pMDI (in addition to that issued at their prescription date) and no FDC ICS/LABA DPI.

Table 5: Phase 1 - persistence of change at 6 months stratified by change drug

	Flutiform® pMDI		Foster® pMDI	
Persistence of change	N	% (one-sided 95% CI)	N	% (one-sided 95% CI)
N not missing	52	100	65	100
No	13	25.00 (0.00, 35.95)	15	23.08 (0.00, 33.64)
Yes	39	75.00 (64.05, 100.00)	50	76.92 (67.36, 100.00)

7.1.4 Sub-analysis II: remaining on the same device

Patients were deemed remaining on the same device if they were prescribed ≥1 of the change drug of the same device and no prescriptions of other drugs, regardless of device-type, at 6 months post-index date.

Table 6: Phase 1 – patients remaining on the same device after 6 months

	Total		Flutiform® pMDI		Foster® pMDI	
	N	% (one-sided 95% CI)	N	% (one-sided 95% CI)	N	% (one-sided 95% CI)
N not missing	117	100	52	100	65	100
No	30	25.64 (0.00, 32.78)	15	28.85 (0.00, 40.02)	15	23.08 (0.00, 32.64)
Yes	87	74.36 (67.22, 100.00)	37	71.15 (59.98, 100.00)	50	76.92 (67.36, 100.00)

7.1.5 Patient characteristics

Patients were stratified by those persisting with change (i.e. ≥1 FDC ICS/LABA pMDI and no FDC ICS/LABA DPI during the outcome period) and those not persisting with change to investigate differences in demographics, comorbidities, disease severity, prescribed medication and clinical measurements. A description of the main differences is provided below and the data tables are presented in the appendix, section 12.2.

In terms of demographics, patients who successfully persisted with change from FDC ICS/LABA DPI to pMDI were similar in age (p=0.35) and gender (p=1.00) compared to those who did not persist with change (Table 13). Disease severity was similar between the persistence of change success and failure cohorts (Table 14) and comorbidities were similarly

distributed among patients in both groups (Table 15). Interstitial lung disease, diffuse panbronchiolitis, oral thrush and influenza were rarely recorded.

Asthma-related medication prescribed during the baseline year was similar for the persistence of change success and failure cohorts (Table 16). More patients in the success cohort had LTRA prescriptions during the baseline year (77%) than patients in the failure cohort (19%, p=0.05). Clinical measurements were not available for most patients. Distributions of sputum and blood eosinophil measurements were not significantly different between patients who persisted with change from FDC ICS/LABA DPI to pMDI and those who were non-persistent with the change of treatment (Table 17).

7.2 **Phase 2**

The effectiveness of changing from a DPI to a pMDI inhaler for FDC ICS/LABA therapy was examined over an outcome period of 1 year. A high proportion of patients in the study were found to have poor asthma control (appendix 12.2, section 12.2.2). Analysis for phase 2 was performed as per protocol; however, in addition to the primary outcome of non-inferiority of no exacerbations, asthma control was deemed an important outcome for this study phase.

7.2.1 Patient population

Patients changing from FDC ICS/LABA DPI to pMDI with ≥1 prescription of FDC ICS/LABA pMDI and no prescription of FDC ICS/LABA DPI during the 1-year outcome period were investigated in Phase 2.

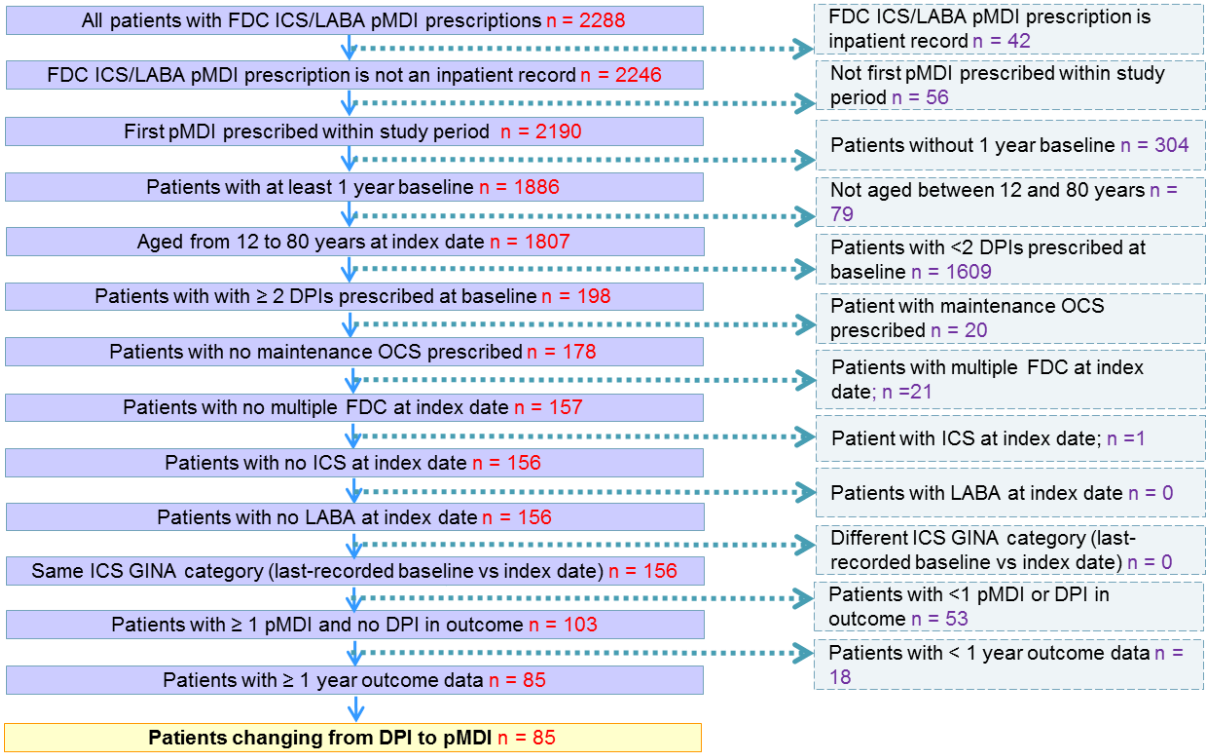

Figure 4: Phase 2 consort diagram

7.2.2 Phase 2 baseline characterisation

Demographics, comorbidities, disease severity, prescribed medication and clinical measurements during the baseline year were described for patients in Phase 2; the data is presented in tables in the appendix, section 12.3 .

7.2.3 Phase 2 outcomes

7.2.3.1 Primary outcome: Non-inferiority of no exacerbations

Non-inferiority of asthma effectiveness, with regards the proportion of patients experiencing no exacerbations, was determined for the population that changed from FDC ICS/LABA DPI to FDC ICS/LABA pMDI with no prescriptions for a DPI during the outcome year.

Table 7: Phase 2 - non-inferiority of no exacerbations

	Patients changing from FDC ICS/LABA DPI to FDC ICS/LABA pMDI (n = 85)	
	Mean difference (CI)*	**Non-inferiority met?**
"No exacerbations" of outcome from baseline (%) - Asthma-related[1] hospital admissions AND - Asthma-related[1] A&E attendance AND - Acute prescription of oral corticosteroids	0.129 (0.0384, 0.2204)	YES

*Paired difference of binomial proportions with Wald confidence intervals

7.2.3.2 Asthma control

A higher proportion of patients that changed from a DPI to a pMDI for FDC ICS/LABA treatment achieved risk domain asthma control (RDAC) (defined by the proportion of patients with no asthma-related: hospital admissions, emergency hospital department attendance, antibiotics and acute courses of oral corticosteroids) during the outcome year, as compared to the year prior (75% vs 58%) (Table 8). Similarly, a higher proportion of patients that changed to FDC ICS/LABA pMDI, from a DPI, achieved overall asthma control (OAC) (defined as RDAC and ≤200µg salbutamol/≤500µg terbutaline average daily dose) during the outcome year (58% vs 46%).

Table 8: Phase 2 – asthma control

	Measure	Baseline (n=85)	Outcome (n=85)	p-value
RDAC	N (%) not missing	85 (100.0)	85 (100.0)	0.001Δ
	No	36 (42.35)	21 (24.71)	
	Yes	49 (57.65)	64 (75.29)	
OAC	N (%) not missing	85 (100.0)	85 (100.0)	0.021Δ
	No	46 (54.12)	36 (42.35)	
	Yes	39 (45.88)	49 (57.65)	

Δ Exact Mcnemar's test with central confidence intervals

7.2.3.3 Exploratory effectiveness outcomes

Other clinical effectiveness measures during the outcome period, as listed in Section 5.5, were compared against the equivalent measures during the baseline year. A significant decrease in the number of severe asthma exacerbations (p=0.01), acute respiratory events (p=0.006), and ICS average daily dose (p<0.001) was determined for patients during the outcome year compared to baseline (Table 9). A significant increase in SABA inhaler average daily dose (p=0.048) was observed for patients during the outcome year; however, a decreased number of these patients received the highest SABA average daily dose during the outcome year as compared to during the baseline period (8% vs 12%).

Table 9: Phase 2 – exploratory effectiveness outcomes

n=85	Measure	Baseline (n=85)	Outcome (n=85)	p-value
No severe asthma exacerbations	N (%) not missing	85 (100.0)	85 (100.0)	0.010Δ
	No	24 (28.24)	13 (15.29)	
	Yes	61 (71.76)	72 (84.71)	
Number of severe asthma exacerbations (continuous)	N (%) not missing	85 (100.0)	85 (100.0)	0.500‡
	Mean (SD)	0.53 (1.22)	0.41 (1.15)	
Presence of severe asthma exacerbations (yes/no)	N (%) not missing	85 (100.0)	85 (100.0)	0.010Δ
	No	61 (71.76)	72 (84.71)	
	Yes	24 (28.24)	13 (15.29)	
Number of severe asthma exacerbations (categorised)	N (%) not missing	85 (100.0)	85 (100.0)	0.030†
	0	61 (71.76)	72 (84.71)	
	1	13 (15.29)	3 (3.53)	
	2	7 (8.24)	5 (5.88)	
	3	3 (3.53)	1 (1.18)	
	4+	1 (1.18)	4 (4.71)	
Acute respiratory events (continuous)	N (%) not missing	85 (100.0)	85 (100.0)	0.272‡
	Mean (SD)	0.76 (1.44)	0.54 (1.19)	
Acute respiratory events (categorised)	N (%) not missing	85 (100.0)	85 (100.0)	0.006†
	0	49 (57.65)	64 (75.29)	
	1	22 (25.88)	9 (10.59)	
	2	7 (8.24)	6 (7.06)	
	3	6 (7.06)	2 (2.35)	
	4+	1 (1.18)	4 (4.71)	
Asthma-related hospitalisations (continuous)	N (%) not missing	85 (100.0)	85 (100.0)	0.100‡
	Mean (SD)	0.11 (0.35)	0.07 (0.65)	
Asthma-related hospitalisations (categorised)	N (%) not missing	85 (100.0)	85 (100.0)	N/A
	0	77 (90.59)	84 (98.82)	
	1	7 (8.24)	0 (0.00)	
	2	1 (1.18)	0 (0.00)	
	3	0 (0.00)	0 (0.00)	
	4+	0 (0.00)	1 (1.18)	
SABA inhaler average daily dose	N (%) not missing	38 (44.71)	31 (36.47)	0.048‡
	Mean (SD)	543.62 (507.25)	558.55 (493.24)	
SABA inhaler average daily dose (categorised)	N (%) not missing	85 (100.0)	85 (100.0)	0.300†
	0	47 (55.29)	54 (63.53)	
	>0 - 200	14 (16.47)	7 (8.24)	
	>200 - 400	7 (8.24)	9 (10.59)	
	>400 - 800	7 (8.24)	8 (9.41)	
	>800	10 (11.76)	7 (8.24)	
ICS average daily dose	N (%) not missing	70 (82.45)	83 (97.65)	<0.001‡
	Mean (SD)	1146.81 (627.72)	767.32 (583.48)	
ICS average daily dose (categorised)	N (%) not missing	85 (100.0)	85 (100.0)	0.001†
	≥100 - 250	0 (0.00)	11 (12.94)	

n=85	Measure	Baseline (n=85)	Outcome (n=85)	p-value
	>250 - 500	9 (10.59)	11 (12.94)	
	>500	76 (89.41)	63 (74.12)	
Treatment stability	N (%) not missing	-	85 (100.0)	N/A
	No	-	70 (82.35)	
	Yes	-	15 (17.65)	
Oral thrush	N (%) not missing	85 (100.0)	85 (100.0)	N/A
	No	84 (98.82)	85 (100.0)	
	Yes	1 (1.18)	0 (0.00)	
Eosinophils/100 leukocytes in Sputum	N (%) not missing	21 (24.71)	3 (3.53)	N/A
	Mean (SD)	39.29 (±34.57)	32.33 (±36.25)	
Blood eosinophils/µL	N (%) not missing	14 (16.47)	2 (2.35)	N/A
	Mean (SD)	507.14 (±368.92)	350.00 (±353.55)	

∆ Exact Mcnemar's test with central confidence intervals, ‡ Wilcoxon signed rank test with continuity correction, † Marginal homogeneity test, N/A – not applicable

7.2.3.4 Sub-analysis I: non-inferiority of no exacerbations (stratified)

Non-inferiority in the proportion of patients experiencing no exacerbations in the outcome year, as compared to during the baseline year, was met for patients changing to either FP/FOR or BDP/FOR ICS/LABA pMDI.

Table 10: Phase 2 – secondary outcome: no exacerbations (stratified by switch drug)

	Patients changing from FDC ICS/LABA DPI to FDC ICS/LABA pMDI (n = 85)	
Change Drug	**Mean difference (CI)***	**Non-inferiority met?**
FP/FOR	0.211 (0.0809, 0.3401)	YES
BDP/FOR	0.064 (-0.0599, 0.1876)	YES

*Paired difference of binomial proportions with Wald confidence intervals

7.2.3.5 Sub-analysis II: asthma control (FP/FOR)

A significantly increased proportion of patients within the group that changed to FDC ICS/LABA FP/FOR pMDI achieved risk domain (82% vs 55%) and overall asthma control (61% vs 42%) in the outcome year compared to the baseline year.

Table 11: Phase 2 – asthma control (FP/FOR)

	Measure	Baseline	Outcome	p-value
RDAC	N (%) not missing	38 (100.0)	38 (100.0)	0.002∆
	No	17 (44.74)	7 (18.42)	
	Yes	21 (55.26)	31 (81.58)	
OAC	N (%) not missing	38 (100.0)	38 (100.0)	0.020∆
	No	22 (57.89)	15 (39.47)	

	Yes	16 (42.11)	23 (60.53)	

∆ Exact Mcnemar's test with central confidence intervals

7.2.3.6 Sub-analysis III: asthma control (BDP/FOR)

No significant differences between the proportions of patients achieving risk domain (p=0.200) or overall asthma control (p=0.500) were observed for patients that changed to FDC ICS/LABA BDP/FOR pMDI in the outcome year as compared to during the baseline year.

Table 12: Phase 2 – asthma control (BDP/FOR)

	Measure	Baseline	Outcome	p-value
RDAC	N (%) not missing	47 (100.0)	47 (100.0)	0.200∆
	No	19 (40.43)	14 (29.79)	
	Yes	28 (59.57)	33 (70.21)	
OAC	N (%) not missing	47 (100.0)	47 (100.0)	0.500∆
	No	24 (51.06)	21 (44.68)	
	Yes	23 (48.94)	26 (55.32)	

∆ Exact Mcnemar's test with central confidence intervals

7.2.3.7 Sub-analysis IV: exploratory effectiveness outcomes (FP/FOR)

Other clinical effectiveness measures during the outcome period, as listed in Section 5.5, were compared against the baseline period for the subgroup of patients who changed to fluticasone/formoterol pMDI (see appendix, section 12.4). A significantly increased proportion of patients within this group experienced no severe exacerbations in the outcome year compared to the baseline year (p=0.008) (Table 22) A decrease in acute respiratory events (p=0.02) and average daily ICS dose (p<0.001) was also observed over the outcome year compared to the baseline year.

7.2.3.8 Sub-analysis V: exploratory effectiveness (BDP/FOR)

Other clinical effectiveness measures during the outcome year, as listed in Section 5.5, were compared against the baseline year for the subgroup of patients who switched to beclomethasone/formoterol (see appendix, section 12.5). A decrease in ICS average daily dose (p=0.001) was determined for these patients in the outcome year as compared to during the baseline period (Table 23).

8 Conclusions

The aim of this study was to assess non-inferiority of asthma effectiveness following the change of inhaler device from a DPI to a pMDI for FDC ICS/LABA asthma therapy, and the associated proportion of patients that persist with this change in therapy. A historical cohort study was performed, using real-life data from the Electronic Medical Record Database at the Allergy and Clinical Immunology Department, Ajou University Hospital, Korea.

The results from exploratory phase 1 of this study showed that 76% of patients (95% CI 69, 100) that changed from a FDC ICS/LABA DPI to a FDC ICS/LABA pMDI persisted with the change of inhaler over a 6 months' study period. Although the lower confidence interval was just outside of the pre-defined clinically significant limit of 70%, the point estimate of 76% is above the pre-defined 'change success' limit set *a priori*[9]. Persistence of change over 6 months was similar for patients who changed to either fluticasone/formoterol (Flutiform®) pMDI or beclomethasone/formoterol (Foster®) pMDI, 75% (95%CI 64, 100) and 76.9% (95%CI 67, 100) of patients respectively. Furthermore, 71% (95%CI 60, 100) of patients changing to fluticasone/formoterol (Flutiform®) pMDI and 77% (95%CI 67, 100) switching to beclomethasone/formoterol (Foster®) received more than 1 prescription for the same inhaler device during the 6 months' study period.

Patients that persisted with change from a DPI to a pMDI for FDC ICS/LABA treatment were found to be comparable, in terms of demographics, comorbidities and disease severity at baseline, to those patients that failed. However, more patients in the success cohort had LTRA prescriptions during the baseline year (p=0.05) than patients that failed with the treatment change.

In phase 2 of the study, the effectiveness of changing from a DPI to a pMDI inhaler for FDC ICS/LABA therapy was examined over an outcome period of 1 year and compared to the baseline year. The change from FDC ICS/LABA DPI to FDC ICS/LABA pMDI resulted in a non-inferior proportion of patients experiencing no severe exacerbations. Non-inferiority was achieved for patients switching to either fluticasone/formoterol (Flutiform®) pMDI or beclomethasone/formoterol (Foster®) pMDI. Patients that persisted with change to either fluticasone/formoterol (Flutiform®) pMDI or beclomethasone/formoterol (Foster®) pMDI had statistically significant decreases in ICS average daily dose (p<0.001) during the year following the change in therapy compared to baseline.

[9] EnCEPP protocol

In phase 1, a high proportion of patients within the study cohort was determined to have poor asthma control. It is not known whether the change in therapy from a pMDI to a DPI was instigated for clinical or cost reasons, hence asthma control was also examined as an important outcome in phase 2. A significantly increased proportion of patients that changed to FDC ICS/LABA pMDI, from a DPI, were found to have achieved risk domain (p=0.001) and overall asthma control (p=0.021) in the year following the change in therapy as compared to the year prior. Results from the sub-analyses demonstrated that the significance was driven by patients changing to fluticasone/formoterol (Flutiform®) treatment and that these patients also had significantly decreased acute respiratory events (p=0.02) over the one-year outcome period.

In summary, the above results show that changing from a DPI to a pMDI inhaler for FDC ICS/LABA asthma treatment is as effective as remaining on DPI treatment in terms of exacerbation prevention. The majority of patients studied persisted with the change in therapy over 6 months. In the year following the switch to ICS/LABA pMDI treatment, patients achieved superior asthma control, decreased acute respiratory events and decreased average ICS daily dose.

The strength of the study is that it is based on real-life data, obtained from a high-quality database. The retrospective nature of this study means that patients were not influenced in any way. The datasets represent information collected for clinical and routine use however, rather than specifically for research purposes. The validity and completeness of individual patient records cannot be assessed; as such there may be omissions or errors.

This study looks solely at the use of FDC ICS/LABA inhalers and does not include/exclude patients by asthma or COPD or other chronic respiratory disease diagnosis. It is also noted that some asthma drugs are prescribed with COPD as a diagnosis due to strict reimbursement criteria in Korea. Having COPD as an exclusion criterion would unnecessarily exclude asthma patients who are prescribed drugs affected by this reimbursement criteria. It was deemed that the study would not be greatly affected by this limitation, and there was no statistically significant difference detected for chronic respiratory diseases when comparing patients who failed/persisted in the change from DPI to pMDI.

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12 Appendix

12.1 Appendix 1: Definitions

Definitions were updated based on discussions with the steering committee to be clinically relevant.

Term	Old definition	New definition
Asthma- related	Principal or secondary diagnosis of asthma (KCD-6 codes: J45– J46, J82) OR lower respiratory tract infection (LRTI) diagnosis [whooping cough (A37), influenza (J09-J12), pneumonia (J13-J18), bronchitis (J40), bronchitis (J20-22)], OR respiratory diagnosis [respiratory failure (J96), disorders of breathing (R06)] on the same day as an event of interest	i) primary diagnosis of asthma (J45-J46, J82) OR ii) primary dx of LRTI (J09-J18, J20, J22, J45-46, J82, J96, R06) and secondary diagnosis of asthma OR iii) primary diagnosis of LRTI dx and previous asthma dx
Maintenance oral corticosteroids	"Maintenance therapy" is defined as: daily dosing instructions of <=10mg Prednisolone (or equivalent) or prescriptions for 1mg or 2.5mg Prednisolone (or equivalent) tablets where daily dosing instructions are not available	≥5 prescriptions of ≤10mg Prednisolone equivalent oral corticosteroids AND no prescription of >10mg Prednisolone equivalent oral corticosteroids during an inpatient admission
Asthma-related acute course of oral corticosteroid	Asthma-related 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. 30mg as directed) 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.	oral corticosteroid prescription of ≥15mg AND duration greater or equal to than 3 days
Asthma- related antibiotics prescription	An antibiotic prescription with principal or secondary diagnosis of asthma (KCD-6 codes: J45– J46, J82) OR lower respiratory tract infection (LRTI) diagnosis [whooping cough (A37), influenza (J09-J12), pneumonia (J13-J18), bronchitis (J40), bronchitis (J20-22)], OR respiratory diagnosis [respiratory failure (J96), disorders of breathing (R06)]	An antibiotics prescription of duration more than 7 days without an upper respiratory diagnosis (J01-J06, J30-J39)

12.2 Phase 1 – Patient characteristics

12.2.1 Demographics

Table 13: Phase 1 - Demographics

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
Age at IPD (years)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.35
	Mean (SD)	56.71 (16.13)	53.38 (16.99)	54.18 (16.78)	
	Median (IQR)	58.00 (47.25, 68.00)	54.00 (41.00, 67.00)	55.00 (43.00, 68.00)	
Age at IPD (years) (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.47
	12-18, n (%)	0 (0.00)	2 (2.25)	2 (1.71)	
	19-65, n (%)	17 (60.71)	61 (68.54)	78 (66.67)	
	66-80, n (%)	11 (39.29)	26 (29.21)	37 (31.62)	
Gender	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	Female, n (%)	13 (46.43)	42 (47.19)	55 (47.01)	
	Male, n (%)	15 (53.57)	47 (52.81)	62 (52.99)	

* Mann-Whitney test for continuous variables and Chi-squared test for categorical variables

12.2.2 Disease severity

Table 14: Phase 1 – disease severity

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
All hospitalisations	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.69
	Mean (SD)	0.71 (2.45)	0.29 (0.57)	0.39 (1.29)	
	Median (IQR)	0.00 (0.00, 1.00)	0.00 (0.00, 0.00)	0.00 (0.00, 1.00)	
All hospitalisations (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.37
	0, n (%)	20 (71.43)	67 (75.28)	87 (74.36)	
	1, n (%)	7 (25.00)	19 (21.35)	26 (22.22)	
	2, n (%)	0 (0.00)	2 (2.25)	2 (1.71)	
	3, n (%)	0 (0.00)	1 (1.12)	1 (0.85)	
	≥4, n (%)	1 (3.57)	0 (0.00)	1 (0.85)	
All hospitalisation days	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.56
	Mean (SD)	4.86 (13.96)	4.89 (23.04)	4.88 (21.17)	
	Median (IQR)	0.00 (0.00, 5.25)	0.00 (0.00, 0.00)	0.00 (0.00, 2.00)	
All hospitalisation days (categorised)	N (%) not missing	8 (28.57)	22 (24.72)	30 (25.64)	0.62
	1-3, n (%)	0 (0.00)	2 (2.25)	2 (1.71)	
	4-6, n (%)	2 (7.14)	7 (7.87)	9 (7.69)	
	7-13, n (%)	3 (10.71)	9 (10.11)	12 (10.26)	
	≥14, n (%)	3 (10.71)	4 (4.49)	7 (5.98)	

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
Asthma-related hospitalisations	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.52
	Mean (SD)	0.07 (0.26)	0.13 (0.40)	0.12 (0.38)	
	Median (IQR)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
Asthma-related hospitalisations (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.69
	0, n (%)	26 (92.86)	79 (88.76)	105 (89.74)	
	1, n (%)	2 (7.14)	8 (8.99)	10 (8.55)	
	2, n (%)	0 (0.00)	2 (2.25)	2 (1.71)	
Asthma-related hospitalisation days	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.54
	Mean (SD)	0.54 (2.01)	1.47 (6.39)	1.25 (5.66)	
	Median (IQR)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
Asthma-related hospitalisation days (categorised)	N (%) not missing	2 (7.14)	10 (11.24)	12 (10.26)	0.75
	1-3, n (%)	0 (0.00)	1 (1.12)	1 (0.85)	
	4-6, n (%)	0 (0.00)	3 (3.37)	3 (2.56)	
	7-13, n (%)	1 (3.57)	3 (3.37)	4 (3.42)	
	≥14, n (%)	1 (3.57)	3 (3.37)	4 (3.42)	
All outpatient attendances	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.07
	Mean (SD)	19.71 (14.40)	13.75 (8.06)	15.18 (10.20)	
	Median (IQR)	15.50 (9.75, 24.25)	12.00 (8.00, 17.00)	12.00 (8.00, 19.00)	
All outpatient attendances (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.50
	3-5, n (%)	3 (10.71)	7 (7.87)	10 (8.55)	
	6-8, n (%)	3 (10.71)	18 (20.22)	21 (17.95)	
	≥9, n (%)	22 (78.57)	64 (71.91)	86 (73.50)	
Asthma-related outpatient attendances	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.17
	Mean (SD)	2.50 (3.13)	3.34 (3.42)	3.14 (3.36)	
	Median (IQR)	0.00 (0.00, 5.00)	3.00 (0.00, 5.00)	2.00 (0.00, 5.00)	
Asthma-related outpatient attendances (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.35
	0, n (%)	15 (53.57)	30 (33.71)	45 (38.46)	
	1-2, n (%)	2 (7.14)	13 (14.61)	15 (12.82)	
	3-5, n (%)	6 (21.43)	24 (26.97)	30 (25.64)	
	6-8, n (%)	4 (14.29)	13 (14.61)	17 (14.53)	
	≥9, n (%)	1 (3.57)	9 (10.11)	10 (8.55)	
All emergency attendances	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.81
	Mean (SD)	0.68 (1.72)	0.34 (0.67)	0.42 (1.03)	
	Median (IQR)	0.00 (0.00, 0.25)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
All emergency attendances (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.12
	0, n (%)	21 (75.00)	68 (76.40)	89 (76.07)	
	1, n (%)	4 (14.29)	13 (14.61)	17 (14.53)	
	2, n (%)	1 (3.57)	7 (7.87)	8 (6.84)	

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
	3, n (%)	0 (0.00)	1 (1.12)	1 (0.85)	
	≥4, n (%)	2 (7.14)	0 (0.00)	2 (1.71)	
Asthma-related emergency attendances	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.69
	Mean (SD)	0.21 (0.96)	0.10 (0.30)	0.13 (0.53)	
	Median (IQR)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
Asthma-related emergency attendances (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.12
	0, n (%)	26 (92.86)	80 (89.89)	106 (90.60)	
	1, n (%)	1 (3.57)	9 (10.11)	10 (8.55)	
	2, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
	3, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
	≥4, n (%)	1 (3.57)	0 (0.00)	1 (0.85)	
Asthma-related exacerbations (ATS)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.96
	Mean (SD)	0.86 (1.86)	0.57 (1.26)	0.64 (1.42)	
	Median (IQR)	0.00 (0.00, 0.25)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	
Asthma-related exacerbations (ATS) (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.21
	0, n (%)	21 (75.00)	63 (70.79)	84 (71.79)	
	1, n (%)	1 (3.57)	13 (14.61)	14 (11.97)	
	2, n (%)	2 (7.14)	8 (8.99)	10 (8.55)	
	3, n (%)	1 (3.57)	3 (3.37)	4 (3.42)	
	≥4, n (%)	3 (10.71)	2 (2.25)	5 (4.27)	
Asthma-related respiratory events	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.60
	Mean (SD)	1.07 (1.80)	0.75 (1.44)	0.83 (1.53)	
	Median (IQR)	0.00 (0.00, 1.25)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	
Asthma-related respiratory events (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.58
	0, n (%)	16 (57.14)	52 (58.43)	68 (58.12)	
	1, n (%)	5 (17.86)	23 (25.84)	28 (23.93)	
	2, n (%)	2 (7.14)	7 (7.87)	9 (7.69)	
	3, n (%)	3 (10.71)	5 (5.62)	8 (6.84)	
	≥4, n (%)	2 (7.14)	2 (2.25)	4 (3.42)	
Risk domain asthma control	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.91
	Yes	16 (57.14)	52 (59.43)	68 (58.12)	
	No	12 (42.86)	37 (40.57)	49 (41.88)	
Antibiotic prescription for LRTI	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.17
	Mean (SD)	0.79 (1.45)	0.39 (0.87)	0.49 (1.05)	
	Median (IQR)	0.00 (0.00, 1.00)	0.00 (0.00, 0.00)	0.00 (0.00, 1.00)	
Antibiotic prescription for LRTI (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.45
	0, n (%)	18 (64.29)	68 (76.40)	86 (73.50)	
	1, n (%)	6 (21.43)	14 (15.73)	20 (17.09)	
	2, n (%)	0 (0.00)	2 (2.25)	2 (1.71)	

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
	3, n (%)	2 (7.14)	3 (3.37)	5 (4.27)	
	≥4, n (%)	2 (7.14)	2 (2.25)	4 (3.42)	
Acute oral steroids unique day prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.37
	Mean (SD)	0.75 (1.46)	0.44 (1.23)	0.51 (1.29)	
	Median (IQR)	0.00 (0.00, 0.25)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
Acute oral steroids unique day prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.33
	0, n (%)	21 (75.00)	72 (80.90)	93 (79.49)	
	1, n (%)	1 (3.57)	7 (7.87)	8 (6.84)	
	2, n (%)	1 (3.57)	5 (5.62)	6 (5.13)	
	3, n (%)	3 (10.71)	3 (3.37)	6 (5.13)	
	≥4, n (%)	2 (7.14)	2 (2.25)	4 (3.42)	
Acute oral steroids total number of courses	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.38
	Mean (SD)	0.79 (1.47)	0.53 (1.48)	0.59 (1.47)	
	Median (IQR)	0.00 (0.00, 0.50)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
Acute oral steroids total number of courses (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.33
	0, n (%)	21 (75.00)	72 (80.90)	93 (79.49)	
	1, n (%)	0 (0.00)	5 (5.62)	5 (4.27)	
	2, n (%)	2 (7.14)	6 (6.74)	8 (6.84)	
	3, n (%)	3 (10.71)	3 (3.37)	6 (5.13)	
	≥4, n (%)	2 (7.14)	3 (3.37)	5 (4.27)	
Non-acute oral steroids unique day prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.63
	Mean (SD)	1.50 (1.91)	1.48 (2.14)	1.49 (2.08)	
	Median (IQR)	1.00 (0.00, 2.25)	0.00 (0.00, 2.00)	0.00 (0.00, 2.00)	
Non-acute oral steroids unique day prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.68
	0, n (%)	12 (42.86)	47 (52.81)	59 (50.43)	
	1, n (%)	6 (21.43)	10 (11.24)	16 (13.68)	
	2, n (%)	3 (10.71)	10 (11.24)	13 (11.11)	
	3, n (%)	3 (10.71)	7 (7.87)	10 (8.55)	
	≥4, n (%)	4 (14.29)	15 (16.85)	19 (16.24)	
Non-acute oral steroids total number of courses	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.69
	Mean (SD)	1.96 (2.85)	1.94 (3.27)	1.95 (3.16)	
	Median (IQR)	1.00 (0.00, 3.00)	0.00 (0.00, 3.00)	0.00 (0.00, 3.00)	
Non-acute oral steroids total number of courses (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.09
	0, n (%)	12 (42.86)	47 (52.81)	59 (50.43)	
	1, n (%)	6 (21.43)	6 (6.74)	12 (10.26)	
	2, n (%)	2 (7.14)	10 (11.24)	12 (10.26)	
	3, n (%)	4 (14.29)	5 (5.62)	9 (7.69)	
	≥4, n (%)	4 (14.29)	21 (23.60)	25 (21.37)	

* Mann-Whitney test for continuous variables and Chi-squared test for categorical variables

12.2.3 Comorbidities

Table 15: Phase 1 – comorbidities

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
Asthma	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.79
	No, n (%)	5 (17.86)	12 (13.48)	17 (14.53)	
	Yes, n (%)	23 (82.14)	77 (86.52)	100 (85.47)	
Asthma (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.95
	No, n (%)	3 (10.71)	12 (13.48)	15 (12.82)	
	Yes, n (%)	25 (89.29)	77 (86.52)	102 (87.18)	
COPD	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.88
	No, n (%)	21 (75.00)	70 (78.65)	91 (77.78)	
	Yes, n (%)	7 (25.00)	19 (21.35)	26 (22.22)	
COPD (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.98
	No, n (%)	21 (75.00)	69 (77.53)	90 (76.92)	
	Yes, n (%)	7 (25.00)	20 (22.47)	27 (23.08)	
Tuberculosis	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	No, n (%)	27 (96.43)	87 (97.75)	114 (97.44)	
	Yes, n (%)	1 (3.57)	2 (2.25)	3 (2.56)	
Tuberculosis (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	No, n (%)	27 (96.43)	85 (95.51)	112 (95.73)	
	Yes, n (%)	1 (3.57)	4 (4.49)	5 (4.27)	
Interstitial lung disease	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	No, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
	Yes, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
Interstitial lung disease (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	No, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
	Yes, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
Bronchiectasis	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	No, n (%)	26 (92.86)	81 (91.01)	107 (91.45)	
	Yes, n (%)	2 (7.14)	8 (8.99)	10 (8.55)	
Bronchiectasis (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	No, n (%)	25 (89.29)	81 (91.01)	106 (90.60)	
	Yes, n (%)	3 (10.71)	8 (8.99)	11 (9.40)	
Lung cancer	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	No, n (%)	28 (100.00)	88 (98.88)	116 (99.15)	
	Yes, n (%)	0 (0.00)	1 (1.12)	1 (0.85)	
Lung cancer (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.97
	No, n (%)	27 (96.43)	88 (98.88)	115 (98.29)	
	Yes, n (%)	1 (3.57)	1 (1.12)	2 (1.71)	
Diffuse panbronchiolitis	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	No, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
	Yes, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
Diffuse panbronchiolitis (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	No, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
	Yes, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
Oral thrush	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	No, n (%)	28 (100.00)	88 (98.88)	116 (99.15)	
	Yes, n (%)	0 (0.00)	1 (1.12)	1 (0.85)	
Oral thrush (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	No, n (%)	28 (100.00)	88 (98.88)	116 (99.15)	
	Yes, n (%)	0 (0.00)	1 (1.12)	1 (0.85)	
Eczema (active)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	No, n (%)	26 (92.86)	82 (92.13)	108 (92.31)	
	Yes, n (%)	2 (7.14)	7 (7.87)	9 (7.69)	
Eczema (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.79
	No, n (%)	24 (85.71)	80 (89.89)	104 (88.89)	
	Yes, n (%)	4 (14.29)	9 (10.11)	13 (11.11)	
GERD (active)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.27
	No, n (%)	24 (85.71)	84 (94.38)	108 (92.31)	
	Yes, n (%)	4 (14.29)	5 (5.62)	9 (7.69)	
GERD (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.44
	No, n (%)	23 (82.14)	80 (89.89)	103 (88.03)	
	Yes, n (%)	5 (17.86)	9 (10.11)	14 (11.97)	
Ischaemic heart disease (baseline)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.87
	No, n (%)	27 (96.43)	83 (93.26)	110 (94.02)	
	Yes, n (%)	1 (3.57)	6 (6.74)	7 (5.98)	
Ischaemic heart disease (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	No, n (%)	26 (92.86)	81 (91.01)	107 (91.45)	
	Yes, n (%)	2 (7.14)	8 (8.99)	10 (8.55)	
Influenza (baseline)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	No, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
	Yes, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
Influenza (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.97
	No, n (%)	27 (96.43)	88 (98.88)	115 (98.29)	
	Yes, n (%)	1 (3.57)	1 (1.12)	2 (1.71)	
Nasal polyps (baseline)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	No, n (%)	28 (100.00)	87 (97.75)	115 (98.29)	
	Yes, n (%)	0 (0.00)	2 (2.25)	2 (1.71)	
Nasal polyps (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.28
	No, n (%)	28 (100.00)	82 (92.13)	110 (94.02)	
	Yes, n (%)	0 (0.00)	7 (7.87)	7 (5.98)	
Pneumonia (baseline)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	No, n (%)	26 (92.86)	81 (91.01)	107 (91.45)	

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
	Yes, n (%)	2 (7.14)	8 (8.99)	10 (8.55)	
Pneumonia (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	No, n (%)	24 (85.71)	78 (87.64)	102 (87.18)	
	Yes, n (%)	4 (14.29)	11 (12.36)	15 (12.82)	
Rhinitis (active)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.52
	No, n (%)	18 (64.29)	65 (73.03)	83 (70.94)	
	Yes, n (%)	10 (35.71)	24 (26.97)	34 (29.06)	
Rhinitis (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.26
	No, n (%)	12 (42.86)	51 (57.30)	63 (53.85)	
	Yes, n (%)	16 (57.14)	38 (42.70)	54 (46.15)	
Other Lung Diseases (ever)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	No, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
	Yes, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
Charlson Comorbidity Index (CCI)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.58
	Mean (SD)	1.36 (1.03)	1.20 (0.66)	1.24 (0.76)	
	Median (IQR)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	
Charlson Comorbidity Index (CCI) (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.20
	0-1, n (%)	23 (82.14)	74 (83.15)	97 (82.91)	
	2-5, n (%)	4 (14.29)	15 (16.85)	19 (16.24)	
	6-10, n (%)	1 (3.57)	0 (0.00)	1 (0.85)	

* Mann-Whitney test for continuous variables and Chi-squared to test for categorical variables

12.2.4 Medication during the baseline year

Table 16: Phase 1 – medication during baseline year

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
FDC ICS+LABA prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.16
	Mean (SD)	7.79 (9.63)	6.00 (9.19)	6.43 (9.28)	
	Median (IQR)	4.00 (3.00, 6.00)	3.00 (3.00, 5.00)	4.00 (3.00, 6.00)	
FDC ICS+LABA prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.14
	2-3, n (%)	9 (32.14)	45 (50.56)	54 (46.15)	
	≥4, n (%)	19 (67.86)	44 (49.44)	63 (53.85)	
Seretide DPI prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.38
	Mean (SD)	4.96 (8.94)	2.99 (3.99)	3.46 (5.60)	
	Median (IQR)	2.50 (0.00, 5.00)	2.00 (0.00, 4.00)	2.00 (0.00, 4.00)	
Seretide DPI prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.46
	0, n (%)	10 (35.71)	37 (41.57)	47 (40.17)	
	1-3, n (%)	6 (21.43)	25 (28.09)	31 (26.50)	

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
	≥4, n (%)	12 (42.86)	27 (30.34)	39 (33.33)	
Symbicort DPI prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.63
	Mean (SD)	2.82 (6.48)	3.01 (9.05)	2.97 (8.48)	
	Median (IQR)	0.00 (0.00, 3.25)	0.00 (0.00, 3.00)	0.00 (0.00, 3.00)	
Symbicort DPI prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.17
	0, n (%)	18 (64.29)	47 (52.81)	65 (55.56)	
	1-3, n (%)	3 (10.71)	25 (28.09)	28 (23.93)	
	≥4, n (%)	7 (25.00)	17 (19.10)	24 (20.51)	
ICS only inhaler prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.97
	Mean (SD)	0.25 (0.80)	0.89 (4.69)	0.74 (4.11)	
	Median (IQR)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
ICS only inhaler prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	No, n (%)	24 (85.71)	77 (86.52)	101 (86.32)	
	Yes, n (%)	4 (14.29)	12 (13.48)	16 (13.68)	
ICS only inhaler prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.93
	0, n (%)	24 (85.71)	77 (86.52)	101 (86.32)	
	1-3, n (%)	3 (10.71)	7 (7.87)	10 (8.55)	
	4-6, n (%)	1 (3.57)	3 (3.37)	4 (3.42)	
	7-9, n (%)	0 (0.00)	1 (1.12)	1 (0.85)	
	10-12, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
	≥13, n (%)	0 (0.00)	1 (1.12)	1 (0.85)	
ICS average daily dose (fluticasone propionate equivalent µg)[10]	N (%) not missing	19 (67.86)	73 (82.02)	92 (78.63)	0.98
	Mean (SD)	1087.08 (493.93)	1139.13 (624.07)	1128.38 (597.37)	
	Median (IQR)	910.96 (698.08, 1476.85)	1040.55 (627.95, 1506.85)	978.63 (698.08, 1506.85)	
ICS average daily dose (fluticasone propionate equivalent µg) (categorised)[10]	N (%) not missing	19 (67.86)	73 (82.02)	92 (78.63)	0.06
	>0 to ≤250, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
	>250 to ≤500, n (%)	1 (5.26)	11 (15.07)	12 (13.04)	
	>500, n (%)	18 (94.74)	62 (84.93)	80 (86.96)	
Intravenous / intramuscular corticosteroid prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.45
	Mean (SD)	1.46 (3.77)	0.67 (1.66)	0.86 (2.35)	
	Median (IQR)	0.00 (0.00, 1.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
Intravenous / intramuscular corticosteroid prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.68
	No, n (%)	20 (71.43)	69 (77.53)	89 (76.07)	
	Yes, n (%)	8 (28.57)	20 (22.47)	28 (23.93)	

[10] ICS average daily doses greater than 3000µg were coded as missing as values were deemed too high to be clinically likely

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
Intravenous / intramuscular corticosteroid prescription (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.47
	0, n (%)	20 (71.43)	69 (77.53)	89 (76.07)	
	1-3, n (%)	5 (17.86)	14 (15.73)	19 (16.24)	
	4-6, n (%)	1 (3.57)	4 (4.49)	5 (4.27)	
	7-9, n (%)	1 (3.57)	2 (2.25)	3 (2.56)	
	10-12, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
	≥13, n (%)	1 (3.57)	0 (0.00)	1 (0.85)	
SABA prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.73
	Mean (SD)	3.29 (6.79)	3.06 (8.21)	3.11 (7.87)	
	Median (IQR)	0.00 (0.00, 3.25)	0.00 (0.00, 4.00)	0.00 (0.00, 4.00)	
SABA prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.70
	No, n (%)	16 (57.14)	45 (50.56)	61 (52.14)	
	Yes, n (%)	12 (42.86)	44 (49.44)	56 (47.86)	
SABA prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.54
	0, n (%)	16 (57.14)	45 (50.56)	61 (52.14)	
	1-3, n (%)	5 (17.86)	20 (22.47)	25 (21.37)	
	4-6, n (%)	2 (7.14)	14 (15.73)	16 (13.68)	
	7-9, n (%)	2 (7.14)	6 (6.74)	8 (6.84)	
	10-12, n (%)	0 (0.00)	1 (1.12)	1 (0.85)	
	≥13, n (%)	3 (10.71)	3 (3.37)	6 (5.13)	
SABA inhaler prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.86
	Mean (SD)	2.82 (6.37)	1.67 (2.63)	1.95 (3.86)	
	Median (IQR)	0.00 (0.00, 3.00)	0.00 (0.00, 2.00)	0.00 (0.00, 3.00)	
SABA inhaler prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.68
	No, n (%)	17 (60.71)	48 (53.93)	65 (55.56)	
	Yes, n (%)	11 (39.29)	41 (46.07)	52 (44.44)	
SABA inhaler prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.06
	0, n (%)	17 (60.71)	48 (53.93)	65 (55.56)	
	1-3, n (%)	5 (17.86)	21 (23.60)	26 (22.22)	
	4-6, n (%)	2 (7.14)	16 (17.98)	18 (15.38)	
	7-9, n (%)	2 (7.14)	2 (2.25)	4 (3.42)	
	10-12, n (%)	0 (0.00)	2 (2.25)	2 (1.71)	
	≥13, n (%)	2 (7.14)	0 (0.00)	2 (1.71)	
SABA inhaler average daily dose (µg)	N (% missing)	11 (60.71)	41 (53.93)	52 (55.56)	0.30
	Mean (SD)	712.33 (729.41)	542.60 (548.88)	578.50 (587.80)	
	Median (IQR)	438.36 (191.78, 904.11)	273.97 (109.59, 767.12)	328.77 (109.59, 808.22)	
	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.92
	0, n (%)	17 (60.71)	48 (53.93)	65 (55.56)	

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
SABA inhaler average daily dose (µg) (categorised)	>0 to ≤200, n (%)	3 (10.71)	15 (16.85)	18 (15.38)	
	>200 to ≤400, n (%)	2 (7.14)	8 (8.99)	10 (8.55)	
	>400 to ≤800, n (%)	3 (10.71)	8 (8.99)	11 (9.40)	
	>800, n (%)	3 (10.71)	10 (11.24)	13 (11.11)	
SABA nebuliser prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.93
	Mean (SD)	0.46 (1.50)	1.36 (7.74)	1.15 (6.79)	
	Median (IQR)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
SABA nebuliser prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	No, n (%)	24 (85.71)	76 (85.39)	100 (85.47)	
	Yes, n (%)	4 (14.29)	13 (14.61)	17 (14.53)	
SABA nebuliser prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.81
	0, n (%)	24 (85.71)	76 (85.39)	100 (85.47)	
	1-3, n (%)	2 (7.14)	8 (8.99)	10 (8.55)	
	4-6, n (%)	1 (3.57)	2 (2.25)	3 (2.56)	
	7-9, n (%)	1 (3.57)	1 (1.12)	2 (1.71)	
	10-12, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
	≥13, n (%)	0 (0.00)	2 (2.25)	2 (1.71)	
SABA nebuliser average daily dose (µg)	N (% missing)	4 (85.71)	13 (85.39)	17 (85.47)	0.65
	Mean (SD)	20.22 (11.54)	23.89 (11.26)	23.02 (11.07)	
	Median (IQR)	21.25 (16.29, 25.17)	22.69 (20.68, 30.56)	22.50 (20.00, 30.56)	
SABA nebuliser average daily dose (µg) (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.17
	0, n (%)	24 (85.71)	76 (85.39)	100 (85.47)	
	>0-5, n (%)	0 (0.00)	2 (2.25)	2 (1.71)	
	>5-10, n (%)	1 (3.57)	0 (0.00)	1 (0.85)	
	>10-20, n (%)	1 (3.57)	1 (1.12)	2 (1.71)	
	>20, n (%)	2 (7.14)	10 (11.24)	12 (10.26)	
SABA oral prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	Mean (SD)	0.00 (0.00)	0.02 (0.21)	0.02 (0.18)	
	Median (IQR)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
SABA oral prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	No, n (%)	28 (100.00)	88 (98.88)	116 (99.15)	
	Yes, n (%)	0 (0.00)	1 (1.12)	1 (0.85)	
SABA oral prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	1.00
	0, n (%)	28 (100.00)	88 (98.88)	116 (99.15)	
	1-3, n (%)	0 (0.00)	1 (1.12)	1 (0.85)	
	4-6, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
	7-9, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
	10-12, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
	≥13, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
SAMA prescriptions	N (%) not missing	28 (100.0)	88 (98.88)	116 (99.15)	
	Mean (SD)	0.54 (1.64)	2.17 (14.31)	1.78 (12.51)	0.64
	Median (IQR)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
SAMA prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	
	No, n (%)	25 (89.29)	75 (84.27)	100 (85.47)	0.73
	Yes, n (%)	3 (10.71)	14 (15.73)	17 (14.53)	
SAMA prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	
	0, n (%)	25 (89.29)	75 (84.27)	100 (85.47)	
	1-3, n (%)	0 (0.00)	8 (8.99)	8 (6.84)	
	4-6, n (%)	2 (7.14)	2 (2.25)	4 (3.42)	0.33
	7-9, n (%)	1 (3.57)	1 (1.12)	2 (1.71)	
	10-12, n (%)	0 (0.00)	1 (1.12)	1 (0.85)	
	>13, n (%)	0 (0.00)	2 (2.25)	2 (1.71)	
FDC SABA/SAMA prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	N/A
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
FDC SABA/SAMA prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	No, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
FDC SABA/SAMA prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	0, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
LABA inhaler prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	N/A
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
LABA inhaler prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	No, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
LABA inhaler prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	0, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
LABA patch prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	NA
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
LABA patch prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	No, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
LABA patch prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	0, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.54

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
LABA oral prescriptions	Mean (SD)	0.04 (0.19)	0.00 (0.00)	0.01 (0.09)	
	Median (IQR)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
LABA oral prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	
	No, n (%)	27 (96.43)	89 (100.00)	116 (99.15)	0.54
	Yes, n (%)	1 (3.57)	0 (0.00)	1 (0.85)	
LABA oral prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	
	0, n (%)	27 (96.43)	89 (100.00)	116 (99.15)	
	1-3, n (%)	1 (3.57)	0 (0.00)	1 (0.85)	
	4-6, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	0.54
	7-9, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
	10-12, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
	≥13, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
LAMA prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	
	Mean (SD)	1.21 (2.30)	2.15 (5.16)	1.92 (4.64)	0.97
	Median (IQR)	0.00 (0.00, 0.50)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
LAMA prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	
	No, n (%)	21 (75.00)	69 (77.53)	90 (76.92)	0.98
	Yes, n (%)	7 (25.00)	20 (22.47)	27 (23.08)	
LAMA prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	
	0, n (%)	21 (75.00)	69 (77.53)	90 (76.92)	
	1-3, n (%)	1 (3.57)	1 (1.12)	2 (1.71)	
	4-6, n (%)	4 (14.29)	7 (7.87)	11 (9.40)	0.61
	7-9, n (%)	2 (7.14)	6 (6.74)	8 (6.84)	
	10-12, n (%)	0 (0.00)	1 (1.12)	1 (0.85)	
	≥13, n (%)	0 (0.00)	5 (5.62)	5 (4.27)	
LTRA prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	
	Mean (SD)	6.57 (10.65)	5.99 (8.45)	6.13 (8.98)	0.45
	Median (IQR)	4.00 (0.00, 7.00)	4.00 (3.00, 6.00)	4.00 (2.00, 6.00)	
LTRA prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	
	No, n (%)	9 (32.14)	12 (13.48)	21 (17.95)	0.05
	Yes, n (%)	19 (67.86)	77 (86.52)	96 (82.05)	
LTRA prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	
	0, n (%)	9 (32.14)	12 (13.48)	21 (17.95)	
	1-3, n (%)	4 (14.29)	19 (21.35)	23 (19.66)	
	4-6, n (%)	7 (25.00)	38 (42.70)	45 (38.46)	0.08
	7-9, n (%)	2 (7.14)	7 (7.87)	9 (7.69)	
	10-12, n (%)	1 (3.57)	7 (7.87)	8 (6.84)	
	≥13, n (%)	5 (17.86)	6 (6.74)	11 (9.40)	
	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.16

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
Theophylline or other methylxanthines prescriptions	Mean (SD)	3.75 (6.55)	3.01 (9.56)	3.19 (8.91)	
	Median (IQR)	1.00 (0.00, 5.25)	0.00 (0.00, 3.00)	0.00 (0.00, 3.00)	
Theophylline or other methylxanthines prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.44
	No, n (%)	14 (50.00)	54 (60.67)	68 (58.12)	
	Yes, n (%)	14 (50.00)	35 (39.33)	49 (41.88)	
Theophylline or other methylxanthines prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.12
	0, n (%)	14 (50.00)	54 (60.67)	68 (58.12)	
	1-3, n (%)	3 (10.71)	19 (21.35)	22 (18.80)	
	4-6, n (%)	5 (17.86)	6 (6.74)	11 (9.40)	
	7-9, n (%)	5 (17.86)	6 (6.74)	11 (9.40)	
	10-12, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
	≥13, n (%)	1 (3.57)	4 (4.49)	5 (4.27)	
Cromone prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
Cromone prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	No, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
Cromone prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	0, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
Omalizumab prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
Omalizumab prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	No, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
Omalizumab prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	N/A
	0, n (%)	28 (100.00)	89 (100.00)	117 (100.00)	
NSAID prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.11
	Mean (SD)	1.39 (2.95)	0.65 (2.10)	0.83 (2.34)	
	Median (IQR)	0.00 (0.00, 1.25)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
NSAID prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.22
	No, n (%)	20 (71.43)	75 (84.27)	95 (81.20)	
	Yes, n (%)	8 (28.57)	14 (15.73)	22 (18.80)	
NSAID prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.37
	0, n (%)	20 (71.43)	75 (84.27)	95 (81.20)	
	1-3, n (%)	4 (14.29)	8 (8.99)	12 (10.26)	
	4-6, n (%)	2 (7.14)	3 (3.37)	5 (4.27)	

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
	7-9, n (%)	1 (3.57)	2 (2.25)	3 (2.56)	
	10-12, n (%)	1 (3.57)	0 (0.00)	1 (0.85)	
	≥13, n (%)	0 (0.00)	1 (1.12)	1 (0.85)	
Paracetamol prescriptions	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.36
	Mean (SD)	0.96 (1.88)	0.73 (1.62)	0.79 (1.68)	
	Median (IQR)	0.00 (0.00, 1.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	
Paracetamol prescriptions (yes/no)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.43
	No, n (%)	19 (67.86)	69 (77.53)	88 (75.21)	
	Yes, n (%)	9 (32.14)	20 (22.47)	29 (24.79)	
Paracetamol prescriptions (categorised)	N (%) not missing	28 (100.0)	89 (100.0)	117 (100.0)	0.51
	0, n (%)	19 (67.86)	69 (77.53)	88 (75.21)	
	1-3, n (%)	6 (21.43)	11 (12.36)	17 (14.53)	
	4-6, n (%)	2 (7.14)	8 (8.99)	10 (8.55)	
	7-9, n (%)	1 (3.57)	1 (1.12)	2 (1.71)	
	10-12, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
	≥13, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	

* Mann-Whitney test for continuous variables and Chi-squared test for categorical variables

12.2.5 Clinical measurements during baseline year

Table 17: Phase 1 - clinical measurements during baseline year

		Non-Persistent Cohort (N=28)	Persistent Cohort (N=89)	Total Cohort (N=117)	P-value*
Eosinophils/100 leukocytes in Sputum	N (%) not missing	4 (14.29)	24 (26.97)	28 (23.93)	0.67
	Mean (SD)	22.50 (18.06)	38.50 (34.44)	36.21 (32.85)	
	Median (IQR)	20.00 (11.50, 31.00)	19.00 (7.50, 76.00)	19.00 (7.50, 72.75)	
Blood eosinophils/µL	N (%) not missing	5 (17.86)	14 (15.73)	19 (16.24)	0.32
	Mean (SD)	320.00 (268.33)	514.29 (361.32)	463.16 (343.53)	
	Median (IQR)	200.00 (100.00, 500.00)	500.00 (225.00, 750.00)	500.00 (150.00, 650.00)	

* Mann-Whitney test for continuous variables and Chi-squared test for categorical variables

12.3 Phase 2 – baseline characterisation

12.3.1 Demographics

Table 18: Phase 2 - demographics

		Patients changing from DPI to pMDI (n = 85)
Age	N (%) not missing	85 (100.0)
	Mean (SD)	52.92 (15.89)
	Median (IQR)	54.00 (41.00, 65.00)
Age (categorised)	N (%) not missing	85 (100.0)
	12-18, n (%)	1 (1.18)
	19-64, n (%)	62 (72.94)
	65-80, n (%)	22 (25.88)
Gender	N (%) not missing	85 (100.0)
	Female, n (%)	43 (50.59)
	Male, n (%)	42 (49.41)

12.3.2 Comorbidities

Table 19: Phase 2 – comorbidities

		Patients changing from DPI to pMDI (n = 85)
Asthma	N (%) not missing	85 (100.0)
	No, n (%)	12 (14.12)
	Yes, n (%)	73 (85.88)
Asthma (ever)	N (%) not missing	85 (100.0)
	No, n (%)	11 (12.94)
	Yes, n (%)	74 (87.06)
COPD	N (%) not missing	85 (100.0)
	No, n (%)	69 (81.18)
	Yes, n (%)	16 (18.82)
COPD (ever)	N (%) not missing	85 (100.0)
	No, n (%)	68 (80.00)
	Yes, n (%)	17 (20.00)
Tuberculosis	N (%) not missing	85 (100.0)
	No, n (%)	85 (100.00)
	Yes, n (%)	0 (0.00)
Tuberculosis (ever)	N (%) not missing	85 (100.0)
	No, n (%)	83 (97.65)
	Yes, n (%)	2 (2.35)
Interstitial lung disease	N (%) not missing	85 (100.0)
	No, n (%)	85 (100.00)
	Yes, n (%)	0 (0.00)

		Patients changing from DPI to pMDI (n = 85)
Interstitial lung disease (ever)	N (%) not missing	85 (100.0)
	No, n (%)	85 (100.00)
	Yes, n (%)	0 (0.00)
Bronchiectasis	N (%) not missing	85 (100.0)
	No, n (%)	77 (90.59)
	Yes, n (%)	8 (9.41)
Bronchiectasis (ever)	N (%) not missing	85 (100.0)
	No, n (%)	77 (90.59)
	Yes, n (%)	8 (9.41)
Lung cancer	N (%) not missing	85 (100.0)
	No, n (%)	84 (98.82)
	Yes, n (%)	1 (1.18)
Lung cancer (ever)	N (%) not missing	85 (100.0)
	No, n (%)	84 (98.82)
	Yes, n (%)	1 (1.18)
Diffuse panbronchiolitis	N (%) not missing	85 (100.0)
	No, n (%)	85 (100.00)
	Yes, n (%)	0 (0.00)
Diffuse panbronchiolitis (ever)	N (%) not missing	85 (100.0)
	No, n (%)	85 (100.00)
	Yes, n (%)	0 (0.00)
Oral thrush (baseline)	N (%) not missing	85 (100.0)
	No	84 (98.82)
	Yes	1 (1.18)
Oral thrush (ever)	N (%) not missing	85 (100.0)
	No	84 (98.82)
	Yes	1 (1.18)
Eczema (baseline)	N (%) not missing	85 (100.0)
	No	77 (90.59)
	Yes	8 (9.41)
Eczema (ever)	N (%) not missing	85 (100.0)
	No	74 (87.06)
	Yes	11 (12.94)
GERD (baseline)	N (%) not missing	85 (100.0)
	No	82 (96.47)
	Yes	3 (3.53)
GERD (ever)	N (%) not missing	85 (100.0)
	No	77 (90.59)
	Yes	8 (9.41)
IHD (baseline)	N (%) not missing	85 (100.0)

		Patients changing from DPI to pMDI (n = 85)
	No	78 (91.76)
	Yes	7 (8.24)
IHD (ever)	N (%) not missing	85 (100.0)
	No	76 (89.41)
	Yes	9 (10.59)
Influenza (baseline)	N (%) not missing	85 (100.0)
	No	85 (100.00)
	Yes	0 (0.00)
Influenza (ever)	N (%) not missing	85 (100.0)
	No	84 (98.82)
	Yes	1 (1.18)
OLD (baseline)	N (%) not missing	85 (100.0)
	No	85 (100.00)
	Yes	0 (0.00)
OLD (ever)	N (%) not missing	85 (100.0)
	No	85 (100.00)
	Yes	0 (0.00)
Nasal polyps (baseline)	N (%) not missing	85 (100.0)
	No	83 (97.65)
	Yes	2 (2.35)
Nasal polyps (ever)	N (%) not missing	85 (100.0)
	No	77 (90.59)
	Yes	8 (9.41)
Pneumonia (baseline)	N (%) not missing	85 (100.0)
	No	78 (91.76)
	Yes	7 (8.24)
Pneumonia (ever)	N (%) not missing	85 (100.0)
	No	74 (87.06)
	Yes	11 (12.94)
Rhinitis (baseline)	N (%) not missing	85 (100.0)
	No	63 (74.12)
	Yes	22 (25.88)
Rhinitis (ever)	N (%) not missing	85 (100.0)
	No	47 (55.29)
	Yes	38 (44.71)
CCI Score	N (%) not missing	85 (100.0)
	Mean (SD)	1.16 (0.61)
	Median (IQR)	1.00 (1.00, 1.00)
CCI Score (categorised)	N (%) not missing	85 (100.0)
	0-1	71 (83.53)
	2-5	14 (16.47)

12.3.3 Disease severity

Table 20: Phase 2 – disease severity

		Patients changing from DPI to pMDI (n = 85)
Asthma-related hospitalisations	N (%) not missing	85 (100.0)
	Mean (SD)	0.11 (0.35)
	Median (IQR)	0.00 (0.00, 0.00)
Asthma-related hospitalisations (categorised)	N (%) not missing	85 (100.0)
	0	77 (90.59)
	1	7 (8.24)
	2	1 (1.18)
Asthma-related hospitalisation days	N (%) not missing	85 (100.0)
	Mean (SD)	1.31 (6.38)
	Median (IQR)	0.00 (0.00, 0.00)
Asthma-related hospitalisation days (categorised)	N (%) not missing	8 (9.41)
	1-3	1 (1.18)
	4-6	3 (3.53)
	7-13	1 (1.18)
	14+	3 (3.53)
All hospitalisations	N (%) not missing	85 (100.0)
	Mean (SD)	0.28 (0.55)
	Median (IQR)	0.00 (0.00, 0.00)
All hospitalisations (categorised)	N (%) not missing	85 (100.0)
	0	64 (75.29)
	1	19 (22.35)
	2	1 (1.18)
	3	1 (1.18)
All hospitalisation days	N (%) not missing	85 (100.0)
	Mean (SD)	5.02 (23.55)
	Median (IQR)	0.00 (0.00, 0.00)
All hospitalisation days (categorised)	N (%) not missing	21 (24.71)
	1-3	1 (1.18)
	4-6	10 (11.76)
	7-13	3 (3.53)
	14+	7 (8.24)
Asthma-related outpatient attendances	N (%) not missing	85 (100.0)
	Mean (SD)	3.14 (3.37)
	Median (IQR)	2.00 (0.00, 5.00)
Asthma-related outpatient attendances (categorised)	N (%) not missing	85 (100.0)
	0	31 (36.47)
	1-2	13 (15.29)
	3-5	21 (24.71)
	6-8	12 (14.12)
	9+	8 (9.41)
All outpatient attendances	N (%) not missing	85 (100.0)

		Patients changing from DPI to pMDI (n = 85)
	Mean (SD)	14.38 (8.51)
	Median (IQR)	12.00 (8.00, 18.00)
All outpatient attendances (categorised)	N (%) not missing	85 (100.0)
	3-5	6 (7.06)
	6-8	17 (20.00)
	9+	62 (72.94)
Asthma-related emergency attendances	N (%) not missing	85 (100.0)
	Mean (SD)	0.08 (0.28)
	Median (IQR)	0.00 (0.00, 0.00)
Asthma-related emergency attendances (categorised)	N (%) not missing	85 (100.0)
	0	78 (91.76)
	1	7 (8.24)
All emergency attendances	N (%) not missing	85 (100.0)
	Mean (SD)	0.32 (0.64)
	Median (IQR)	0.00 (0.00, 0.00)
All emergency attendances (categorised)	N (%) not missing	85 (100.0)
	0	65 (76.47)
	1	14 (16.47)
	2	5 (5.88)
	3	1 (1.18)
Asthma-related exacerbations (ATS)	N (%) not missing	85 (100.0)
	Mean (SD)	0.53 (1.22)
	Median (IQR)	0.00 (0.00, 1.00)
Asthma-related exacerbations (ATS) (categorised)	N (%) not missing	85 (100.0)
	0	61 (71.76)
	1	13 (15.29)
	2	7 (8.24)
	3	3 (3.53)
	4+	1 (1.18)
Asthma-related respiratory events	N (%) not missing	85 (100.0)
	Mean (SD)	0.76 (1.44)
	Median (IQR)	0.00 (0.00, 1.00)
Asthma-related respiratory events (categorised)	N (%) not missing	85 (100.0)
	0	49 (57.65)
	1	22 (25.88)
	2	7 (8.24)
	3	6 (7.06)
	4+	1 (1.18)
Antibiotic prescription for LRTI	N (%) not missing	85 (100.0)
	Mean (SD)	0.32 (0.69)
	Median (IQR)	0.00 (0.00, 0.00)
Antibiotic prescription for LRTI (categorised)	N (%) not missing	85 (100.0)
	0	66 (77.65)
	1	14 (16.47)

		Patients changing from DPI to pMDI (n = 85)
	2	2 (2.35)
	3	3 (3.53)
Acute oral steroids total number of courses	N (%) not missing	85 (100.0)
	Mean (SD)	0.46 (1.27)
	Median (IQR)	0.00 (0.00, 0.00)
Acute oral steroids total number of courses (categorised)	N (%) not missing	85 (100.0)
	0	69 (81.18)
	1	5 (5.88)
	2	6 (7.06)
	3	3 (3.53)
	4+	2 (2.35)
Acute oral steroids unique day prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	0.41 (1.20)
	Median (IQR)	0.00 (0.00, 0.00)
Acute oral steroids unique day prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	69 (81.18)
	1	7 (8.24)
	2	5 (5.88)
	3	3 (3.53)
	4+	1 (1.18)
Non-acute oral steroids total number of courses	N (%) not missing	85 (100.0)
	Mean (SD)	1.88 (3.06)
	Median (IQR)	0.00 (0.00, 3.00)
Non-acute oral steroids total number of courses (categorised)	N (%) not missing	85 (100.0)
	0	44 (51.76)
	1	6 (7.06)
	2	10 (11.76)
	3	5 (5.88)
	4+	20 (23.53)
Non-acute oral steroids unique day prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	1.49 (2.11)
	Median (IQR)	0.00 (0.00, 2.00)
Non-acute oral steroids unique day prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	44 (51.76)
	1	9 (10.59)
	2	11 (12.94)
	3	7 (8.24)
	4+	14 (16.47)

12.3.4 Medication during baseline year

Table 21: Phase 2 – medication in baseline year

		Patients changing from DPI to pMDI (n = 85)
FDC ICS/LABA prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	6.11 (9.37)
	Median (IQR)	4.00 (3.00, 5.00)
FDC ICS/LABA prescriptions (categorised)	N (%) not missing	85 (100.0)
	2-3	41 (48.24)
	4+	44 (51.76)
Seretide DPI prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	2.79 (3.78)
	Median (IQR)	2.00 (0.00, 4.00)
Seretide DPI prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	37 (43.53)
	1	22 (25.88)
	4+	26 (30.59)
Symbicort DPI prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	3.32 (9.38)
	Median (IQR)	0.00 (0.00, 3.00)
Symbicort DPI prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	44 (51.76)
	1	23 (27.06)
	4+	18 (21.18)
Flutiform pMDI prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	0.00 (0.00)
	Median (IQR)	0.00 (0.00, 0.00)
Flutiform pMDI prescriptions (categorised)	N (%) not missing	85 (100.0)
	No	85 (100.00)
Foster pMDI prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	0.00 (0.00)
	Median (IQR)	0.00 (0.00, 0.00)
Foster pMDI prescriptions (categorised)	N (%) not missing	85 (100.0)
	No	85 (100.00)
ICS only inhaler prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	0.98 (4.82)
	Median (IQR)	0.00 (0.00, 0.00)
ICS only inhaler prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	73 (85.88)
	Yes	12 (14.12)
ICS only inhaler prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	73 (85.88)
	1-3	6 (7.06)
	4-6	4 (4.71)
	7-9	1 (1.18)

		Patients changing from DPI to pMDI (n = 85)
	13+	1 (1.18)
ICS average daily dose (fluticasone propionate equivalent µg)[10]	N (%) not missing	70 (82.35)
	Mean (SD)	1146.81 (627.72)
	Median (IQR)	978.63 (645.48, 1506.85)
ICS average daily dose (fluticasone propionate equivalent µg) (categorised)[10]	N (%) not missing	70 (82.35)
	>=100-250	0 (0.00)
	>250-500	9 (12.86)
	>500	61 (87.14)
Intravenous / intramuscular corticosteroid prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	0.68 (1.70)
	Median (IQR)	0.00 (0.00, 0.00)
Intravenous / intramuscular corticosteroid prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	67 (78.82)
	Yes	18 (21.18)
Intravenous / intramuscular corticosteroid prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	67 (78.82)
	1-3	12 (14.12)
	4-6	4 (4.71)
	7-9	2 (2.35)
All SABA prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	2.82 (8.21)
	Median (IQR)	0.00 (0.00, 3.00)
All SABA prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	44 (51.76)
	Yes	41 (48.24)
All SABA prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	44 (51.76)
	1-3	20 (23.53)
	4-6	13 (15.29)
	7-9	5 (5.88)
	10-12	1 (1.18)
	13+	2 (2.35)
SABA Inhaler prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	1.54 (2.40)
	Median (IQR)	0.00 (0.00, 2.00)
SABA Inhaler prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	47 (55.29)
	Yes	38 (44.71)
SABA Inhaler prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	47 (55.29)
	1-3	20 (23.53)
	4-6	15 (17.65)
	7-9	2 (2.35)

		Patients changing from DPI to pMDI (n = 85)
	10-12	1 (1.18)
SABA Inhaler average daily dose (µg)	N (%) not missing	38 (44.71)
	Mean (SD)	543.62 (507.25)
	Median (IQR)	301.37 (109.59, 890.41)
SABA Inhaler average daily dose (µg categorised)	N (%) not missing	85 (100.0)
	0	47 (55.29)
	>0-200	14 (16.47)
	>200-400	7 (8.24)
	>400-800	7 (8.24)
	>800	10 (11.76)
SABA Nebuliser prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	1.26 (7.87)
	Median (IQR)	0.00 (0.00, 0.00)
SABA Nebuliser prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	74 (87.06)
	Yes	11 (12.94)
SABA Nebuliser prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	74 (87.06)
	1-3	8 (9.41)
	4-6	1 (1.18)
	13+	2 (2.35)
SABA Nebuliser average daily dose (µg)	N (%) not missing	11 (12.94)
	Mean (SD)	23.55 (12.23)
	Median (IQR)	21.88 (20.34, 31.11)
SABA Nebuliser average daily dose (categorised) (µg)	N (%) not missing	11 (12.94)
	>0-5	2 (2.35)
	>5-10	0 (0.00)
	>10-20	1 (1.18)
	>20	8 (9.41)
SABA Injection prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	0.00 (0.00)
	Median (IQR)	0.00 (0.00, 0.00)
SABA Injection prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	85 (100.00)
SABA Injection prescriptions (categorised)	N (%) not missing	85 (100.0)
	No	85 (100.00)
SABA Oral prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	0.02 (0.22)
	Median (IQR)	0.00 (0.00, 0.00)
SABA Oral prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	84 (98.82)
	Yes	1 (1.18)
SABA Oral prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	84 (98.82)

		Patients changing from DPI to pMDI (n = 85)
	1-3	1 (1.18)
SAMA prescriptions	N (%) not missing	84 (98.82)
	Mean (SD)	0.54 (2.10)
	Median (IQR)	0.00 (0.00, 0.00)
SAMA prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	73 (85.88)
	Yes	12 (14.12)
SAMA prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	73 (85.88)
	1-3	8 (9.41)
	4-6	1 (1.18)
	10-12	1 (1.18)
	13+	2 (2.35)
SABA/SAMA prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	0.00 (0.00)
	Median (IQR)	0.00 (0.00, 0.00)
SABA/SAMA prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	85 (100.00)
SABA/SAMA prescriptions (categorised)	N (%) not missing	85 (100.0)
	No	85 (100.00)
LABA Inhaler prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	0.00 (0.00)
	Median (IQR)	0.00 (0.00, 0.00)
LABA Inhaler prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	85 (100.00)
LABA Inhaler prescriptions (categorised)	N (%) not missing	85 (100.0)
	No	85 (100.00)
LABA Patch prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	0.00 (0.00)
	Median (IQR)	0.00 (0.00, 0.00)
LABA Patch prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	85 (100.00)
LABA Patch prescriptions (categorised)	N (%) not missing	85 (100.0)
	No	85 (100.00)
LABA Oral prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	0.00 (0.00)
	Median (IQR)	0.00 (0.00, 0.00)
LABA Oral prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	85 (100.00)
LABA Oral prescriptions (categorised)	N (%) not missing	85 (100.0)
	No	85 (100.00)
LAMA prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	2.13 (5.25)
	Median (IQR)	0.00 (0.00, 0.00)

		Patients changing from DPI to pMDI (n = 85)
LAMA prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	67 (78.82)
	Yes	18 (21.18)
LAMA prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	67 (78.82)
	1-3	1 (1.18)
	4-6	5 (5.88)
	7-9	6 (7.06)
	10-12	1 (1.18)
	13+	5 (5.88)
LTRA prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	6.13 (8.72)
	Median (IQR)	4.00 (3.00, 6.00)
LTRA prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	13 (15.29)
	Yes	72 (84.71)
LTRA prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	13 (15.29)
	1-3	16 (18.82)
	4-6	36 (42.35)
	7-9	7 (8.24)
	10-12	7 (8.24)
	13+	6 (7.06)
Theophylline prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	2.99 (9.76)
	Median (IQR)	0.00 (0.00, 2.00)
Theophylline prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	52 (61.18)
	Yes	33 (38.82)
Theophylline prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	52 (61.18)
	1-3	19 (22.35)
	4-6	4 (4.71)
	7-9	6 (7.06)
	13+	4 (4.71)
Cromones prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	0.00 (0.00)
	Median (IQR)	0.00 (0.00, 0.00)
Cromones prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	85 (100.00)
Cromones prescriptions (categorised)	N (%) not missing	85 (100.0)
	No	85 (100.00)
NSAID prescriptions	N (%) not missing	85 (100.0)

		Patients changing from DPI to pMDI (n = 85)
	Mean (SD)	0.71 (2.16)
	Median (IQR)	0.00 (0.00, 0.00)
NSAID prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	71 (83.53)
	Yes	14 (16.47)
NSAID prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	71 (83.53)
	1-3	8 (9.41)
	4-6	3 (3.53)
	7-9	2 (2.35)
	13+	1 (1.18)
Omalizumab prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	0.00 (0.00)
	Median (IQR)	0.00 (0.00, 0.00)
Omalizumab prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	85 (100.00)
Omalizumab prescriptions (categorised)	N (%) not missing	85 (100.0)
	No	85 (100.00)
Paracetamol prescriptions	N (%) not missing	85 (100.0)
	Mean (SD)	0.92 (1.81)
	Median (IQR)	0.00 (0.00, 1.00)
Paracetamol prescriptions (yes/no)	N (%) not missing	85 (100.0)
	No	63 (74.12)
	Yes	22 (25.88)
Paracetamol prescriptions (categorised)	N (%) not missing	85 (100.0)
	0	63 (74.12)
	1-3	11 (12.94)
	4-6	10 (11.76)
	7-9	1 (1.18)

12.4 Phase 2 subanalysis – exploratory effectiveness outcomes (FP/FOR)

Table 22: Phase 2 – exploratory effectiveness outcomes (FP/FOR)

n=85	Measure	Baseline (n=38)	Outcome (n=38)	p-value
No severe asthma exacerbations	N (%) not missing	38 (100.0)	38 (100.0)	0.008Δ
	No	12 (31.58)	4 (10.53)	
	Yes	26 (68.42)	34 (89.47)	
Number of severe asthma exacerbations (continuous)	N (%) not missing	38 (100.0)	38 (100.0)	0.040‡
	Mean (SD)	0.71 (1.63)	0.26 (0.86)	
Presence of severe asthma exacerbations (yes/no)	N (%) not missing	38 (100.0)	38 (100.0)	0.008Δ
	No	26 (68.42)	34 (89.47)	
	Yes	12 (31.58)	4 (10.53)	
Number of severe asthma exacerbations (categorised)	N (%) not missing	38 (100.0)	38 (100.0)	0.070†
	0	26 (68.42)	34 (89.47)	
	1	6 (15.79)	1 (2.63)	
	2	3 (7.89)	1 (2.63)	
	3	2 (5.26)	1 (2.63)	
	4+	1 (2.63)	1 (2.63)	
Acute respiratory events (continuous)	N (%) not missing	38 (100.0)	38 (100.0)	0.020‡
	Mean (SD)	0.97 (1.92)	0.37 (0.91)	
Acute respiratory events (categorised)	N (%) not missing	38 (100.0)	38 (100.0)	0.030†
	0	21 (55.26)	31 (81.58)	
	1	9 (23.68)	3 (7.89)	
	2	4 (10.53)	2 (5.26)	
	3	3 (7.89)	1 (2.63)	
	4+	1 (2.63)	1 (2.63)	
Asthma-related hospitalisations (continuous)	N (%) not missing	38 (100.0)	38 (100.0)	N/A
	Mean (SD)	0.16 (0.37)	0.00 (0.00)	
Asthma-related hospitalisations (categorised)	N (%) not missing	38 (100.0)	38 (100.0)	N/A
	0	32 (84.21)	38 (100.0)	
	1	6 (15.79)	0 (0.00)	
	2	0 (0.00)	0 (0.00)	
	3	0 (0.00)	0 (0.00)	
	4+	0 (0.00)	0 (0.00)	
SABA inhaler average daily dose	N (%) not missing	17 (44.74)	16 (42.11)	0.080‡
	Mean (SD)	676.87 (544.49)	671.23 (566.80)	
SABA inhaler average daily dose (categorised)	N (%) not missing	38 (100.0)	38 (100.0)	0.400†
	0	21 (55.26)	22 (57.89)	
	>0 - 200	5 (13.16)	4 (10.53)	

n=85	Measure	Baseline (n=38)	Outcome (n=38)	p-value
	>200 - 400	2 (5.26)	1 (2.63)	
	>400 - 800	4 (10.53)	7 (18.42)	
	>800	6 (15.79)	4 (10.53)	
ICS average daily dose[10]	N (%) missing	29 (76.32)	36 (94.74)	<0.001‡
	Mean (SD)	1347.06 (724.47)	882.56 (674.14)	
ICS average daily dose (categorised)[10]	N (%) not missing	38 (100.0)	38 (100.0)	0.100†
	≥100 - 250	0 (0.00)	4 (10.53)	
	>250 - 500	3 (7.89)	2 (5.26)	
	>500	35 (92.11)	32 (84.21)	
Treatment stability	N (%) not missing	-	38 (100.0)	N/A
	No	-	25 (65.79)	
	Yes	-	13 (34.21)	
Oral thrush	N (%) not missing	38 (100.0)	38 (100.0)	N/A
	No	38 (100.0)	38 (100.0)	
	Yes	0 (0.00)	0 (0.00)	
Blood eosinophils/µL	N (%) not missing	5 (13.16)	2 (5.26)	N/A
	Mean (SD)	340.00 (288.10)	350.00 (353.55)	
	Mean (SD)	-	-	

∆ Exact Mcnemar's test with central confidence intervals, ‡ Wilcoxon signed rank test with continuity correction, † Marginal homogeneity test, N/A – not applicable

12.5 Phase 2 subanalysis – exploratory effectiveness outcomes (BDP/FOR)

Table 23: Phase 2 – exploratory effectiveness outcomes (BDP/FOR)

n=85	Measure	Baseline (n=85)	Outcome (n=85)	p-value
No severe asthma exacerbations	N (%) not missing	47 (100.0)	47 (100.0)	0.508Δ
	No	12 (25.53)	9 (19.15)	
	Yes	35 (74.47)	38 (80.85)	
Number of severe asthma exacerbations (continuous)	N (%) not missing	47 (100.0)	47 (100.0)	0.500‡
	Mean (SD)	0.38 (0.74)	0.53 (1.33)	
Presence of severe asthma exacerbations (yes/no)	N (%) not missing	47 (100.0)	47 (100.0)	0.500Δ
	No	35 (74.47)	38 (80.85)	
	Yes	12 (25.53)	9 (19.15)	
Number of severe asthma exacerbations (categorised)	N (%) not missing	47 (100.0)	47 (100.0)	0.100†
	0	35 (74.47)	38 (80.85)	
	1	7 (14.89)	2 (4.26)	
	2	4 (8.51)	4 (8.51)	
	3	1 (2.13)	0 (0.00)	
	4+	0 (0.00)	3 (6.38)	
RDAC	N (%) not missing	47 (100.0)	47 (100.0)	0.200Δ
	No	19 (40.43)	14 (29.79)	
	Yes	28 (59.57)	33 (70.21)	
OAC	N (%) not missing	47 (100.0)	47 (100.0)	0.500Δ
	No	24 (51.06)	21 (44.68)	
	Yes	23 (48.94)	26 (55.32)	
Acute respiratory events (continuous)	N (%) not missing	47 (100.0)	47 (100.0)	0.500‡
	Mean (SD)	0.60 (0.88)	0.68 (1.37)	
Acute respiratory events (categorised)	N (%) not missing	47 (100.0)	47 (100.0)	0.101†
	0	28 (59.57)	33 (70.21)	
	1	13 (27.66)	6 (12.77)	
	2	3 (6.38)	4 (8.51)	
	3	3 (6.38)	1 (2.13)	
	4+	0 (0.00)	3 (6.38)	
Asthma-related hospitalisations (continuous)	N (%) not missing	47 (100.0)	47 (100.0)	1.00‡
	Mean (SD)	0.06 (0.32)	0.13 (0.88)	
Asthma-related hospitalisations (categorised)	N (%) not missing	47 (100.0)	47 (100.0)	NA
	0	45 (95.74)	46 (97.87)	
	1	1 (2.13)	0 (0.00)	
	2	1 (2.13)	0 (0.00)	
	3	0 (0.00)	0 (0.00)	
	4+	0 (0.00)	1 (2.13)	
SABA inhaler average daily dose	N (%) not missing	21 (44.68)	15 (31.91)	0.400‡
	Mean (SD)	435.75 (459.91)	438.36 (383.56)	
SABA inhaler average daily dose (categorised)	N (%) not missing	47 (100.0)	47 (100.0)	0.080†
	0	26 (55.32)	32 (68.09)	
	>0 - 200	9 (19.15)	3 (6.38)	

n=85	Measure	Baseline (n=85)	Outcome (n=85)	p-value
	>200 - 400	5 (10.64)	8 (17.02)	
	>400 - 800	3 (6.38)	1 (2.13)	
	>800	4 (8.51)	3 (6.38)	
ICS average daily dose[10]	N (%) missing	41 (87.23)	47 (100.0)	0.001‡
	Mean (SD)	1005.17 (512.51)	679.06 (492.70)	
ICS average daily dose (categorised)[10]	N (%) not missing	47 (100.0)	47 (100.0)	0.008†
	≥100 - 250	0 (0.00)	7 (14.89)	
	>250 - 500	6 (12.77)	9 (19.15)	
	>500	41 (87.23)	31 (65.96)	
Treatment stability	N (%) not missing	-	47 (100.0)	N/A
	No	-	43 (91.49)	
	Yes	-	4 (8.51)	
Oral thrush	N (%) not missing	47 (100.0)	47 (100.0)	N/A
	No	46 (100.0)	47 (100.0)	
	Yes	1 (2.13)	0 (0.00)	
Eosinophils/100 leukocytes in Sputum	N (%) not missing	16 (34.04)	1 (2.13)	N/A
	Mean (SD)	40.19 (34.41)	15.00 (N/A)	
Blood eosinophils/µL	N (%) not missing	9 (19.15)	0 (0.0)	N/A
	Mean (SD)	600.00 (390.51)	N/A (N/A)	
Total IgE [Units/volume] in Serum by Radioallergosorbent test (RAST)	N (%) not missing	0 (0.0)	0 (0.0)	N/A
	Mean (SD)	-	-	

∆ Exact Mcnemar's test with central confidence intervals, ‡ Wilcoxon signed rank test with continuity correction, † Marginal homogeneity test, N/A – not applicable