Does changing inhaler device impact real-life asthma outcomes?: clinical and economic evaluation

Chin Kook Rhee MD, PhD[1#], Job FM van Boven PharmD, PhD[2,3#], Simon Wan Yau Ming MD, MSc[4], Hye Yun Park MD, PhD[5], Deog Kyeom Kim MD, PhD[6], Hae-Sim Park MD, PhD[7], Joanna Ling Zhi Jie MSc[4], Kwang-Ha Yoo MD, PhD[8*], David B Price FRCGP[4,9*]

1. Division of Pulmonary, Allergy and Critical Care Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
2. Department of General Practice & Elderly Care Medicine, Groningen Research Institute for Asthma and COPD (GRIAC), University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
3. Unit of PharmacoEpidemiology & PharmacoEconomics, Department of Pharmacy, University of Groningen, Groningen, The Netherlands
4. Observational and Pragmatic Research Institute, Singapore
5. Division of Pulmonary and Critical Care Medicine, Samsung Medical Center, Sungkyun Kwan University School of Medicine, Seoul, Korea
6. Division of Pulmonary and Critical Care Medicine, Seoul National University, SMG-SNU Boramae Medical Center, Seoul, Korea
7. Allergy and Clinical Immunology Department, Ajou University Medical Center, Seoul, Korea
8. Division of Pulmonary and Allergy, Department of Internal Medicine, School of Medicine, Konkuk University, Seoul, Korea
9. Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom

#contributed equally, shared 1st authors; *contributed equally, shared last/corresponding authors

Correspondence:
Prof. Dr. Kwang Ha Yoo
Department of Pulmonology and Allergy
Konkuk University School of Medicine, 4-12 Hwayang-dong, Gwangjin gu, Seoul, 143-729, Korea
Tel: +82-10-8848-3966
Email: khyou@kuh.ac.kr

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Abstract

Background

Inhaler usability and deposition differ between devices. Change of device may therefore impact clinical and economic outcomes.

Objective

We aimed to characterize clinical and economic asthma outcomes surrounding the change from a dry powder inhaler (DPI) to a pressurized metered-dose inhaler (pMDI) for fixed-dose combination inhaled corticosteroids/long-acting beta agonist (FDC ICS/LABA) treatment.

Methods

Three retrospective cohort sub-studies using 2010-2015 data from the Korean Health Insurance and Review Assessment (HIRA) database were performed. Asthma patients receiving a first FDC ICS/LABA pMDI after initially being on FDC ICS/LABA DPI were included. The following outcomes were assessed: (1) persistence of change to pMDI over 6 months; (2) clinical outcomes during the year following the change compared to the baseline year; (3) non-inferiority comparison of costs and effectiveness between patients changing to a pMDI and matched patients that continued their DPI.

Results

Changing patients seem to represent a more severe sub-population. Fifty-eight % of patients (95%CI: 56-60) persisted with the change. Following the change in therapy, an increased proportion of patients remained free from severe exacerbations (58.3%) compared to the year prior (47.4%, $p<0.001$). Patients that changed to pMDIs had significantly less severe exacerbations, acute respiratory events and lower SABA inhaler average daily dose, but higher ICS average daily dose (all, $p<0.05$), compared to matched patients remaining on a DPI. Total costs were similar between patients that changed to pMDI therapy compared to those remaining on a DPI.

Conclusion

Changing from a DPI to a pMDI for FDC ICS/LABA asthma treatment can be as effective and cost-effective as remaining on a DPI.

Highlights box

1. *What is already known about this topic?*

Inhaler usability and deposition differ between devices, but real-life clinical differences after inhaler change in asthma patients are unknown.

2. *What does this article add to our knowledge?*

Generally, changing from a dry powder inhaler (DPI) to a pressurized metered-dose inhaler (pMDI) for fixed dose combination inhaled corticosteroids/long-acting beta agonist asthma treatment is at least as effective and cost-effective as remaining on a DPI.

3. *How does this study impact current management guidelines*

The majority of asthma patients can change from DPI to pMDI inhalers devices with maintenance of clinical effectiveness as well as cost-effectiveness, while for some patients additional management strategies are required.

Key words (max 10): asthma, inhaler, dry powder inhaler, pressurized metered-dose inhaler, economic evaluation, cost-effectiveness

List of abbreviations

AE	Adverse Event
A&E	Accident and Emergency
ATS	American Thoracic Society
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
FP	Fluticasone Propionate
GERD	Gastroesophageal Reflux Disease
GINA	Global Initiative for Asthma
GP	General Practitioner
ICS	Inhaled Corticosteroids
IHD	Ischaemic Heart Disease
IPD	Index Prescription Date
IQR	Interquartile Range
KRW	South Korean Won
LABA	Long-Acting $Beta_2$ Agonist
LAMA	Long-Acting Muscarinic Antagonist
LTRA	Leukotriene Receptor Antagonist
LRTI	Lower Respiratory Tract Infection
OAC	Overall Asthma Control
OR	Odds Ratio
pMDI	Pressurised Metered-Dose Inhaler
RCC	Relative Change in Coefficient
RDAC	Risk Domain Asthma Control
RR	Rate Ratio
SABA	Short-Acting $Beta_2$ Agonist
SAMA	Short-Acting Muscarinic Antagonist
SMD	Standardised Mean Difference

Introduction

Asthma is a chronic inflammatory airway disease with increasing global prevalence and significant morbidity and mortality worldwide.[1] In Korea, asthma is recognized as both a clinical as well as economic burden, with an estimated prevalence of 2.7% in the over 10-year old population.[2]

The international Global Initiative for Asthma provides an evidence-based approach to asthma management, while national Korean guidelines have also been introduced.[3,4] Both guidelines recommend inhaled corticosteroids (ICS) and ICS/long-acting beta agonist (LABA) combination therapy by an inhaled route of administration, dependent upon the treatment step required. Current inhaler devices available for ICS/LABA combination therapy include dry powder inhalers (DPIs) and pressurized metered-dose inhalers (pMDIs). Optimal delivery to the lung requires a different inhalation technique and breathing pattern for each device-type.[5] DPIs are breath-activated, requiring deep and forceful inhalation, while pMDIs require coordination of inhalation with actuation of the inhaler. Both devices types have been shown to be effective in controlled settings with patients trained on how to correctly use the device.[6,7] In daily practice however, incorrect inhaler technique is frequent and is associated with poor asthma control and reduced adherence.[8-10]

In Korea, current prescribing patterns for ICS/LABA therapy are dominated by DPIs. However, pMDIs may be equally 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.[11] Furthermore, the use of multiple mixed devices is associated with increased inhaler technique errors and decreased asthma control.[12] Since the use of pMDI short-acting beta agonist (SABA) relievers are common among patients with asthma, use of controllers with the same type as the reliever device might improve health and economic outcomes by simplifying the process of learning inhaler technique and reducing confusion compared to patients being on mixed DPI and pMDI devices.

The aim of this study is to evaluate real-life clinical effectiveness and cost outcomes of changing from a DPI to a pMDI for FDC ICS/LABA therapy in patients with asthma.

Methods

Study design

This was a retrospective cohort database study evaluating three outcomes (Figure 1).

Outcome 1 (persistence with change): a 1-year baseline and a 6 months' outcome period, designed to evaluate the proportion of asthma patients that persisted with collecting prescriptions of FDC ICS/LABA pMDI (including beclomethasone/formoterol, fluticasone/formoterol) after their initial change to this inhaler from a DPI (including fluticasone/salmeterol, budesonide/formoterol).

Outcome 2 (pre-change vs post-change outcomes): a 1-year baseline characterisation of the cohort who received ≥2 separate FDC ICS/LABA pMDI prescriptions, and no prescription for a FDC ICS/LABA DPI, for a period of 1 year. Asthma outcomes during the 1-year outcome period were compared to those during the baseline year.

Outcome 3 (changed vs non-changed matched cohort outcomes): a 1-year baseline characterisation and a 1-year outcome period. Asthma effectiveness and economic outcomes were compared between patients that changed to FDC ICS/LABA pMDI treatment and those that remained on FDC ICS/LABA DPI treatment.

Data source

For this study, data from the Korean Health Insurance Review and Assessment (HIRA) Service database were used. In South Korea, all patients have a mandatory and universal health plan. The HIRA database covers the complete medical healthcare utilisation data for the entire population of South Korea (>50 million people). It provides a unique and unbiased overview of healthcare utilisation (including almost all primary care, pharmacy and hospital data) on a national level. The HIRA database has been extensively described[13] and has been used in several previous studies including respiratory research.[14-16] For this study, HIRA data from January 2010 to December 2015 were accessed.

Inclusion and exclusion criteria

The following general inclusion criteria were applied for all three outcomes: (i) aged 12-80 years at date of first prescription for FDC ICS/LABA pMDI, (ii) at least 1 year baseline electronic medical records available, (iii) actively treated asthma, defined as ≥ 2 prescriptions (prescribed on different dates) for FDC ICS/LABA DPI during the baseline year and (iv) same ICS daily fluticasone Propionate equivalent dose [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. We excluded

patients with the following criteria: (i) prescription of FDC ICS/LABA pMDI prior to study period, (ii) received maintenance oral corticosteroids (defined as ≥5 prescriptions of ≤10mg prednisolone-equivalent oral corticosteroids during the baseline year) and (iii) received multiple different types of FDC ICS/LABA or separate ICS or LABA prescriptions at index date. In addition, several outcome specific inclusion and exclusion criteria were applied (Appendix 1).

[FIGURE 1]

For each of the three study outcomes, one primary and multiple secondary exploratory clinical and cost endpoints were defined.

Primary clinical outcomes

Outcome 1 was persisting with change, defined as: percentage of ICS/LABA pMDI patients who, at 6 months post-index date, received ≥1 prescription of ICS/LABA pMDI (in addition to that issued at their prescription date) and no prescription for an ICS/LABA DPI over the same period. Patient characteristics of those that persisted with the change were compared to those not persisting with the change. A sub-analysis was performed to assess the number of patients remaining on the same pMDI device-drug combination while having no DPI prescriptions AND no other pMDI prescriptions.

Outcome 2 was a non-inferiority assessment powered on the “no-exacerbation” endpoint defined as: the proportion of patients prescribed ≥2 FDC ICS/LABA pMDIs who had no severe exacerbations within 1 year of changing from a FDC ICS/LABA DPI device, compared to the baseline year. Non-inferiority was claimed if the lower limit of the 95% confidence interval (CI) of the mean difference in patient proportions with no severe exacerbations (outcome year – baseline year) was ≥ -0.125.

Outcome 3 was a non-inferiority assessment powered on the “no-exacerbation” endpoint defined as: the proportion of patients prescribed ≥2 FDC ICS/LABA pMDIs who had no severe exacerbations within 1 year of changing from a FDC ICS/LABA DPI, compared to the repeat cohort that remained on FDC ICS/LABA DPI treatment. Notably, patients with no severe exacerbations, as defined by the ATS/ERS Task Force 2015, had the absence of asthma-related hospital admissions, Accident & Emergency (A&E) attendances and acute courses of oral corticosteroids. Non-inferiority was claimed if the lower limit of the 95%CI of the mean difference (between change to pMDI and repeat DPI cohort) in patient proportions with no severe exacerbations in the outcome year was ≥-0.10. Note that this criterion for outcome 3 was stricter than the one for outcome 2 given that this was a between-group comparison and

outcome 2 was a within-group comparison (where usually larger differences are observed).

Secondary outcomes

The following secondary exploratory endpoints were investigated for outcomes 2 and 3: severe asthma exacerbation rate, acute respiratory events, risk domain asthma control (RDAC), overall asthma control (OAC), treatment stability, asthma exacerbation-related hospitalization rate, average daily SABA usage, average daily ICS dose and incidence of oral thrush. Their exact definitions are specified in appendix 2.

Cost outcomes

Exploratory cost outcomes, assessed as part of outcome 3, included change in asthma-related costs such as asthma medication prescriptions (ICS/LABA, ICS, LABA, SABA/SAMA, LABA/LAMA, SABA, short-acting muscarinic antagonists [SAMA], long-acting muscarinic antagonists [LAMA], leukotriene receptor antagonists [LTRA], theophylline, acute oral corticosteroids and antibiotics for lower respiratory tract infections [LRTIs]), respiratory-related hospital costs, inpatient hospitalisation costs, outpatient hospitalization costs and A&E costs.

Sample size calculations

For outcome 1, a sample size of 100 patients 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”. For outcome 2, at N=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 when the expected difference in proportions is 0.0, assuming that the proportion of discordant pairs is 0.242. For outcome 3, when the sample sizes in the groups are 208 and 208, a two-group large-sample normal approximation test of proportions with a one-sided 0.025 significance level has 90% power to reject the null hypothesis that the proportions are non-inferior.

Statistical analyses

A characterisation of all baseline demographics, co-morbidities, disease severity and other patient characteristics was performed and presented for each arm. The difference between the arms was quantified using the Standardised Mean Difference (SMD). This measure is not affected by the number of observations, and is thus a better way to judge imbalance than a p-value of a hypothesis test of difference.[17] The SMD was calculated for both continuous and categorical variables: an SMD ≤0.1 indicates sufficient balance between the treatment and the reference groups.[18] Bias potential was measured using the relative change in co-efficient (RCC) of the exposure when the covariate was added into the model predicting outcome.

Conditional regression analysis was performed on the matched dataset, taking into account the matched pairs. The type of regression used was dependent upon the outcome: linear regression for a continuous outcome, logistic regression for a binary outcome, Poisson regression for rates and proportional hazards regression for a time-to-event outcome. Adjustment for variables with residual confounding was made.

All statistical analyses were conducted using SAS® Enterprise® Guide 6.1 (SAS Institute, Cary, North Carolina, USA). Statistically significant results were defined as $P<.05$. The statistical tests used in the analysis are summarized in appendix 3 and the full statistical plan including detailed sample size calculations, baseline characterisation, bias assessment, matching process and analyses is provided in appendix 4.

Ethical approval

This study was approved by the institutional review board of Konkuk University Hospital, Korea, with registration number KUH1010751. The study was registered at the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance website with registration number EUPAS12275.

Results

Outcome 1: persistence of change to pMDI

In total, 1991 patients fulfilled our inclusion criteria. A patient flow diagram for the patient selection process is provided in appendix 5. During the 6-month outcome period, n=1152 (57.9%) of patients received ≥1 prescription for FDC ICS/LABA pMDI, in addition to that issued at the index date, and no FDC ICS/LABA DPI prescriptions (Table 1). In total, n=1128 (56.7%) of patients that persisted with the change to FDC ICS/LABA pMDI treatment remained on the same device over the 6 months (Table 1).

[TABLE 1]

The full patient population details are provided in appendix 5. Overall, patients within the "persistence of change" group were statistically younger (i.e. 1.8 years) and had a different distribution of insurance-type compared to those who did not persist with the change to FDC ICS/LABA pMDI. The distribution of comorbidities was found to be similar for both groups, except for comorbid gastroesophageal reflux disease (GERD), which was higher in patients that did not persist with the change from a DPI to a pMDI. Oral thrush, influenza and nasal polyps were rarely recorded. In terms of disease severity, patients that persisted with the change to FDC ICS/LABA pMDI treatment had less inpatient admissions, outpatient visits and emergency visits than non-persistent patients during the baseline year. Persistent patients also had less severe exacerbations and acute respiratory events compared to those that failed with the change in therapy. During the baseline year, patients that successfully changed to pMDI treatment had fewer FDC ICS/LABA, IV/IM corticosteroid, SABA and theophylline (or other methylxanthine) prescriptions and decreased average ICS daily dose. A lower percentage of patients within the persistence of change group were prescribed SAMA, however the mean number of SAMA prescriptions was higher for these patients than for those that did not persist with the change. Non-persistent patients were found to have increased LAMA prescriptions during the baseline year, as compared to patients that persisted with the change to a pMDI inhaler.

Outcome 2: 1-year pre versus 1-year post-change outcomes

In total, 667 patients met the inclusion criteria for this outcome. They represented a population that was treated with a DPI for at least one year, was switched (for unknown reasons) to a pMDI and subsequently followed for one year. A patient flow diagram and full baseline patient characteristics are provided in appendix 6. Briefly, mean age of the population was 58.1 years

(SD: 15.1), 54.9% was male, mean (SD) number of all-cause admissions was 0.9 (1.8) of which 0.2 (0.8) asthma-related admissions, mean (SD) number of FDC ICS/LABA prescriptions was 4.7 (2.7) with mean (SD) ICS dose of 400.8 µg (279.3) and mean number of SABA inhalers was 1.8 (4.2).

Non-inferiority of effectiveness (i.e. the proportion of patients free from exacerbations) during the outcome year (n=389; 58.3%) was determined for the population that changed from DPI to FDC ICS/LABA pMDI therapy as compared to the year prior to the change (n=316; 47.4%). Results indicated that the non-inferiority criterion was met (Table 2).

[TABLE 2]

The number of severe exacerbations (RR [95%CI] 1.56 [1.31, 1.86]) and acute respiratory events (RR [95%CI] 1.31 [1.14, 1.50]) were found (appendix 6, table A7) to have increased in the year following the change from a DPI to a pMDI for FDC ICS/LABA therapy, as compared to the year prior. Statistical significance for both outcomes was driven by an increase in the proportion of patients experiencing ≥2 severe exacerbations (7.9% vs 1.0%) or ≥3 acute respiratory events (14.5% vs 7.5%). However, an increased proportion of patients remained free from severe exacerbations (58.3%) or acute respiratory events (45.3%) during the year following the change to a pMDI as compared to during the baseline year (47.4% and 32.8% respectively).

The proportion of patients that achieved overall asthma control was significantly increased during the outcome year as compared to the baseline year (*P*=.024, OR [95%CI] 1.18 [1.02, 1.37]), reflecting the decreased average SABA daily dose following change of inhaler device (*P*<.001, OR [95%CI] 0.51 [0.43, 0.59]). Incidence of oral thrush was low and found to be decreased during the outcome year (OR [95%CI] 0.35 [0.14, 0.88]) as compared to the year prior to the change to pMDI therapy. In total, 41% of patients that changed to FDC ICS/LABA pMDI attained treatment stability.

Outcome 3: changed versus non-changed cohort outcomes

Based on SMD and clinical judgement, the 667 patients that changed from DPI to pMDI (identified for outcome 2) were matched to patients continuing on DPI based on baseline variables age, gender, COPD diagnosis, categorised SABA average daily dose, categorised ICS average daily dose and categorised ERS/ATS exacerbations.[19] Patients were then randomly picked with a maximum of 1:3 matching. The final cohort consisted of 642 FDC ICS/LABA pMDI “changed” patients and 1926 FDC ICS/LABA “repeat” DPI patients. Consort

diagram, full patient demographics, comorbidities, disease severity, prescribed medication and other characteristics are described in appendix 7.

Following matching, patients in the DPI repeat and pMDI change cohorts were similar in age and gender (appendix 7, Table A8). Comorbidities were also matching between cohorts, with the exception of COPD (ever), oral thrush (ever), GERD, influenza, other respiratory disease and rhinitis having a high SMD. However, bias (RCC) for each of these indications was less than 2% and variables were therefore not candidates for adjustment. Disease severity distributions during the baseline year were found to be similar between the pMDI change and the DPI continuation cohorts after matching, apart from antibiotic use, which was deemed a candidate for adjustment. Asthma-related medication prescribed during the baseline year was also similar in terms of SMD for both cohorts following matching, except for ICS, SABA nebuliser, LABA, SAMA and LTRA prescriptions. SAMA and LTRA prescriptions were deemed candidates for adjustment. Asthma-related costs during the baseline year for the matched pMDI change and DPI repeat cohorts were similar and no cost variables were candidates for adjustment.

Clinical outcomes

The primary outcome, i.e. non-inferiority of effectiveness, with regards the proportion of patients that remained free from severe exacerbations during the outcome year, was met for the matched cohorts. Superiority was not met and the sample size requirements to enable demonstration of superiority were not achieved (Table 3).

[TABLE 3]

Secondary exploratory outcomes were compared between patients changing to a pMDI and those that repeated their DPI during the outcome year (Figure 2, appendix 7). Patients changing to pMDI had significantly less severe exacerbations (*P*=.015, RR [95%CI] 0.79 [0.65, 0.95]) and acute respiratory events (*P*=.018, RR [95%CI] 0.84 [0.73, 0.97]), lower SABA inhaler average daily dose (*P*<.001, OR [95%CI] 0.71 [0.61, 0.84]) and higher ICS average daily dose category (*P*<.001, OR [95%CI] 1.57 [1.35, 1.81]) as compared to patients continuing with DPI treatment.

[FIGURE 2]

Cost outcomes

Asthma-related cost outcomes during the year following index date were compared and presented in Table 4. Patients that changed to a pMDI incurred lower costs for FDC ICS/LABA

(*P*=.027), oral (*P*=.014) and inhaled (*P*<.001) SABA and oral LABA (*P*=.002) treatment and higher costs for leukotriene receptor antagonist treatment (*P*<.001) compared to those that continued with a DPI inhaler. The DPI group had higher medication cost, but slightly (non-significantly) lower hospital costs. Total treatment costs over the outcome year were similar between patients that changed to FDC ICS/LABA pMDI therapy compared to those remaining on a DPI (KRW 2,073,305 versus KRW 1,927,458 respectively, *P*=0.451).

[TABLE 4]

Discussion

Main findings

This study aimed to characterize clinical asthma outcomes and assess the economic effects surrounding the change of inhaler from a DPI to a pMDI for ICS/LABA treatment in real-life Korean practice. A historical cohort study with three outcomes was performed using data extracted from the HIRA database. Generally, patients who changed inhaler seem to represent a sub-population with more uncontrolled asthma. In summary, in total, 58% of patients that changed inhaler from a DPI to a pMDI persisted with the change over 6 months. The remaining group of patients did not seem to receive benefit from the change in inhalers leading to failure of persistence with the switch. In persistent changers, the year following the change from a DPI to a pMDI for FDC ICS/LABA therapy was associated with increased asthma control, decreased acute respiratory events and decreased severe exacerbations. Changing to a pMDI for ICS/LABA therapy in patients with asthma was found to be associated with similar costs as remaining on a DPI. Finally, the results of this study showed that changing from a DPI to a pMDI inhaler for FDC ICS/LABA asthma treatment is associated with non-inferior effectiveness, compared to remaining on a DPI, in terms of exacerbation prevention. Yet, following the change, higher ICS doses were observed. In summary, for the majority of asthma patients, these results indicate equal effectiveness regarding asthma outcomes following the change from a DPI to a pMDI.

Interpretation

Overall results of this study are in line with previous reviews that indicated no differences between inhaler devices regarding clinical efficacy.[6,7] Yet, looking deeper into the characteristics of the patients whose medication was changed, they may represent a more uncontrolled sub-population based on severity and possibly on the match of inhaler to patient. When physicians confront patients with uncontrolled asthma in daily practice, they apply multiple strategies of which some are performed alongside each other, including increasing

the ICS dose, enhancing adherence, adding drugs, switching or better matching of inhalers (such as aligning device types for rescue and maintenance medication). Patients who persist with the switch overall do better in terms of exacerbations, overall control, decreased SABA use, but a subgroup, presumably with more severe and uncontrolled asthma, experience worse outcomes such as more frequent exacerbations. In this subgroup, switching inhalers was apparently not (sufficiently) effective and patients may have been switched back to their original inhaler and/or had step-up treatment with e.g. biologicals.

Notably, an important determinant for switch success may have been the guidance patients received during their switch. There are a few previous studies that specifically focused on the impact of device switching in asthma patients. A UK-based study (N=824) looked at patients (6-65 years) that switched ICS-containing devices without consulting their GP.[20] Over half of the switches (53%) involved a switch from DPIs to pMDIs. It was found that patients that switched without GP consultation had worse asthma control as defined by SABA use, oral steroids use and hospitalizations. Direct comparison with this study is difficult given the fact that in our study, no distinction could be made between patients that had or did not have a consultation at the day of device switching. In addition, we used a higher age criterion thereby excluding younger children that may have more difficulties in switching. Results from this study do highlight the importance of close guidance and monitoring during the switch. Notably, from the patient perspective, there are indications that a non-consented switch may reduce patients' relationship with their doctor, confidence in their medication and control over their asthma.[21] The finding of a higher ICS dose after changing to pMDIs deserves a comment. We hypothesize that the physician's decision for changing devices may be partly driven by asthma control. Loss of control may have been tackled by both better matching and device and patient as well as increasing ICS dose.

Strengths and limitations

The strength of the study is that it is based on real-life data, obtained from a high-quality database reflective of the total population of South Korea that includes all medical resource utilization and cost data.[13] To the best of our knowledge, this is the first nationwide study that shows the effects of changing from a DPI to a pMDI. The retrospective nature of this study means that patients were not influenced in any way and reduces recall bias. The datasets represent information collected for clinical and routine use, rather than specifically for research purposes. The validity and completeness of individual patient records cannot be assessed; as such there may be omissions or errors. Specific limitations were that the database did not provide any specific reasons for changing inhalers, did not provide data on exact daily SABA

usage as possible indication for the occurrence of non-severe exacerbations and no indirect cost data.[22] A limitation of all observational studies is the possibility of confounding of the results, arising from systematic differences between the patients being compared. In this study, confounding was minimised where possible by fitting multivariate models which were adjusted by clinical variables and patient characteristics that varied between patient groups. Despite the measures taken, confounding by unmeasured variables (such as adherence to medication) may be present. This study looks solely at the use of FDC ICS/LABA inhalers and does not include/exclude patients by asthma or COPD diagnosis or use of a spacer. 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, however, unnecessarily exclude asthma patients who are prescribed drugs affected by these reimbursement criteria.

Implications for clinical practice, policy and future research

While the data from this study indicate that FDC ICS/LABA device switching could be done without compromised asthma treatment effectiveness, in practice this switch should always be supervised and guided by an experienced physician. Reasons for switching should be properly explained to the patient[23] and for patients with insufficient breath-hand coordination, pMDIs should always be co-prescribed with a spacer. Moreover, inhaler instructions for the new device are essential and should preferably be repeated periodically.[24-26] Generally, prescribers of asthma inhalers should aim to match the device to patients' preferences, capacities and needs.[27] In addition, they should strive for uniformity of devices, including a good match between controller and reliever device handling characteristics. We recommend future studies aiming to confirm our findings by the means of prospective, randomized study designs including cost-effectiveness assessments. Furthermore, more studies focusing on the switch from pMDIs to DPIs, and their specific subtypes, should be performed. Showing no difference in outcomes regardless of the direction of the switch would convincingly fulfill their objective of showing that there is no difference between DPI and pMDIs. Lastly, the Korean healthcare system is unique and differs from other countries. In order to generalize the results of this study, validation studies in other countries are mandatory.

Conclusion

In real-life Korean practice, changing from a DPI to a pMDI for FDC ICS/LABA asthma treatment is as effective and cost-effective as remaining on a DPI. Taking into account patient subgroup characteristics and careful guidance surrounding the change are warranted.

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Figure legends

[FIGURE 1]

DPI: dry powder inhaler; FDC: fixed-dose combination; ICS/LABA: inhaled corticosteroids/long-acting beta agonist; pMDI: pressurized metered-dose inhaler; Rx: prescription

Figure 1: Study design for outcomes 1, 2, and 3

[FIGURE 2]

CI: confidence interval; DPI: dry powder inhaler; ICS: inhaled corticosteroids; pMDI: pressurized metered dose inhaler; SABA: short-acting beta agonist

Figure 2: Outcomes comparison between DPI repeat (M=1926) and pMDI change (N=642) cohort

Repository tables

Table A1: Outcome specific inclusion criteria

Inclusion criteria (outcome 1 specific)
➢ ≥1 prescription of FDC ICS/LABA during outcome period ➢ Index date pMDI prescription between January 2010 to December 2015 (1 year baseline, 6 months outcome)
Inclusion criteria (outcome 2 specific)
➢ ≥2 prescriptions of FDC ICS/LABA pMDI (prescribed on different dates) during outcome period ➢ Index date pMDI prescription between January 2010 to December 2015 (1 year baseline, 1 year outcome)
Exclusion criteria (outcome 2 specific)
➢ Prescription of FDC ICS/LABA DPI during outcome period
Inclusion criteria (ouicome 3 specific)
➢ ≥2 prescriptions of FDC ICS/LABA pMDI/DPI (change arm/repeat arm), prescribed on different dates, during outcome period ➢ Index date pMDI/matched DPI prescription between January 2010 to December 2015 (1 year baseline, 1 year outcome)
Exclusion criteria (outcome 3 specific)
➢ Change of FDC ICS/LABA inhaler-type during outcome period

Table A2: Statistical tests

Statistical test	Variable type	Distribution	Groups compared	Data type
Mann-Whitney (Wilcoxon rank sum)	Continuous	not normal	2	Independent
Kruskal-Wallis test	Continuous	not normal	>2	Independent
Chi-squared test	Categorical	n/a	≥2	Independent
Wilcoxon signed rank sum test	Continuous	not normal	2	Paired
McNemar's test	Categorical	n/a	2	Dependent
Marginal homogeneity test	Categorical	n/a	>2	Dependent
Linear regression	Continuous	Gaussian	2	Independent
Logistic regression	Binary	Binomial	2	Independent
Ordinal logistic regression	Ordinal	Multinomial	≥2	Independent
Poisson regression	Counts	Poisson	>2	Independent
Conditional linear regression	Continuous	Gaussian	≥2	Dependent
Conditional logistic regression	Binary	Binomial	2	Dependent
Conditional ordinal logistic regression	Ordinal	Multinomial	≥2	Dependent
Conditional Poisson regression	Counts	Poisson	>2	Dependent

Table A3: Formulae for Standardised Mean Difference

Covariate type	**Formula**
Continuous	$SMD = \frac{(\overline{x_t} - \overline{x_r})}{\sqrt{\frac{s_t^2 + s_r^2}{2}}}$, where $\overline{x_t}$, $\overline{x_r}$ denote the sample means and s_t, s_r the standard deviations
Binary	$SMD = \frac{(\widehat{p_t} - \widehat{p_r})}{\sqrt{\frac{\hat{p}_t(1-\hat{p}_t)+\hat{p}_r(1-\hat{p}_r)}{2}}}$, where $\widehat{p_t}$, $\widehat{p_r}$ denote the proportion of patients in each category
Categorical (>2 categories)	$SMD = \sqrt{(T-C)'S^{-1}(T-C)}$ where S is a $(k-1) \times (k-1)$ covariance matrix: $S = [S_{kl}] = \begin{cases} \frac{\hat{p}_{1k}(1-\hat{p}_{1k}) + \hat{p}_{2k}(1-\hat{p}_{2k})}{2}, & k = l \\ \frac{\hat{p}_{1k}\hat{p}_{1l} + \hat{p}_{2k}\hat{p}_{2l}}{2}, & k \neq l \end{cases}$, $T = (\hat{p}_{12}, \dots, \hat{p}_{1k})'$, $C = (\hat{p}_{22}, \dots, \hat{p}_{2k})'$ and $\hat{p}_{jk} = P(category\ k | treatment\ arm\ j)$, $j = 1,2$, $k = 2,3, \dots, k$

Table A4: Formulae for Relative Change in Co-efficient

Outcome type	**Regression type**	**Formula**
Continuous	Linear	$RCC = abs\left\{\frac{(\beta_{crude} - \beta_{adjusted})}{\beta_{crude}}\right\}$
Binary	Logistic	$RCC = abs(1 - e^{(\beta_{adjusted} - \beta_{crude})})$
Time-to-event	Cox-Proportional Hazard	
Count	Poisson	

Note: where β_{crude} is the co-efficient of exposure in the crude model and $\beta_{adjusted}$ is the co-efficient of exposure after adding the covariate in the model.

Table A5: Detailed results outcome 1

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
Age at IPD (years)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.015
	Mean (SD)	57.9 (15.6)	59.7 (14.7)	58.6 (15.2)	
	Median (IQR)	60 (48, 71)	62 (52, 72)	61 (50, 71)	
	Min, Max	(12, 80)	(13, 80)	(12, 80)	
Age at IPD (years) (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.106
	12-18, n (%)	7 (0.6)	6 (0.7)	13 (0.7)	
	19-35, n (%)	118 (10.2)	67 (8.0)	185 (9.3)	
	36-65, n (%)	582 (50.5)	402 (47.9)	984 (49.4)	
	66-80, n (%)	445 (38.6)	364 (43.4)	809 (40.6)	
Gender	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.309
	Male, n (%)	617 (53.6)	430 (51.3)	1047 (52.6)	
	Female, n (%)	535 (46.4)	409 (48.7)	944 (47.4)	
Insurance	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.031
	Medical insurance, n (%)	1006 (87.3)	698 (83.2)	1704 (85.6)	
	Medical aid, n (%)	144 (12.5)	138 (16.4)	282 (14.2)	
	Veterans cover, n (%)	2 (0.2)	3 (0.4)	5 (0.3)	
COMORBIDITIES					
	Measure	**Persistent Cohort**	**Non-Persistent Cohort**	**Total Cohort**	**p-value***
COPD	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.865
	No, n (%)	420 (36.5)	309 (36.8)	729 (36.6)	
	Yes, n (%)	732 (63.5)	530 (63.2)	1262 (63.4)	
COPD (ever)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.288
	No, n (%)	258 (22.4)	205 (24.4)	463 (23.3)	
	Yes, n (%)	894 (77.6)	634 (75.6)	1528 (76.7)	
Oral thrush	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.474
	No, n (%)	1142 (99.1)	829 (98.8)	1971 (99.0)	
	Yes, n (%)	10 (0.9)	10 (1.2)	20 (1.0)	
Oral thrush (ever)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.364
	No, n (%)	1136 (98.6)	823 (98.1)	1959 (98.4)	
	Yes, n (%)	16 (1.4)	16 (1.9)	32 (1.6)	
Comorbid eczema	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.840

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
	No, n (%)	1102 (95.7)	801 (95.5)	1903 (95.6)	
	Yes, n (%)	50 (4.3)	38 (4.5)	88 (4.4)	
Comorbid eczema (ever)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.992
	No, n (%)	1031 (89.5)	751 (89.5)	1782 (89.5)	
	Yes, n (%)	121 (10.5)	88 (10.5)	209 (10.5)	
Comorbid GERD	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.024
	No, n (%)	806 (70.0)	547 (65.2)	1353 (68.0)	
	Yes, n (%)	346 (30.0)	292 (34.8)	638 (32.0)	
Comorbid GERD (ever)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.050
	No, n (%)	606 (52.6)	404 (48.2)	1010 (50.7)	
	Yes, n (%)	546 (47.4)	435 (51.8)	981 (49.3)	
Ischaemic heart disease	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.540
	No, n (%)	1054 (91.5)	761 (90.7)	1815 (91.2)	
	Yes, n (%)	98 (8.5)	78 (9.3)	176 (8.8)	
Ischaemic heart disease (ever)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.982
	No, n (%)	1000 (86.8)	728 (86.8)	1728 (86.8)	
	Yes, n (%)	152 (13.2)	111 (13.2)	263 (13.2)	
Influenza	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.081
	No, n (%)	1128 (97.9)	830 (98.9)	1958 (98.3)	
	Yes, n (%)	24 (2.1)	9 (1.1)	33 (1.7)	
Influenza (ever)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.712
	No, n (%)	1110 (96.4)	811 (96.7)	1921 (96.5)	
	Yes, n (%)	42 (3.6)	28 (3.3)	70 (3.5)	
Other chronic lung diseases	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.990
	No, n (%)	680 (59.0)	495 (59.0)	1175 (59.0)	
	Yes, n (%)	472 (41.0)	344 (41.0)	816 (41.0)	
Other chronic lung diseases (ever)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.149
	No, n (%)	445 (38.6)	351 (41.8)	796 (40.0)	
	Yes, n (%)	707 (61.4)	488 (58.2)	1195 (60.0)	
	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.817

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
Comorbid nasal polyps	No, n (%)	1129 (98.0)	821 (97.9)	1950 (97.9)	
	Yes, n (%)	23 (2.0)	18 (2.1)	41 (2.1)	
Comorbid nasal polyps (ever)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	No, n (%)	1098 (95.3)	804 (95.8)	1902 (95.5)	0.582
	Yes, n (%)	54 (4.7)	35 (4.2)	89 (4.5)	
Pneumonia	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	No, n (%)	1043 (90.5)	742 (88.4)	1785 (89.7)	0.129
	Yes, n (%)	109 (9.5)	97 (11.6)	206 (10.3)	
Pneumonia (ever)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	No, n (%)	950 (82.5)	687 (81.9)	1637 (82.2)	0.737
	Yes, n (%)	202 (17.5)	152 (18.1)	354 (17.8)	
Comorbid rhinitis (active)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	No, n (%)	411 (35.7)	324 (38.6)	735 (36.9)	0.179
	Yes, n (%)	741 (64.3)	515 (61.4)	1256 (63.1)	
Comorbid rhinitis (ever)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	No, n (%)	226 (19.6)	167 (19.9)	393 (19.7)	0.874
	Yes, n (%)	926 (80.4)	672 (80.1)	1598 (80.3)	
Charlson Comorbidity Index (CCI)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	Mean (SD)	1.4 (0.9)	1.5 (0.9)	1.4 (0.9)	0.058
	Median (IQR)	1 (1, 1)	1 (1, 1)	1 (1, 1)	
	Min, Max	(0, 7)	(0, 6)	(0, 7)	
Charlson Comorbidity Index (CCI) (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	0-1, n (%)	920 (79.9)	641 (76.4)	1561 (78.4)	0.152
	2-5, n (%)	228 (19.8)	193 (23.0)	421 (21.1)	
	6-10 n (%)	4 (0.3)	5 (0.6)	9 (0.5)	
DISEASE SEVERITY & HEALTHCARE UTILIZATION					
	Measure	**Persistent Cohort**	**Non-Persistent Cohort**	**Total Cohort**	**p-value**
All inpatient admissions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	Mean (SD)	0.9 (1.9)	1.1 (2.3)	1.0 (2.1)	0.022

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
	Median (IQR)	0 (0, 1)	0 (0, 1)	0 (0, 1)	
	Min, Max	(0, 24)	(0, 18)	(0, 24)	
All inpatient admissions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.038
	0, n (%)	728 (63.2)	489 (58.3)	1217 (61.1)	
	1, n (%)	210 (18.2)	175 (20.9)	385 (19.3)	
	2, n (%)	101 (8.8)	72 (8.6)	173 (8.7)	
	3, n (%)	47 (4.1)	30 (3.6)	77 (3.9)	
	≥4, n (%)	66 (5.7)	73 (8.7)	139 (7.0)	
All inpatient admissions days	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.015
	Mean (SD)	9.0 (26.7)	12.0 (34.7)	10.3 (30.4)	
	Median (IQR)	0 (0, 7)	0 (0, 9)	0 (0, 8)	
	Min, Max	(0, 318)	(0, 388)	(0, 388)	
All inpatient admissions days (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	Data visualisation only
	0, n (%)	728 (63.2)	489 (58.3)	1217 (61.1)	
	1-3, n (%)	70 (6.1)	50 (6.0)	120 (6.0)	
	4-6, n (%)	58 (5.0)	51 (6.1)	109 (5.5)	
	7-13, n (%)	102 (8.9)	84 (10.0)	186 (9.3)	
	≥14, n (%)	194 (16.8)	165 (19.7)	359 (18.0)	
LRTI-related inpatient admissions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.003
	Mean (SD)	0.3 (0.7)	0.4 (0.9)	0.3 (0.8)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 7)	(0, 10)	(0, 10)	
LRTI-related inpatient admissions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.045
	0, n (%)	933 (81.0)	634 (75.6)	1567 (78.7)	
	1, n (%)	160 (13.9)	143 (17.0)	303 (15.2)	
	2, n (%)	39 (3.4)	39 (4.6)	78 (3.9)	
	3, n (%)	10 (0.9)	9 (1.1)	19 (1.0)	
	≥4, n (%)	10 (0.9)	14 (1.7)	24 (1.2)	
	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.003
	Mean (SD)	3.5 (13.6)	4.5 (14.4)	3.9 (14.0)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
LRTI-related inpatient admissions days	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 259)	(0, 156)	(0, 259)	
LRTI-related inpatient admissions days (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	Data visualisation only
	0, n (%)	933 (81.0)	634 (75.6)	1567 (78.7)	
	1-3, n (%)	27 (2.3)	21 (2.5)	48 (2.4)	
	4-6, n (%)	37 (3.2)	37 (4.4)	74 (3.7)	
	7-13, n (%)	68 (5.9)	63 (7.5)	131 (6.6)	
	≥14, n (%)	87 (7.6)	84 (10.0)	171 (8.6)	
Asthma-related inpatient admissions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.025
	Mean (SD)	0.2 (0.8)	0.3 (0.9)	0.3 (0.9)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 12)	(0, 12)	(0, 12)	
Asthma-related inpatient admissions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.255
	0, n (%)	978 (84.9)	680 (81.0)	1658 (83.3)	
	1, n (%)	118 (10.2)	110 (13.1)	228 (11.5)	
	2, n (%)	35 (3.0)	31 (3.7)	66 (3.3)	
	3, n (%)	8 (0.7)	6 (0.7)	14 (0.7)	
	≥4, n (%)	13 (1.1)	12 (1.4)	25 (1.3)	
Asthma-related inpatient admissions days	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.026
	Mean (SD)	2.6 (11.6)	3.1 (12.0)	2.8 (11.8)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 259)	(0, 156)	(0, 259)	
Asthma-related inpatient admissions days (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	Data visualisation only
	0, n (%)	978 (84.9)	680 (81.0)	1658 (83.3)	
	1-3, n (%)	22 (1.9)	22 (2.6)	44 (2.2)	
	4-6, n (%)	33 (2.9)	29 (3.5)	62 (3.1)	
	7-13, n (%)	54 (4.7)	52 (6.2)	106 (5.3)	
	≥14, n (%)	65 (5.6)	56 (6.7)	121 (6.1)	
Asthma exacerbation-	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	<0.001
	Mean (SD)	0.1 (0.4)	0.2 (0.6)	0.1 (0.5)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
related inpatient admissions	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 5)	(0, 7)	(0, 7)	
Asthma exacerbation-related inpatient admissions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.011
	0, n (%)	1095 (95.1)	765 (91.2)	1860 (93.4)	
	1, n (%)	38 (3.3)	44 (5.2)	82 (4.1)	
	2, n (%)	12 (1.0)	18 (2.1)	30 (1.5)	
	3, n (%)	4 (0.3)	5 (0.6)	9 (0.5)	
	≥4, n (%)	3 (0.3)	7 (0.8)	10 (0.5)	
Asthma exacerbation-related inpatient admissions days	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	<0.001
	Mean (SD)	0.7 (4.6)	1.7 (9.2)	1.1 (7.0)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 78)	(0, 156)	(0, 156)	
Asthma exacerbation-related inpatient admissions days (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	Data visualisation only
	0, n (%)	1095 (95.1)	765 (91.2)	1860 (93.4)	
	1-3, n (%)	9 (0.8)	11 (1.3)	20 (1.0)	
	4-6, n (%)	14 (1.2)	11 (1.3)	25 (1.3)	
	7-13, n (%)	16 (1.4)	22 (2.6)	38 (1.9)	
	≥14, n (%)	18 (1.6)	30 (3.6)	48 (2.4)	
All outpatient attendances	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	<0.001
	Mean (SD)	33.0 (26.5)	37.1 (27.3)	34.8 (26.9)	
	Median (IQR)	26 (16, 42)	30 (18, 48)	27 (17, 44)	
	Min, Max	(2, 225)	(3, 220)	(2, 225)	
All outpatient attendances (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	<0.001
	1-12, n (%)	181 (15.7)	102 (12.2)	283 (14.2)	
	13-24, n (%)	366 (31.8)	229 (27.3)	595 (29.9)	
	25-36, n (%)	244 (21.2)	174 (20.7)	418 (21.0)	
	37-48, n (%)	154 (13.4)	125 (14.9)	279 (14.0)	
	≥48, n (%)	207 (18.0)	209 (24.9)	416 (20.9)	
	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	<0.001
	Mean (SD)	28.1 (22.6)	31.5 (23.7)	29.5 (23.1)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
LRTI-related outpatient attendances	Median (IQR)	22 (14, 35)	25 (15, 40)	23 (14, 37)	
	Min, Max	(2, 216)	(3, 207)	(2, 216)	
LRTI-related outpatient attendances (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	<0.001
	1-12, n (%)	236 (20.5)	135 (16.1)	371 (18.6)	
	13-24, n (%)	416 (36.1)	271 (32.3)	687 (34.5)	
	25-36, n (%)	234 (20.3)	175 (20.9)	409 (20.5)	
	37-48, n (%)	127 (11.0)	114 (13.6)	241 (12.1)	
	≥48, n (%)	139 (12.1)	144 (17.2)	283 (14.2)	
Asthma-related outpatient attendances	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	<0.001
	Mean (SD)	7.5 (8.6)	8.9 (9.8)	8.1 (9.1)	
	Median (IQR)	6 (3, 9)	7 (3, 11)	6 (3, 10)	
	Min, Max	(0, 105)	(0, 135)	(0, 135)	
Asthma-related outpatient attendances (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.005
	0, n (%)	87 (7.6)	49 (5.8)	136 (6.8)	
	1-3, n (%)	263 (22.8)	165 (19.7)	428 (21.5)	
	4-6, n (%)	306 (26.6)	200 (23.8)	506 (25.4)	
	7-9, n (%)	214 (18.6)	153 (18.2)	367 (18.4)	
	10-12, n (%)	107 (9.3)	101 (12.0)	208 (10.4)	
	≥13, n (%)	175 (15.2)	171 (20.4)	346 (17.4)	
All emergency attendances	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.051
	Mean (SD)	0.4 (1.0)	0.5 (1.0)	0.4 (1.0)	
	Median (IQR)	0 (0, 0)	0 (0, 1)	0 (0, 1)	
	Min, Max	(0, 15)	(0, 9)	(0, 15)	
All emergency attendances (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.032
	0, n (%)	866 (75.2)	604 (72.0)	1470 (73.8)	
	1, n (%)	195 (16.9)	136 (16.2)	331 (16.6)	
	2, n (%)	56 (4.9)	53 (6.3)	109 (5.5)	
	3, n (%)	15 (1.3)	24 (2.9)	39 (2.0)	
	≥4, n (%)	20 (1.7)	22 (2.6)	42 (2.1)	
	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.051

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
LRTI-related emergency attendances	Mean (SD)	0.4 (1.0)	0.5 (1.0)	0.4 (1.0)	
	Median (IQR)	0 (0, 0)	0 (0, 1)	0 (0, 1)	
	Min, Max	(0, 15)	(0, 9)	(0, 15)	
LRTI-related emergency attendances (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.027
	0, n (%)	866 (75.2)	604 (72.0)	1470 (73.8)	
	1, n (%)	202 (17.5)	141 (16.8)	343 (17.2)	
	2, n (%)	50 (4.3)	51 (6.1)	101 (5.1)	
	3, n (%)	17 (1.5)	27 (3.2)	44 (2.2)	
	≥4, n (%)	17 (1.5)	16 (1.9)	33 (1.7)	
Asthma-related emergency attendances	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.397
	Mean (SD)	0.1 (0.5)	0.1 (0.5)	0.1 (0.5)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 7)	(0, 5)	(0, 7)	
Asthma-related emergency attendances (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.419
	0, n (%)	1049 (91.1)	755 (90.0)	1804 (90.6)	
	1, n (%)	80 (6.9)	61 (7.3)	141 (7.1)	
	2, n (%)	15 (1.3)	13 (1.5)	28 (1.4)	
	3, n (%)	6 (0.5)	4 (0.5)	10 (0.5)	
	≥4, n (%)	2 (0.2)	6 (0.7)	8 (0.4)	
Antibiotics	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.156
	Mean (SD)	1.1 (1.9)	1.3 (2.4)	1.2 (2.1)	
	Median (IQR)	0 (0, 1)	0 (0, 2)	0 (0, 2)	
	Min, Max	(0, 15)	(0, 24)	(0, 24)	
Antibiotics (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.424
	0, n (%)	645 (56.0)	445 (53.0)	1090 (54.7)	
	1-3, n (%)	404 (35.1)	313 (37.3)	717 (36.0)	
	4-6, n (%)	69 (6.0)	51 (6.1)	120 (6.0)	
	7-9, n (%)	25 (2.2)	16 (1.9)	41 (2.1)	
	10-12, n (%)	5 (0.4)	8 (1.0)	13 (0.7)	
	≥13, n (%)	4 (0.3)	6 (0.7)	10 (0.5)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
Acute OCS	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.444
	Mean (SD)	1.2 (2.7)	1.2 (2.3)	1.2 (2.5)	
	Median (IQR)	0 (0, 1)	0 (0, 1)	0 (0, 1)	
	Min, Max	(0, 36)	(0, 26)	(0, 36)	
Acute OCS (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.826
	0, n (%)	686 (59.5)	486 (57.9)	1172 (58.9)	
	1, n (%)	205 (17.8)	146 (17.4)	351 (17.6)	
	2, n (%)	88 (7.6)	71 (8.5)	159 (8.0)	
	3, n (%)	64 (5.6)	55 (6.6)	119 (6.0)	
	≥4, n (%)	109 (9.5)	81 (9.7)	190 (9.5)	
Non-acute OCS	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.458
	Mean (SD)	0.7 (1.2)	0.7 (1.2)	0.7 (1.2)	
	Median (IQR)	0 (0, 1)	0 (0, 1)	0 (0, 1)	
	Min, Max	(0, 9)	(0, 11)	(0, 11)	
Non-acute OCS (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.061
	0, n (%)	742 (64.4)	519 (61.9)	1261 (63.3)	
	1, n (%)	191 (16.6)	167 (19.9)	358 (18.0)	
	2, n (%)	108 (9.4)	86 (10.3)	194 (9.7)	
	3, n (%)	68 (5.9)	31 (3.7)	99 (5.0)	
	≥4, n (%)	43 (3.7)	36 (4.3)	79 (4.0)	
Severe exacerbations (ATS/ERS)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.019
	Mean (SD)	0.7 (0.8)	0.8 (0.9)	0.7 (0.9)	
	Median (IQR)	1 (0, 1)	1 (0, 1)	1 (0, 1)	
	Min, Max	(0, 9)	(0, 7)	(0, 9)	
Severe exacerbations (ATS/ERS) (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.007
	0, n (%)	531 (46.1)	353 (42.1)	884 (44.4)	
	1, n (%)	525 (45.6)	390 (46.5)	915 (46.0)	
	2, n (%)	69 (6.0)	51 (6.1)	120 (6.0)	
	3, n (%)	15 (1.3)	25 (3.0)	40 (2.0)	
	≥4, n (%)	12 (1.0)	20 (2.4)	32 (1.6)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
Acute respiratory event	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.022
	Mean (SD)	1.2 (1.4)	1.4 (2.0)	1.3 (1.7)	
	Median (IQR)	1 (0, 1)	1 (0, 2)	1 (0, 2)	
	Min, Max	(0, 12)	(0, 24)	(0, 24)	
Acute respiratory event (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.070
	0, n (%)	375 (32.6)	245 (29.2)	620 (31.1)	
	1, n (%)	502 (43.6)	363 (43.3)	865 (43.4)	
	2, n (%)	139 (12.1)	96 (11.4)	235 (11.8)	
	3, n (%)	58 (5.0)	61 (7.3)	119 (6.0)	
	≥4, n (%)	78 (6.8)	74 (8.8)	152 (7.6)	
MEDICATION USE					
	Measure	**Persistent Cohort**	**Non-Persistent Cohort**	**Total Cohort**	**p-value**
FDC ICS/LABA prescriptions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	<0.001
	Mean (SD)	4.5 (2.7)	5.3 (2.8)	4.8 (2.8)	
	Median (IQR)	4 (2, 6)	5 (3, 7)	4 (3, 6)	
	Min, Max	(2, 21)	(2, 14)	(2, 21)	
FDC ICS/LABA prescriptions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	<0.001
	2-3, n (%)	529 (45.9)	282 (33.6)	811 (40.7)	
	≥4, n (%)	623 (54.1)	557 (66.4)	1180 (59.3)	
ICS only prescriptions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.688
	Mean (SD)	0.5 (1.5)	0.7 (2.6)	0.6 (2.1)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 24)	(0, 63)	(0, 63)	
ICS only prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.877
	No, n (%)	874 (75.9)	634 (75.6)	1508 (75.7)	
	Yes, n (%)	278 (24.1)	205 (24.4)	483 (24.3)	
ICS only prescriptions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.170
	0, n (%)	874 (75.9)	634 (75.6)	1508 (75.7)	
	1, n (%)	148 (12.8)	100 (11.9)	248 (12.5)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
	2, n (%)	62 (5.4)	35 (4.2)	97 (4.9)	
	3, n (%)	29 (2.5)	26 (3.1)	55 (2.8)	
	≥4, n (%)	39 (3.4)	44 (5.2)	83 (4.2)	
ICS average daily dose	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	<0.001
	Mean (SD)	373.7 (271.9)	406.3 (268.1)	387.5 (270.7)	
	Median (IQR)	303.1 (179.8, 467.5)	328.8 (205.5, 534.2)	314.0 (205.5, 493.2)	
	Min, Max	(65.8, 3565.2)	(49.3, 2381.6)	(49.3, 3565.2)	
ICS average daily dose (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.005
	>0-250, n (%)	475 (41.2)	297 (35.4)	772 (38.8)	
	>250-500, n (%)	430 (37.3)	315 (37.5)	745 (37.4)	
	>500, n (%)	247 (21.4)	227 (27.1)	474 (23.8)	
IV/IM CS prescriptions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.002
	Mean (SD)	2.3 (4.5)	3.0 (6.1)	2.6 (5.2)	
	Median (IQR)	1 (0, 3)	1 (0, 3)	1 (0, 3)	
	Min, Max	(0, 51)	(0, 80)	(0, 80)	
IV/IM CS prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.018
	No, n (%)	485 (42.1)	309 (36.8)	794 (39.9)	
	Yes, n (%)	667 (57.9)	530 (63.2)	1197 (60.1)	
IV/IM CS prescriptions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.102
	0, n (%)	485 (42.1)	309 (36.8)	794 (39.9)	
	1-3, n (%)	433 (37.6)	323 (38.5)	756 (38.0)	
	4-8, n (%)	162 (14.1)	141 (16.8)	303 (15.2)	
	9-13, n (%)	34 (3.0)	32 (3.8)	66 (3.3)	
	≥13, n (%)	38 (3.3)	34 (4.1)	72 (3.6)	
SABA prescriptions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	<0.001
	Mean (SD)	3.3 (6.2)	4.1 (6.7)	3.6 (6.4)	
	Median (IQR)	1 (0, 4)	2 (0, 5)	1 (0, 4)	
	Min, Max	(0, 64)	(0, 68)	(0, 68)	
	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.003

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
SABA prescriptions (yes/no)	No, n (%)	426 (37.0)	257 (30.6)	683 (34.3)	
	Yes, n (%)	726 (63.0)	582 (69.4)	1308 (65.7)	
SABA prescriptions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	0, n (%)	426 (37.0)	257 (30.6)	683 (34.3)	
	1-3, n (%)	436 (37.8)	299 (35.6)	735 (36.9)	
	4-6, n (%)	118 (10.2)	123 (14.7)	241 (12.1)	0.001
	7-9, n (%)	67 (5.8)	59 (7.0)	126 (6.3)	
	10-12, n (%)	38 (3.3)	30 (3.6)	68 (3.4)	
	≥13, n (%)	67 (5.8)	71 (8.5)	138 (6.9)	
SABA inhaler prescriptions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	Mean (SD)	1.7 (3.8)	2.1 (4.0)	1.8 (3.9)	0.011
	Median (IQR)	0 (0, 1)	0 (0, 2)	0 (0, 2)	
	Min, Max	(0, 64)	(0, 32)	(0, 64)	
SABA inhaler prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	No, n (%)	650 (56.4)	437 (52.1)	1087 (54.6)	0.055
	Yes, n (%)	502 (43.6)	402 (47.9)	904 (45.4)	
SABA inhaler prescriptions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	0, n (%)	650 (56.4)	437 (52.1)	1087 (54.6)	
	1-3, n (%)	345 (29.9)	254 (30.3)	599 (30.1)	
	4-6, n (%)	71 (6.2)	63 (7.5)	134 (6.7)	0.166
	7-9, n (%)	37 (3.2)	33 (3.9)	70 (3.5)	
	10-12, n (%)	23 (2.0)	28 (3.3)	51 (2.6)	
	≥13, n (%)	26 (2.3)	24 (2.9)	50 (2.5)	
SABA inhaler average daily dose	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	Mean (SD)	127.4 (362.9)	157.3 (358.3)	140.0 (361.2)	0.011
	Median (IQR)	0 (0, 110)	0 (0, 110)	0 (0, 110)	
	Min, Max	(0, 6630)	(0, 4384)	(0, 6630)	
SABA inhaler average daily dose (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	0, n (%)	650 (56.4)	437 (52.1)	1087 (54.6)	0.060
	>0-200, n (%)	327 (28.4)	235 (28.0)	562 (28.2)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
	>200-400, n (%)	74 (6.4)	64 (7.6)	138 (6.9)	
	>400-800, n (%)	57 (4.9)	63 (7.5)	120 (6.0)	
	≥800, n (%)	44 (3.8)	40 (4.8)	84 (4.2)	
SABA nebuliser prescriptions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.019
	Mean (SD)	1.1 (3.3)	1.3 (3.5)	1.2 (3.4)	
	Median (IQR)	0 (0, 1)	0 (0, 1)	0 (0, 1)	
	Min, Max	(0, 50)	(0, 51)	(0, 51)	
SABA nebuliser prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.039
	No, n (%)	743 (64.5)	503 (60.0)	1246 (62.6)	
	Yes, n (%)	409 (35.5)	336 (40.0)	745 (37.4)	
SABA nebuliser prescriptions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.063
	0, n (%)	743 (64.5)	503 (60.0)	1246 (62.6)	
	1-3, n (%)	325 (28.2)	249 (29.7)	574 (28.8)	
	4-6, n (%)	50 (4.3)	57 (6.8)	107 (5.4)	
	7-9, n (%)	12 (1.0)	12 (1.4)	24 (1.2)	
	10-12, n (%)	7 (0.6)	10 (1.2)	17 (0.9)	
	≥13, n (%)	15 (1.3)	8 (1.0)	23 (1.2)	
SABA oral prescriptions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.035
	Mean (SD)	0.5 (2.3)	0.7 (3.0)	0.6 (2.6)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 45)	(0, 51)	(0, 51)	
SABA oral prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.039
	No, n (%)	1003 (87.1)	703 (83.8)	1706 (85.7)	
	Yes, n (%)	149 (12.9)	136 (16.2)	285 (14.3)	
SABA oral prescriptions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.088
	0, n (%)	1003 (87.1)	703 (83.8)	1706 (85.7)	
	1-3, n (%)	105 (9.1)	89 (10.6)	194 (9.7)	
	4-6, n (%)	19 (1.6)	20 (2.4)	39 (2.0)	
	7-9, n (%)	12 (1.0)	9 (1.1)	21 (1.1)	
	10-12, n (%)	7 (0.6)	4 (0.5)	11 (0.6)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
	≥13, n (%)	6 (0.5)	14 (1.7)	20 (1.0)	
FDC SABA/SAMA prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.394
	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)	
	Min, Max	(0, 1)	(0, 0)	(0, 1)	
SAMA prescriptions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.044
	Mean (SD)	0.6 (2.6)	0.5 (2.2)	0.6 (2.5)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 50)	(0, 51)	(0, 51)	
SAMA prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.041
	No, n (%)	915 (79.4)	634 (75.6)	1549 (77.8)	
	Yes, n (%)	237 (20.6)	205 (24.4)	442 (22.2)	
SAMA prescriptions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.169
	0, n (%)	915 (79.4)	634 (75.6)	1549 (77.8)	
	1, n (%)	140 (12.2)	125 (14.9)	265 (13.3)	
	2, n (%)	48 (4.2)	31 (3.7)	79 (4.0)	
	3, n (%)	17 (1.5)	17 (2.0)	34 (1.7)	
	≥4, n (%)	32 (2.8)	32 (3.8)	64 (3.2)	
LAMA prescriptions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.219
	Mean (SD)	1.3 (2.8)	1.5 (3.1)	1.4 (2.9)	
	Median (IQR)	0 (0, 1)	0 (0, 1)	0 (0, 1)	
	Min, Max	(0, 14)	(0, 15)	(0, 15)	
LAMA prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.274
	No, n (%)	864 (75.0)	611 (72.8)	1475 (74.1)	
	Yes, n (%)	288 (25.0)	228 (27.2)	516 (25.9)	
LAMA prescriptions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	<0.001
	0, n (%)	864 (75.0)	611 (72.8)	1475 (74.1)	
	1-2, n (%)	62 (5.4)	63 (7.5)	125 (6.3)	
	3-4, n (%)	90 (7.8)	31 (3.7)	121 (6.1)	
	≥5, n (%)	136 (11.8)	134 (16.0)	270 (13.6)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
FDC LABA/LAMA prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.393
	No, n (%)	1151 (99.9)	839 (100.0)	1990 (99.9)	
	Yes, n (%)	1 (0.1)	0 (0.0)	1 (0.1)	
LABA inhaler prescriptions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.785
	Mean (SD)	0.1 (0.5)	0.1 (0.6)	0.1 (0.5)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 10)	(0, 12)	(0, 12)	
LABA inhaler prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.782
	No, n (%)	1128 (97.9)	823 (98.1)	1951 (98.0)	
	Yes, n (%)	24 (2.1)	16 (1.9)	40 (2.0)	
LABA inhaler prescriptions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.904
	0, n (%)	1128 (97.9)	823 (98.1)	1951 (98.0)	
	1, n (%)	14 (1.2)	8 (1.0)	22 (1.1)	
	2, n (%)	2 (0.2)	3 (0.4)	5 (0.3)	
	3, n (%)	3 (0.3)	2 (0.2)	5 (0.3)	
	≥4, n (%)	5 (0.4)	3 (0.4)	8 (0.4)	
LABA oral prescriptions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.136
	Mean (SD)	1.4 (3.3)	1.7 (4.4)	1.5 (3.8)	
	Median (IQR)	0 (0, 1)	0 (0, 1)	0 (0, 1)	
	Min, Max	(0, 34)	(0, 49)	(0, 49)	
LABA oral prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.149
	No, n (%)	804 (69.8)	560 (66.7)	1364 (68.5)	
	Yes, n (%)	348 (30.2)	279 (33.3)	627 (31.5)	
LABA oral prescriptions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.563
	0, n (%)	804 (69.8)	560 (66.7)	1364 (68.5)	
	1-3, n (%)	199 (17.3)	151 (18.0)	350 (17.6)	
	4-6, n (%)	67 (5.8)	56 (6.7)	123 (6.2)	
	7-11, n (%)	51 (4.4)	42 (5.0)	93 (4.7)	
	≥12, n (%)	31 (2.7)	30 (3.6)	61 (3.1)	
	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.660

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
LABA patch prescriptions	Mean (SD)	0.3 (1.5)	0.4 (1.9)	0.3 (1.7)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 19)	(0, 31)	(0, 31)	
LABA patch prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	No, n (%)	1041 (90.4)	753 (89.7)	1794 (90.1)	0.650
	Yes, n (%)	111 (9.6)	86 (10.3)	197 (9.9)	
LABA patch prescriptions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	0, n (%)	1041 (90.4)	753 (89.7)	1794 (90.1)	
	1-2, n (%)	69 (6.0)	51 (6.1)	120 (6.0)	
	3-4, n (%)	16 (1.4)	17 (2.0)	33 (1.7)	0.484
	5-6, n (%)	6 (0.5)	8 (1.0)	14 (0.7)	
	≥7, n (%)	20 (1.7)	10 (1.2)	30 (1.5)	
LTRA prescriptions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	Mean (SD)	5.0 (5.5)	5.2 (7.2)	5.1 (6.3)	
	Median (IQR)	4 (1, 7)	4 (0, 7)	4 (1, 7)	0.378
	Min, Max	(0, 77)	(0, 123)	(0, 123)	
LTRA prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	No, n (%)	268 (23.3)	211 (25.1)	479 (24.1)	0.331
	Yes, n (%)	884 (76.7)	628 (74.9)	1512 (75.9)	
LTRA prescriptions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	0, n (%)	268 (23.3)	211 (25.1)	479 (24.1)	
	1-3, n (%)	257 (22.3)	206 (24.6)	463 (23.3)	
	4-6, n (%)	279 (24.2)	165 (19.7)	444 (22.3)	0.176
	7-11, n (%)	212 (18.4)	155 (18.5)	367 (18.4)	
	≥12, n (%)	136 (11.8)	102 (12.2)	238 (12.0)	
Theophylline or other methylxanthine prescriptions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	Mean (SD)	4.6 (6.4)	5.9 (8.1)	5.1 (7.2)	
	Median (IQR)	2 (0, 7)	3 (0, 9)	3 (0, 8)	0.001
	Min, Max	(0, 76)	(0, 73)	(0, 76)	
	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.061

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
Theophylline or other methylxanthine prescriptions (yes/no)	No, n (%)	372 (32.3)	238 (28.4)	610 (30.6)	
	Yes, n (%)	780 (67.7)	601 (71.6)	1381 (69.4)	
Theophylline or other methylxanthine prescriptions (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.003
	0, n (%)	372 (32.3)	238 (28.4)	610 (30.6)	
	1-3, n (%)	274 (23.8)	188 (22.4)	462 (23.2)	
	4-6, n (%)	198 (17.2)	131 (15.6)	329 (16.5)	
	7-11, n (%)	174 (15.1)	135 (16.1)	309 (15.5)	
	≥12, n (%)	134 (11.6)	147 (17.5)	281 (14.1)	

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

Table A6: Baseline characteristics outcome 2

	Measure	Patients changing from DPI to pMDI
Age at IPD (years)	N (% not missing)	667 (100.0)
	Mean (SD)	58.1 (15.1)
	Median (IQR)	60 (49, 70)
	Min, Max	(12, 80)
Age at IPD (years) (categorised)	N (% not missing)	667(100)
	12-18, n (%)	2 (0.3)
	19-35, n (%)	63 (9.4)
	36-65, n (%)	347 (52.0)
	66-80, n (%)	255 (38.2)
Gender	N (% not missing)	667(100)
	Male, n (%)	366 (54.9)
	Female, n (%)	301 (45.1)
Insurance	N (% not missing)	667(100)
	Medical insurance, n (%)	586 (87.9)
	Medical aid, n (%)	79 (11.8)
	Veterans cover, n (%)	2 (0.3)
COMORBIDITIES		
	Measure	**Patients changing from DPI to pMDI**
COPD	N (% not missing)	667(100)
	No, n (%)	247 (37.0)
	Yes, n (%)	420 (63.0)
COPD (ever)	N (% not missing)	667(100)
	No, n (%)	170 (25.5)
	Yes, n (%)	497 (74.5)
Oral thrush	N (% not missing)	667(100)
	No, n (%)	659 (98.8)
	Yes, n (%)	8 (1.2)
Oral thrush (ever)	N (% not missing)	667(100)
	No, n (%)	653 (97.9)

	Measure	Patients changing from DPI to pMDI
	Yes, n (%)	14 (2.1)
Comorbid eczema	N (% not missing)	667(100)
	No, n (%)	638 (95.7)
	Yes, n (%)	29 (4.3)
Comorbid eczema (ever)	N (% not missing)	667(100)
	No, n (%)	601 (90.1)
	Yes, n (%)	66 (9.9)
Comorbid GERD	N (% not missing)	667(100)
	No, n (%)	470 (70.5)
	Yes, n (%)	197 (29.5)
Comorbid GERD (ever)	N (% not missing)	667(100)
	No, n (%)	367 (55.0)
	Yes, n (%)	300 (45.0)
Ischaemic heart disease	N (% not missing)	667(100)
	No, n (%)	613 (91.9)
	Yes, n (%)	54 (8.1)
Ischaemic heart disease (ever)	N (% not missing)	667(100)
	No, n (%)	584 (87.6)
	Yes, n (%)	83 (12.4)
Influenza	N (% not missing)	667(100)
	No, n (%)	654 (98.1)
	Yes, n (%)	13 (1.9)
Influenza (ever)	N (% not missing)	667(100)
	No, n (%)	645 (96.7)
	Yes, n (%)	22 (3.3)
Other chronic lung diseases	N (% not missing)	667(100)
	No, n (%)	407 (61.0)
	Yes, n (%)	260 (39.0)
Other chronic lung diseases (ever)	N (% not missing)	667(100)
	No, n (%)	292 (43.8)

	Measure	Patients changing from DPI to pMDI
	Yes, n (%)	375 (56.2)
Comorbid nasal polyps	N (% not missing)	667(100)
	No, n (%)	653 (97.9)
	Yes, n (%)	14 (2.1)
Comorbid nasal polyps (ever)	N (% not missing)	667(100)
	No, n (%)	640 (96.0)
	Yes, n (%)	27 (4.0)
Pneumonia	N (% not missing)	667(100)
	No, n (%)	606 (90.9)
	Yes, n (%)	61 (9.1)
Pneumonia (ever)	N (% not missing)	667(100)
	No, n (%)	562 (84.3)
	Yes, n (%)	105 (15.7)
Comorbid rhinitis (active)	N (% not missing)	667(100)
	No, n (%)	241 (36.1)
	Yes, n (%)	426 (63.9)
Comorbid rhinitis (ever)	N (% not missing)	667(100)
	No, n (%)	146 (21.9)
	Yes, n (%)	521 (78.1)
Charlson Comorbidity Index (CCI)	N (% not missing)	667 (100.0)
	Mean (SD)	1.4 (0.9)
	Median (IQR)	1 (1, 1)
	Min, Max	(0, 7)
Charlson Comorbidity Index (CCI) (categorised)	N (% not missing)	667(100)
	0-1, n (%)	531 (79.6)
	2-5, n (%)	133 (19.9)
	6-10 n (%)	3 (0.4)
DISEASE SEVERITY & HEALTHCARE UTILIZATION		
	Measure	**Patients changing from DPI to pMDI**
All inpatient admissions	N (% not missing)	667 (100.0)

	Measure	Patients changing from DPI to pMDI
	Mean (SD)	0.9 (1.8)
	Median (IQR)	0 (0, 1)
	Min, Max	(0, 24)
All inpatient admissions (categorised)	N (% not missing)	667(100)
	0, n (%)	414 (62.1)
	1, n (%)	125 (18.7)
	2, n (%)	68 (10.2)
	3, n (%)	29 (4.3)
	≥4, n (%)	31 (4.6)
All inpatient admissions days	N (% not missing)	667 (100.0)
	Mean (SD)	8.3 (23.8)
	Median (IQR)	0 (0, 7)
	Min, Max	(0, 312)
All inpatient admissions days (categorised)	N (% not missing)	667(100)
	1-3, n (%)	44 (17.4)
	4-6, n (%)	38 (15.0)
	7-13, n (%)	58 (22.9)
	≥14, n (%)	113 (44.7)
LRTI-related inpatient admissions	N (% not missing)	667 (100.0)
	Mean (SD)	0.3 (0.6)
	Median (IQR)	0 (0, 0)
	Min, Max	(0, 5)
LRTI-related inpatient admissions (categorised)	N (% not missing)	667(100)
	0, n (%)	543 (81.4)
	1, n (%)	93 (13.9)
	2, n (%)	22 (3.3)
	3, n (%)	5 (0.7)
	≥4, n (%)	4 (0.6)
LRTI-related inpatient admissions days	N (% not missing)	667 (100.0)
	Mean (SD)	3.0 (10.9)

	Measure	Patients changing from DPI to pMDI
	Median (IQR)	0 (0, 0)
	Min, Max	(0, 161)
LRTI-related inpatient admissions days (categorised)	N (% not missing)	667 (100)
	1-3, n (%)	14 (11.3)
	4-6, n (%)	22 (17.7)
	7-13, n (%)	43 (34.7)
	≥14, n (%)	45 (36.3)
Asthma-related inpatient admissions	N (% not missing)	667 (100.0)
	Mean (SD)	0.2 (0.7)
	Median (IQR)	0 (0, 0)
	Min, Max	(0, 5)
Asthma-related inpatient admissions (categorised)	N (% not missing)	667 (100)
	0, n (%)	567 (85.0)
	1, n (%)	72 (10.8)
	2, n (%)	18 (2.7)
	3, n (%)	4 (0.6)
	≥4, n (%)	6 (0.9)
Asthma-related inpatient admissions days	N (% not missing)	667 (100.0)
	Mean (SD)	2.1 (7.6)
	Median (IQR)	0 (0, 0)
	Min, Max	(0, 99)
Asthma-related inpatient admissions days (categorised)	N (% not missing)	667 (100)
	1-3, n (%)	13 (13.0)
	4-6, n (%)	20 (20.0)
	7-13, n (%)	35 (35.0)
	≥14, n (%)	32 (32.0)
Asthma exacerbation-related inpatient admissions	N (% not missing)	667 (100.0)
	Mean (SD)	0.1 (0.4)
	Median (IQR)	0 (0, 0)
	Min, Max	(0, 5)

	Measure	Patients changing from DPI to pMDI
Asthma exacerbation-related inpatient admissions (categorised)	N (% not missing)	667 (100)
	0, n (%)	629 (94.3)
	1, n (%)	26 (3.9)
	2, n (%)	8 (1.2)
	3, n (%)	2 (0.3)
	≥4, n (%)	2 (0.3)
Asthma exacerbation-related inpatient admissions days	N (% not missing)	667 (100.0)
	Mean (SD)	0.9 (5.3)
	Median (IQR)	0 (0, 0)
	Min, Max	(0, 78)
Asthma exacerbation-related inpatient admissions days (categorised)	N (% not missing)	667 (100)
	1-3, n (%)	8 (21.1)
	4-6, n (%)	5 (13.2)
	7-13, n (%)	11 (28.9)
	≥14, n (%)	14 (36.8)
All outpatient attendances	N (% not missing)	667 (100.0)
	Mean (SD)	33.7 (26.9)
	Median (IQR)	27 (16, 41)
	Min, Max	(2, 220)
All outpatient attendances (categorised)	N (% not missing)	667(100)
	1-12, n (%)	88 (13.2)
	13-24, n (%)	221 (33.1)
	25-36, n (%)	149 (22.3)
	37-48, n (%)	91 (13.6)
	≥48, n (%)	118 (17.7)
LRTI-related outpatient attendances	N (% not missing)	667 (100.0)
	Mean (SD)	28.9 (23.9)
	Median (IQR)	22 (14, 35)
	Min, Max	(2, 216)
	N (% not missing)	667 (100)

	Measure	Patients changing from DPI to pMDI
LRTI-related outpatient attendances (categorised)	1-12, n (%)	120 (18.0)
	13-24, n (%)	251 (37.6)
	25-36, n (%)	141 (21.1)
	37-48, n (%)	72 (10.8)
	≥48, n (%)	83 (12.4)
Asthma-related outpatient attendances	N (% not missing)	667 (100.0)
	Mean (SD)	7.3 (7.6)
	Median (IQR)	6 (3, 9)
	Min, Max	(0, 85)
Asthma-related outpatient attendances (categorised)	N (% not missing)	667 (100)
	0, n (%)	47 (7.0)
	1-3, n (%)	146 (21.9)
	4-6, n (%)	184 (27.6)
	7-9, n (%)	129 (19.3)
	10-12, n (%)	65 (9.7)
	≥13, n (%)	96 (14.4)
All emergency attendances	N (% not missing)	667 (100.0)
	Mean (SD)	0.4 (0.9)
	Median (IQR)	0 (0, 1)
	Min, Max	(0, 11)
All emergency attendances (categorised)	N (% not missing)	667 (100)
	0, n (%)	497 (74.5)
	1, n (%)	119 (17.8)
	2, n (%)	38 (5.7)
	3, n (%)	5 (0.7)
	≥4, n (%)	8 (1.2)
LRTI-related emergency attendances	N (% not missing)	667 (100.0)
	Mean (SD)	0.4 (0.8)
	Median (IQR)	0 (0, 1)
	Min, Max	(0, 9)

	Measure	Patients changing from DPI to pMDI
LRTI-related emergency attendances (categorised)	N (% not missing)	667 (100)
	0, n (%)	497 (74.5)
	1, n (%)	123 (18.4)
	2, n (%)	35 (5.2)
	3, n (%)	5 (0.7)
	≥4, n (%)	7 (1.0)
Asthma-related emergency attendances	N (% not missing)	667 (100.0)
	Mean (SD)	0.1 (0.4)
	Median (IQR)	0 (0, 0)
	Min, Max	(0, 4)
Asthma-related emergency attendances (categorised)	N (% not missing)	667 (100)
	0, n (%)	603 (90.4)
	1, n (%)	51 (7.6)
	2, n (%)	10 (1.5)
	3, n (%)	2 (0.3)
	≥4, n (%)	1 (0.1)
Antibiotics	N (% not missing)	667 (100.0)
	Mean (SD)	1.2 (2.1)
	Median (IQR)	0 (0, 2)
	Min, Max	(0, 15)
Antibiotics (categorised)	N (% not missing)	667 (100)
	0, n (%)	375 (56.2)
	1-3, n (%)	224 (33.6)
	4-6, n (%)	43 (6.4)
	7-9, n (%)	19 (2.8)
	10-12, n (%)	3 (0.4)
	≥13, n (%)	3 (0.4)
Acute OCS	N (% not missing)	667 (100.0)
	Mean (SD)	1.2 (2.4)
	Median (IQR)	0 (0, 1)

	Measure	Patients changing from DPI to pMDI
	Min, Max	(0, 18)
Acute OCS (categorised)	N (% not missing)	667 (100)
	0, n (%)	408 (61.2)
	1, n (%)	107 (16.0)
	2, n (%)	47 (7.0)
	3, n (%)	38 (5.7)
	≥4, n (%)	67 (10.0)
Non-acute OCS	N (% not missing)	667 (100.0)
	Mean (SD)	0.6 (1.2)
	Median (IQR)	0 (0, 1)
	Min, Max	(0, 9)
Non-acute OCS (categorised)	N (% not missing)	667 (100)
	0, n (%)	450 (67.5)
	1, n (%)	107 (16.0)
	2, n (%)	49 (7.3)
	3, n (%)	37 (5.5)
	≥4, n (%)	24 (3.6)
MEDICATION USE DURING BASELINE YEAR		
	Measure	**Patients changing from DPI to pMDI**
FDC ICS/LABA prescriptions	N (% not missing)	667 (100.0)
	Mean (SD)	4.7 (2.7)
	Median (IQR)	4 (3, 6)
	Min, Max	(2, 14)
FDC ICS/LABA prescriptions (categorised)	N (% not missing)	667 (100)
	2-3, n (%)	288 (43.2)
	≥4, n (%)	379 (56.8)
ICS only prescriptions	N (% not missing)	667 (100.0)
	Mean (SD)	0.5 (1.4)
	Median (IQR)	0 (0, 0)
	Min, Max	(0, 18)

	Measure	Patients changing from DPI to pMDI
ICS only prescriptions (yes/no)	N (% not missing)	667(100)
	No, n (%)	504 (75.6)
	Yes, n (%)	163 (24.4)
ICS only prescriptions (categorised)	N (% not missing)	667(100)
	0, n (%)	504 (75.6)
	1, n (%)	90 (13.5)
	2, n (%)	40 (6.0)
	3, n (%)	10 (1.5)
	≥4, n (%)	23 (3.4)
ICS average daily dose	N (% not missing)	667 (100.0)
	Mean (SD)	400.8 (279.3)
	Median (IQR)	328.8 (205.5, 498.1)
	Min, Max	(65.8, 2219.2)
ICS average daily dose (categorised)	N (% not missing)	667(100)
	>0-250, n (%)	243 (36.4)
	>250-500, n (%)	259 (38.8)
	>500, n (%)	165 (24.7)
IV/IM CS prescriptions	N (% not missing)	667 (100.0)
	Mean (SD)	2.3 (4.5)
	Median (IQR)	1 (0, 3)
	Min, Max	(0, 48)
IV/IM CS prescriptions (yes/no)	N (% not missing)	667 (100)
	No, n (%)	294 (44.1)
	Yes, n (%)	373 (55.9)
IV/IM CS prescriptions (categorised)	N (% not missing)	667 (100)
	0, n (%)	294 (44.1)
	1-3, n (%)	244 (36.6)
	4-8, n (%)	87 (13.0)
	9-13, n (%)	20 (3.0)
	≥13, n (%)	22 (3.3)

	Measure	Patients changing from DPI to pMDI
SABA prescriptions	N (% not missing)	667 (100.0)
	Mean (SD)	3.3 (6.5)
	Median (IQR)	1 (0, 3)
	Min, Max	(0, 64)
SABA prescriptions (yes/no)	N (% not missing)	667 (100)
	No, n (%)	245 (36.7)
	Yes, n (%)	422 (63.3)
SABA prescriptions (categorised)	N (% not missing)	667 (100)
	0, n (%)	245 (36.7)
	1-3, n (%)	260 (39.0)
	4-6, n (%)	65 (9.7)
	7-9, n (%)	34 (5.1)
	10-12, n (%)	26 (3.9)
	≥13, n (%)	37 (5.5)
SABA inhaler prescriptions	N (% not missing)	667 (100.0)
	Mean (SD)	1.8 (4.2)
	Median (IQR)	0 (0, 1)
	Min, Max	(0, 64)
SABA inhaler prescriptions (yes/no)	N (% not missing)	667 (100)
	No, n (%)	368 (55.2)
	Yes, n (%)	299 (44.8)
SABA inhaler prescriptions (categorised)	N (% not missing)	667 (100)
	0, n (%)	368 (55.2)
	1-3, n (%)	201 (30.1)
	4-6, n (%)	44 (6.6)
	7-9, n (%)	24 (3.6)
	10-12, n (%)	14 (2.1)
	≥13, n (%)	16 (2.4)
SABA inhaler average daily dose	N (% not missing)	667 (100.0)
	Mean (SD)	138.0 (405.5)

	Measure	Patients changing from DPI to pMDI
	Median (IQR)	0 (0, 110)
	Min, Max	(0, 6630)
SABA inhaler average daily dose (categorised)	N (% not missing)	667 (100)
	0, n (%)	368 (55.2)
	>0-200, n (%)	193 (28.9)
	>200-400, n (%)	43 (6.4)
	>400-800, n (%)	34 (5.1)
	≥800, n (%)	29 (4.3)
SABA nebuliser prescriptions	N (% not missing)	667 (100.0)
	Mean (SD)	1.0 (3.2)
	Median (IQR)	0 (0, 1)
	Min, Max	(0, 44)
SABA nebuliser prescriptions (yes/no)	N (% not missing)	667 (100)
	No, n (%)	427 (64.0)
	Yes, n (%)	240 (36.0)
SABA nebuliser prescriptions (categorised)	N (% not missing)	667 (100)
	0, n (%)	427 (64.0)
	1-3, n (%)	200 (30.0)
	4-6, n (%)	23 (3.4)
	7-9, n (%)	4 (0.6)
	10-12, n (%)	5 (0.7)
	≥13, n (%)	8 (1.2)
SABA oral prescriptions	N (% not missing)	667 (100.0)
	Mean (SD)	0.5 (2.0)
	Median (IQR)	0 (0, 0)
	Min, Max	(0, 24)
SABA oral prescriptions (yes/no)	N (% not missing)	667 (100)
	No, n (%)	579 (86.8)
	Yes, n (%)	88 (13.2)
	N (% not missing)	667 (100)

	Measure	Patients changing from DPI to pMDI
SABA oral prescriptions (categorised)	0, n (%)	579 (86.8)
	1-3, n (%)	66 (9.9)
	4-6, n (%)	10 (1.5)
	7-9, n (%)	5 (0.7)
	10-12, n (%)	4 (0.6)
	≥13, n (%)	3 (0.4)
FDC SABA/SAMA prescriptions (yes/no)	N (% not missing)	667 (100.0)
	Mean (SD)	0.0 (0.0)
	Median (IQR)	0 (0, 0)
	Min, Max	(0, 1)
SAMA prescriptions	N (% not missing)	667 (100.0)
	Mean (SD)	0.7 (2.8)
	Median (IQR)	0 (0, 0)
	Min, Max	(0, 44)
SAMA prescriptions (yes/no)	N (% not missing)	667 (100)
	No, n (%)	524 (78.6)
	Yes, n (%)	143 (21.4)
SAMA prescriptions (categorised)	N (% not missing)	667(100)
	0, n (%)	524 (78.6)
	1, n (%)	83 (12.4)
	2, n (%)	26 (3.9)
	3, n (%)	9 (1.3)
	≥4, n (%)	25 (3.7)
LAMA prescriptions	N (% not missing)	667 (100.0)
	Mean (SD)	1.5 (3.1)
	Median (IQR)	0 (0, 1)
	Min, Max	(0, 14)
LAMA prescriptions (yes/no)	N (% not missing)	667 (100)
	No, n (%)	498 (74.7)
	Yes, n (%)	169 (25.3)

	Measure	Patients changing from DPI to pMDI
LAMA prescriptions (categorised)	N (% not missing)	667 (100)
	0, n (%)	498 (74.7)
	1-2, n (%)	28 (4.2)
	3-4, n (%)	50 (7.5)
	≥5, n (%)	91 (13.6)
FDC LABA/LAMA prescriptions (yes/no)	N (% not missing)	667 (100)
	No, n (%)	667 (100.0)
LABA inhaler prescriptions	N (% not missing)	667 (100.0)
	Mean (SD)	0.1 (0.6)
	Median (IQR)	0 (0, 0)
	Min, Max	(0, 10)
LABA inhaler prescriptions (yes/no)	N (% not missing)	667 (100)
	No, n (%)	651 (97.6)
	Yes, n (%)	16 (2.4)
LABA inhaler prescriptions (categorised)	N (% not missing)	667 (100)
	0, n (%)	651 (97.6)
	1, n (%)	9 (1.3)
	2, n (%)	2 (0.3)
	3, n (%)	1 (0.1)
	≥4, n (%)	4 (0.6)
LABA oral prescriptions	N (% not missing)	667 (100.0)
	Mean (SD)	1.3 (3.2)
	Median (IQR)	0 (0, 1)
	Min, Max	(0, 34)
LABA oral prescriptions (yes/no)	N (% not missing)	667 (100)
	No, n (%)	463 (69.4)
	Yes, n (%)	204 (30.6)
LABA oral prescriptions (categorised)	N (% not missing)	667 (100)
	0, n (%)	463 (69.4)
	1-3, n (%)	126 (18.9)

	Measure	Patients changing from DPI to pMDI
	4-6, n (%)	37 (5.5)
	7-11, n (%)	26 (3.9)
	≥12, n (%)	15 (2.2)
LABA patch prescriptions	N (% not missing)	667 (100.0)
	Mean (SD)	0.3 (1.3)
	Median (IQR)	0 (0, 0)
	Min, Max	(0, 12)
LABA patch prescriptions (yes/no)	N (% not missing)	667 (100)
	No, n (%)	605 (90.7)
	Yes, n (%)	62 (9.3)
LABA patch prescriptions (categorised)	N (% not missing)	667(100)
	0, n (%)	605 (90.7)
	1-2, n (%)	38 (5.7)
	3-4, n (%)	9 (1.3)
	5-6, n (%)	4 (0.6)
	≥7, n (%)	11 (1.6)
LTRA prescriptions	N (% not missing)	667 (100.0)
	Mean (SD)	5.0 (5.5)
	Median (IQR)	4 (0, 8)
	Min, Max	(0, 58)
LTRA prescriptions (yes/no)	N (% not missing)	667 (100)
	No, n (%)	180 (27.0)
	Yes, n (%)	487 (73.0)
LTRA prescriptions (categorised)	N (% not missing)	667 (100)
	0, n (%)	180 (27.0)
	1-3, n (%)	132 (19.8)
	4-6, n (%)	153 (22.9)
	7-11, n (%)	119 (17.8)
	≥12, n (%)	83 (12.4)
	N (% not missing)	667 (100.0)

	Measure	Patients changing from DPI to pMDI
Theophylline or other methylxanthine prescriptions	Mean (SD)	4.6 (5.7)
	Median (IQR)	3 (0, 7)
	Min, Max	(0, 65)
Theophylline or other methylxanthine prescriptions (yes/no)	N (% not missing)	667 (100)
	No, n (%)	198 (29.7)
	Yes, n (%)	469 (70.3)
Theophylline or other methylxanthine prescriptions (categorised)	N (% not missing)	667 (100)
	0, n (%)	198 (29.7)
	1-3, n (%)	170 (25.5)
	4-6, n (%)	115 (17.2)
	7-11, n (%)	107 (16.0)
	≥12, n (%)	77 (11.5)
ASTHMA RELATED COST		
	Measure	**Patients changing from DPI to pMDI**
FDC ICS/LABA cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	331480.1 (216955.7)
	Min, Max	(86950, 3437952)
ICS only cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	6992.5 (24096.8)
	Min, Max	(0, 248624)
IV/IM CS cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	5056.9 (16060.6)
	Min, Max	(0, 186724)
SABA inhaler cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	10143.6 (29869.2)
	Min, Max	(0, 487378)
SABA oral cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	788.7 (10713.3)
	Median (IQR)	0 (0, 0)
	Min, Max	(0, 266640)

	Measure	Patients changing from DPI to pMDI
SABA nebuliser cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	2094.3 (11049.5)
	Min, Max	(0, 193129)
FDC SABA/SAMA cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	11.6 (298.6)
	Min, Max	(0, 7713)
SAMA cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	2525.8 (10455.3)
	Min, Max	(0, 174540)
LAMA cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	84249.3 (176232.2)
	Min, Max	(0, 811740)
LABA/LAMA cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	0.0 (0.0)
	Min, Max	(0, 0)
LABA inhaler cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	2511.6 (22363.8)
	Min, Max	(0, 388800)
LABA oral cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	5113.2 (19197.3)
	Min, Max	(0, 218400)
LABA patch cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	2294.2 (14596.3)
	Min, Max	(0, 205920)
LTRA cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	116117.7 (132790.5)
	Min, Max	(0, 554140)
Theophylline or other methylxanthine cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	23493.8 (34530.8)
	Min, Max	(0, 159642)

	Measure	Patients changing from DPI to pMDI
Acute OCS cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	1913.7 (9842.8)
	Min, Max	(0, 209562)
Non-acute OCS cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	399.7 (1768.2)
	Min, Max	(0, 36360)
Antibiotics cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	51814.0 (238078.8)
	Min, Max	(0, 5092382)
All inpatient admissions cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	1499861.0 (4097685.5)
	Min, Max	(0, 53905540)
LRTI-related inpatient admissions cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	581952.0 (2343977.4)
	Min, Max	(0, 43951550)
Asthma-related inpatient admissions cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	338353.1 (1104294.1)
	Min, Max	(0, 11255030)
Asthma exacerbation-related inpatient admissions cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	147886.4 (796022.2)
	Min, Max	(0, 11255030)
All outpatient attendances cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	969568.8 (1331032.1)
	Min, Max	(66520, 24875180)
LRTI-related outpatient attendances cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	969568.8 (1331032.1)
	Min, Max	(66520, 24875180)
Asthma-related outpatient attendances cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	177838.8 (185737.7)
	Min, Max	(0, 1662900)

	Measure	Patients changing from DPI to pMDI
All emergency attendances cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	572961.8 (2386341.7)
	Min, Max	(0, 42381850)
LRTI-related emergency attendances cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	572961.8 (2386341.7)
	Min, Max	(0, 42381850)
Asthma-related emergency attendances cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	142548.1 (701601.2)
	Min, Max	(0, 9598590)
All hospitalisation costs (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	3042391.5 (6501754.7)
	Min, Max	(66520, 97633700)
All asthma-related hospitalisation costs (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	1690417.0 (3115036.8)
	Min, Max	(66520, 43728160)
Drug costs (without ICS) (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	318297.8 (380091.2)
	Min, Max	(0, 5260946)
Drug costs (with ICS) (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	656770.4 (494364.0)
	Min, Max	(100040, 5584425)
Total costs (without ICS) (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	2008714.8 (3330415.6)
	Min, Max	(72455, 48989106)
Total costs (with ICS) (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	2347187.3 (3361235.4)
	Min, Max	(220157, 49312585)

Table A7: Detailed results outcome 2

	Measure	Baseline	Outcome	OR (95%CI)	p-value
Severe exacerbations (ATS/ERS)	N (% not missing)	667 (100.0)	667 (100.0)	1.561 (1.314, 1.856)†	<0.001†
	Mean (SD)	0.6 (0.8)	1.0 (2.3)		
	Median (IQR)	1 (0, 1)	0 (0, 1)		
	Min, Max	(0, 6)	(0, 39)		
Severe exacerbations (ATS/ERS) (categorised)	N (% not missing)	667 (100.0)	667 (100.0)	Data visualisation only	
	0, n (%)	316 (47.4)	389 (58.3)		
	1, n (%)	295 (44.2)	131 (19.6)		
	2, n (%)	42 (6.3)	70 (10.5)		
	3, n (%)	7 (1.0)	24 (3.6)		
	≥4, n (%)	7 (1.0)	53 (7.9)		
Acute respiratory event	N (% not missing)	667 (100.0)	667 (100.0)	1.308 (1.137, 1.504)†	<0.001†
	Mean (SD)	1.2 (1.5)	1.6 (2.6)		
	Median (IQR)	1 (0, 1)	1 (0, 2)		
	Min, Max	(0, 12)	(0, 39)		
Acute respiratory event (categorised)	N (% not missing)	667 (100.0)	667 (100.0)	Data visualisation only	
	0, n (%)	219 (32.8)	302 (45.3)		
	1, n (%)	291 (43.6)	144 (21.6)		
	2, n (%)	83 (12.4)	77 (11.5)		
	3, n (%)	24 (3.6)	47 (7.0)		
	≥4, n (%)	50 (7.5)	97 (14.5)		
Risk domain asthma control	N (% not missing)	667 (100.0)	667 (100.0)	1.112 (0.969, 1.275)Δ	0.131Δ
	No, n (%)	406 (60.9)	389 (58.3)		
	Yes, n (%)	261 (39.1)	278 (41.7)		
Overall asthma control	N (% not missing)	667 (100.0)	667 (100.0)	1.183 (1.022, 1.369)Δ	0.024Δ
	No, n (%)	435 (65.2)	409 (61.3)		
	Yes, n (%)	232 (34.8)	258 (38.7)		
Asthma exacerbation-related inpatient admissions	N (% not missing)	667 (100.0)	667 (100.0)	0.776 (0.422, 1.425)†	0.413†
	Mean (SD)	0.1 (0.4)	0.1 (0.5)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 5)	(0, 10)		

	Measure	Baseline	Outcome	OR (95%CI)	p-value
Asthma exacerbation-related inpatient admissions (categorised)	N (% not missing)	667 (100.0)	667 (100.0)	Data visualisation only	
	0, n (%)	629 (94.3)	640 (96.0)		
	1, n (%)	26 (3.9)	20 (3.0)		
	2, n (%)	8 (1.2)	4 (0.6)		
	3, n (%)	2 (0.3)	1 (0.1)		
	≥4, n (%)	2 (0.3)	2 (0.3)		
SABA inhaler average daily dose, µg (categorised)	N (% not missing)	667 (100.0)	667 (100.0)	0.505 (0.432, 0.589)‡	<0.001‡
	0, n (%)	368 (55.2)	480 (72.0)		
	>0-200, n (%)	193 (28.9)	113 (16.9)		
	>200-400, n (%)	43 (6.4)	32 (4.8)		
	>400-800, n (%)	34 (5.1)	28 (4.2)		
	>800, n (%)	29 (4.3)	14 (2.1)		
Oral thrush	N (% not missing)	667 (100.0)	667 (100.0)	0.352 (0.141, 0.881)Δ	0.026Δ
	No, n (%)	653 (97.9)	662 (99.3)		
	Yes, n (%)	14 (2.1)	5 (0.7)		
ICS average daily dose, µg (categorised)	N (% not missing)	667 (100.0)	667 (100.0)	1.008 (0.875, 1.161)‡	0.913‡
	>0-250, n (%)	243 (36.4)	257 (38.5)		
	>250-500, n (%)	259 (38.8)	226 (33.9)		
	>500, n (%)	165 (24.7)	184 (27.6)		
Treatment stability	N (% not missing)	N/A	667 (100.0)	N/A	N/A
	No, n (%)		394 (59.1)		
	Yes, n (%)		273 (40.9)		

Δ Conditional binary logistic regression (unadjusted); ‡ Conditional ordinal logistic regression (unadjusted); † Conditional Poisson regression (unadjusted); N/A – not applicable (no hypothesis testing conducted); All odds ratios have baseline as the reference category.

Table A8: Baseline characteristics outcome 3

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
Age at IPD (years)	N (% not missing)	1926 (100.0)	642 (100.0)	0.002	0.001
	Mean (SD)	58.6 (14.7)	58.6 (14.8)		
	Median (IQR)	61 (50, 71)	61 (50, 71)		
	Min, Max	(12, 80)	(12, 80)		
Age at IPD (years) (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.009	0.008
	12-18, n (%)	14 (0.7)	2 (0.3)		
	19-35, n (%)	155 (8.0)	55 (8.6)		
	36-65, n (%)	1012 (52.5)	335 (52.2)		
	66-80, n (%)	745 (38.7)	250 (38.9)		
Gender	N (% not missing)	1926 (100.0)	642 (100.0)	0.000	0.000
	Male, n (%)	1062 (55.1)	354 (55.1)		
	Female, n (%)	864 (44.9)	288 (44.9)		
Insurance	N (% not missing)	1926 (100.0)	642 (100.0)	0.076	0.004
	Medical insurance, n (%)	1678 (87.1)	565 (88.0)		
	Medical aid, n (%)	220 (11.4)	75 (11.7)		
	Veterans cover, n (%)	28 (1.5)	2 (0.3)		
COMORBIDITIES					
	Measure	**DPI Repeat Cohort**	**pMDI Change Cohort**	**SMD**	**RCC**
COPD	N (% not missing)	1926 (100.0)	642 (100.0)	0.000	0.000
	No, n (%)	717 (37.2)	239 (37.2)		
	Yes, n (%)	1209 (62.8)	403 (62.8)		
COPD (ever)	N (% not missing)	1926 (100.0)	642 (100.0)	0.143	0.005
	No, n (%)	629 (32.7)	168 (26.2)		
	Yes, n (%)	1297 (67.3)	474 (73.8)		
Oral thrush	N (% not missing)	1926 (100.0)	642 (100.0)	0.059	0.006
	No, n (%)	1913 (99.3)	634 (98.8)		
	Yes, n (%)	13 (0.7)	8 (1.2)		
Oral thrush (ever)	N (% not missing)	1926 (100.0)	642 (100.0)	0.111	0.009
	No, n (%)	1910 (99.2)	628 (97.8)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
	Yes, n (%)	16 (0.8)	14 (2.2)		
Comorbid eczema	N (% not missing)	1926 (100.0)	642 (100.0)	0.062	0.001
	No, n (%)	1816 (94.3)	614 (95.6)		
	Yes, n (%)	110 (5.7)	28 (4.4)		
Comorbid eczema (ever)	N (% not missing)	1926 (100.0)	642 (100.0)	0.060	0.004
	No, n (%)	1770 (91.9)	579 (90.2)		
	Yes, n (%)	156 (8.1)	63 (9.8)		
Comorbid GERD	N (% not missing)	1926 (100.0)	642 (100.0)	0.104	0.006
	No, n (%)	1459 (75.8)	457 (71.2)		
	Yes, n (%)	467 (24.2)	185 (28.8)		
Comorbid GERD (ever)	N (% not missing)	1926 (100.0)	642 (100.0)	0.264	0.008
	No, n (%)	1319 (68.5)	358 (55.8)		
	Yes, n (%)	607 (31.5)	284 (44.2)		
Ischaemic heart disease	N (% not missing)	1926 (100.0)	642 (100.0)	0.002	0.000
	No, n (%)	1774 (92.1)	591 (92.1)		
	Yes, n (%)	152 (7.9)	51 (7.9)		
Ischaemic heart disease (ever)	N (% not missing)	1926 (100.0)	642 (100.0)	0.098	0.003
	No, n (%)	1745 (90.6)	562 (87.5)		
	Yes, n (%)	181 (9.4)	80 (12.5)		
Influenza	N (% not missing)	1926 (100.0)	642 (100.0)	0.095	0.003
	No, n (%)	1909 (99.1)	629 (98.0)		
	Yes, n (%)	17 (0.9)	13 (2.0)		
Influenza (ever)	N (% not missing)	1926 (100.0)	642 (100.0)	0.101	0.004
	No, n (%)	1891 (98.2)	620 (96.6)		
	Yes, n (%)	35 (1.8)	22 (3.4)		
Other chronic lung diseases	N (% not missing)	1926 (100.0)	642 (100.0)	0.024	0.001
	No, n (%)	1210 (62.8)	396 (61.7)		
	Yes, n (%)	716 (37.2)	246 (38.3)		
Other chronic lung diseases (ever)	N (% not missing)	1926 (100.0)	642 (100.0)	0.215	0.010
	No, n (%)	1064 (55.2)	286 (44.5)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
	Yes, n (%)	862 (44.8)	356 (55.5)		
Comorbid nasal polyps	N (% not missing)	1926 (100.0)	642 (100.0)	0.004	0.000
	No, n (%)	1888 (98.0)	629 (98.0)		
	Yes, n (%)	38 (2.0)	13 (2.0)		
Comorbid nasal polyps (ever)	N (% not missing)	1926 (100.0)	642 (100.0)	0.073	0.002
	No, n (%)	1876 (97.4)	617 (96.1)		
	Yes, n (%)	50 (2.6)	25 (3.9)		
Pneumonia	N (% not missing)	1926 (100.0)	642 (100.0)	0.027	0.005
	No, n (%)	1674 (86.9)	552 (86.0)		
	Yes, n (%)	252 (13.1)	90 (14.0)		
Pneumonia (ever)	N (% not missing)	1926 (100.0)	642 (100.0)	0.096	0.016
	No, n (%)	1591 (82.6)	506 (78.8)		
	Yes, n (%)	335 (17.4)	136 (21.2)		
Comorbid rhinitis (active)	N (% not missing)	1926 (100.0)	642 (100.0)	0.133	0.000
	No, n (%)	821 (42.6)	232 (36.1)		
	Yes, n (%)	1105 (57.4)	410 (63.9)		
Comorbid rhinitis (ever)	N (% not missing)	1926 (100.0)	642 (100.0)	0.315	0.010
	No, n (%)	702 (36.4)	143 (22.3)		
	Yes, n (%)	1224 (63.6)	499 (77.7)		
Charlson Comorbidity Index (CCI)	N (% not missing)	1926 (100.0)	642 (100.0)	0.018	0.003
	Mean (SD)	1.4 (0.9)	1.4 (0.9)		
	Median (IQR)	1 (1, 1)	1 (1, 1)		
	Min, Max	(0, 7)	(0, 6)		
Charlson Comorbidity Index (CCI) (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.024	0.003
	0-1, n (%)	1546 (80.3)	508 (79.1)		
	2-5, n (%)	371 (19.3)	132 (20.6)		
	6-10 n (%)	9 (0.5)	2 (0.3)		
DISEASE SEVERITY & HEALTHCARE UTILIZATION					
	Measure	**DPI Repeat Cohort**	**pMDI Change Cohort**	**SMD**	**RCC**
	N (% not missing)	1926 (100.0)	642 (100.0)	0.075	0.006

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
All inpatient admissions	Mean (SD)	0.7 (1.5)	0.8 (1.7)		
	Median (IQR)	0 (0, 1)	0 (0, 1)		
	Min, Max	(0, 24)	(0, 24)		
All inpatient admissions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.087	0.008
	0, n (%)	1308 (67.9)	402 (62.6)		
	1, n (%)	332 (17.2)	122 (19.0)		
	2, n (%)	149 (7.7)	65 (10.1)		
	3, n (%)	46 (2.4)	27 (4.2)		
	≥4, n (%)	91 (4.7)	26 (4.0)		
All inpatient admissions days	N (% not missing)	1926 (100.0)	642 (100.0)	0.073	0.002
	Mean (SD)	5.9 (19.9)	7.4 (21.6)		
	Median (IQR)	0 (0, 4)	0 (0, 6)		
	Min, Max	(0, 380)	(0, 312)		
All inpatient admissions days (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	Data visualisation only	
	0, n (%)	1308 (67.9)	402 (62.6)		
	1-3, n (%)	112 (5.8)	43 (6.7)		
	4-6, n (%)	108 (5.6)	38 (5.9)		
	7-13, n (%)	182 (9.4)	56 (8.7)		
	≥14, n (%)	216 (11.2)	103 (16.0)		
LRTI-related inpatient admissions	N (% not missing)	1926 (100.0)	642 (100.0)	0.031	0.005
	Mean (SD)	0.2 (0.6)	0.2 (0.6)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 5)	(0, 5)		
LRTI-related inpatient admissions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.033	0.005
	0, n (%)	1609 (83.5)	527 (82.1)		
	1, n (%)	246 (12.8)	88 (13.7)		
	2, n (%)	48 (2.5)	21 (3.3)		
	3, n (%)	17 (0.9)	3 (0.5)		
	≥4, n (%)	6 (0.3)	3 (0.5)		
	N (% not missing)	1926 (100.0)	642 (100.0)	0.049	0.002

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
LRTI-related inpatient admissions days	Mean (SD)	2.3 (9.9)	2.8 (10.5)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 295)	(0, 161)		
LRTI-related inpatient admissions days (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	Data visualisation only	
	0, n (%)	1609 (83.5)	527 (82.1)		
	1-3, n (%)	30 (1.6)	12 (1.9)		
	4-6, n (%)	67 (3.5)	22 (3.4)		
	7-13, n (%)	123 (6.4)	40 (6.2)		
	≥14, n (%)	97 (5.0)	41 (6.4)		
Asthma-related inpatient admissions	N (% not missing)	1926 (100.0)	642 (100.0)	0.070	0.006
	Mean (SD)	0.2 (0.5)	0.2 (0.6)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 10)	(0, 5)		
Asthma-related inpatient admissions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.070	0.000
	0, n (%)	1685 (87.5)	549 (85.5)		
	1, n (%)	190 (9.9)	69 (10.7)		
	2, n (%)	37 (1.9)	18 (2.8)		
	3, n (%)	9 (0.5)	2 (0.3)		
	≥4, n (%)	5 (0.3)	4 (0.6)		
Asthma-related inpatient admissions days	N (% not missing)	1926 (100.0)	642 (100.0)	0.050	0.001
	Mean (SD)	1.5 (8.3)	1.9 (6.9)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 295)	(0, 99)		
Asthma-related inpatient admissions days (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	Data visualisation only	
	0, n (%)	1685 (87.5)	549 (85.5)		
	1-3, n (%)	27 (1.4)	12 (1.9)		
	4-6, n (%)	64 (3.3)	19 (3.0)		
	7-13, n (%)	95 (4.9)	34 (5.3)		
	≥14, n (%)	55 (2.9)	28 (4.4)		
	N (% not missing)	1926 (100.0)	642 (100.0)	0.068	0.009

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
Asthma exacerbation-related inpatient admissions	Mean (SD)	0.1 (0.3)	0.1 (0.4)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 4)	(0, 5)		
Asthma exacerbation-related inpatient admissions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.065	0.006
	0, n (%)	1849 (96.0)	608 (94.7)		
	1, n (%)	58 (3.0)	24 (3.7)		
	2, n (%)	16 (0.8)	8 (1.2)		
	3, n (%)	1 (0.1)	1 (0.2)		
	≥4, n (%)	2 (0.1)	1 (0.2)		
Asthma exacerbation-related inpatient admissions days	N (% not missing)	1926 (100.0)	642 (100.0)	0.058	0.006
	Mean (SD)	0.5 (3.3)	0.7 (4.3)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 65)	(0, 65)		
Asthma exacerbation-related inpatient admissions days (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	Data visualisation only	
	0, n (%)	1849 (96.0)	608 (94.7)		
	1-3, n (%)	5 (0.3)	8 (1.2)		
	4-6, n (%)	15 (0.8)	4 (0.6)		
	7-13, n (%)	39 (2.0)	10 (1.6)		
	≥14, n (%)	18 (0.9)	12 (1.9)		
All outpatient attendances	N (% not missing)	1926 (100.0)	642 (100.0)	0.086	0.017
	Mean (SD)	31.3 (25.2)	33.6 (27.1)		
	Median (IQR)	25 (15, 39)	27 (16, 41)		
	Min, Max	(2, 278)	(2, 220)		
All outpatient attendances (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.080	0.023
	1-12, n (%)	327 (17.0)	88 (13.7)		
	13-24, n (%)	630 (32.7)	210 (32.7)		
	25-36, n (%)	429 (22.3)	146 (22.7)		
	37-48, n (%)	226 (11.7)	86 (13.4)		
	≥48, n (%)	314 (16.3)	112 (17.4)		
	N (% not missing)	1926 (100.0)	642 (100.0)	0.092	0.020

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
LRTI-related outpatient attendances	Mean (SD)	26.8 (21.9)	28.9 (24.1)		
	Median (IQR)	21 (13, 33)	22 (14, 35)		
	Min, Max	(1, 275)	(2, 216)		
LRTI-related outpatient attendances (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.089	0.016
	1-12, n (%)	419 (21.8)	119 (18.5)		
	13-24, n (%)	722 (37.5)	239 (37.2)		
	25-36, n (%)	397 (20.6)	136 (21.2)		
	37-48, n (%)	180 (9.3)	69 (10.7)		
	≥48, n (%)	208 (10.8)	79 (12.3)		
Asthma-related outpatient attendances	N (% not missing)	1926 (100.0)	642 (100.0)	0.029	0.008
	Mean (SD)	7.4 (6.9)	7.2 (7.2)		
	Median (IQR)	6 (3, 10)	6 (3, 9)		
	Min, Max	(0, 62)	(0, 85)		
Asthma-related outpatient attendances (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.031	0.014
	0, n (%)	137 (7.1)	45 (7.0)		
	1-3, n (%)	416 (21.6)	142 (22.1)		
	4-6, n (%)	546 (28.3)	176 (27.4)		
	7-9, n (%)	319 (16.6)	126 (19.6)		
	10-12, n (%)	192 (10.0)	62 (9.7)		
	≥13, n (%)	316 (16.4)	91 (14.2)		
All emergency attendances	N (% not missing)	1926 (100.0)	642 (100.0)	0.012	0.001
	Mean (SD)	0.3 (0.8)	0.4 (0.9)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 13)	(0, 11)		
All emergency attendances (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.001	0.010
	0, n (%)	1493 (77.5)	486 (75.7)		
	1, n (%)	299 (15.5)	114 (17.8)		
	2, n (%)	89 (4.6)	32 (5.0)		
	3, n (%)	17 (0.9)	4 (0.6)		
	≥4, n (%)	28 (1.5)	6 (0.9)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
LRTI-related emergency attendances	N (% not missing)	1926 (100.0)	642 (100.0)	0.018	0.000
	Mean (SD)	0.3 (0.8)	0.3 (0.8)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 12)	(0, 9)		
LRTI-related emergency attendances (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.007	0.009
	0, n (%)	1493 (77.5)	486 (75.7)		
	1, n (%)	315 (16.4)	118 (18.4)		
	2, n (%)	76 (3.9)	29 (4.5)		
	3, n (%)	20 (1.0)	4 (0.6)		
	≥4, n (%)	22 (1.1)	5 (0.8)		
Asthma-related emergency attendances	N (% not missing)	1926 (100.0)	642 (100.0)	0.033	0.002
	Mean (SD)	0.1 (0.4)	0.1 (0.4)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 4)	(0, 4)		
Asthma-related emergency attendances (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.033	0.002
	0, n (%)	1770 (91.9)	585 (91.1)		
	1, n (%)	132 (6.9)	47 (7.3)		
	2, n (%)	17 (0.9)	7 (1.1)		
	3, n (%)	5 (0.3)	2 (0.3)		
	≥4, n (%)	2 (0.1)	1 (0.2)		
Antibiotics	N (% not missing)	1926 (100.0)	642 (100.0)	0.117	0.028
	Mean (SD)	0.9 (1.9)	1.2 (2.1)		
	Median (IQR)	0 (0, 1)	0 (0, 1)		
	Min, Max	(0, 29)	(0, 15)		
Antibiotics (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.125	0.033
	0, n (%)	1190 (61.8)	366 (57.0)		
	1-3, n (%)	600 (31.2)	210 (32.7)		
	4-6, n (%)	99 (5.1)	42 (6.5)		
	7-9, n (%)	18 (0.9)	18 (2.8)		
	10-12, n (%)	12 (0.6)	3 (0.5)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
	≥13, n (%)	7 (0.4)	3 (0.5)		
Acute OCS	N (% not missing)	1926 (100.0)	642 (100.0)	0.030	0.015
	Mean (SD)	1.1 (2.3)	1.2 (2.4)		
	Median (IQR)	0 (0, 1)	0 (0, 1)		
	Min, Max	(0, 25)	(0, 18)		
Acute OCS (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.007	0.001
	0, n (%)	1189 (61.7)	394 (61.4)		
	1, n (%)	297 (15.4)	103 (16.0)		
	2, n (%)	155 (8.0)	46 (7.2)		
	3, n (%)	97 (5.0)	35 (5.5)		
	≥4, n (%)	188 (9.8)	64 (10.0)		
Non-acute OCS	N (% not missing)	1926 (100.0)	642 (100.0)	0.086	0.021
	Mean (SD)	0.7 (1.4)	0.6 (1.2)		
	Median (IQR)	0 (0, 1)	0 (0, 1)		
	Min, Max	(0, 21)	(0, 9)		
Non-acute OCS (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.090	0.029
	0, n (%)	1251 (65.0)	435 (67.8)		
	1, n (%)	306 (15.9)	104 (16.2)		
	2, n (%)	150 (7.8)	45 (7.0)		
	3, n (%)	115 (6.0)	35 (5.5)		
	≥4, n (%)	104 (5.4)	23 (3.6)		
MEDICATION USE DURING BASELINE YEAR					
	Measure	**DPI Repeat Cohort**	**pMDI Change Cohort**	**SMD**	**RCC**
FDC ICS/LABA prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)	0.035	0.003
	Mean (SD)	4.8 (2.9)	4.7 (2.7)		
	Median (IQR)	4 (2, 6)	4 (3, 6)		
	Min, Max	(2, 21)	(2, 14)		
FDC ICS/LABA prescriptions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.005	0.000
	2-3, n (%)	829 (43.0)	278 (43.3)		
	≥4, n (%)	1097 (57.0)	364 (56.7)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
ICS only prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)	0.036	0.006
	Mean (SD)	0.6 (2.0)	0.5 (1.2)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 47)	(0, 10)		
ICS only prescriptions (yes/no)	N (% not missing)	1926 (100.0)	642 (100.0)	0.109	0.008
	No, n (%)	1548 (80.4)	487 (75.9)		
	Yes, n (%)	378 (19.6)	155 (24.1)		
ICS only prescriptions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.029	0.001
	0, n (%)	1548 (80.4)	487 (75.9)		
	1, n (%)	187 (9.7)	87 (13.6)		
	2, n (%)	74 (3.8)	38 (5.9)		
	3, n (%)	37 (1.9)	10 (1.6)		
	≥4, n (%)	80 (4.2)	20 (3.1)		
ICS average daily dose	N (% not missing)	1926 (100.0)	642 (100.0)	0.049	0.004
	Mean (SD)	383.2 (274.2)	396.7 (279.5)		
	Median (IQR)	328.8 (164.4, 493.2)	320.1 (198.9, 493.2)		
	Min, Max	(26.3, 2137.0)	(65.8, 2219.2)		
ICS average daily dose (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.000	0.000
	>0-250, n (%)	720 (37.4)	240 (37.4)		
	>250-500, n (%)	741 (38.5)	247 (38.5)		
	>500, n (%)	465 (24.1)	155 (24.1)		
IV/IM CS prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)	0.068	0.009
	Mean (SD)	2.0 (4.1)	2.3 (4.5)		
	Median (IQR)	1 (0, 2)	1 (0, 3)		
	Min, Max	(0, 73)	(0, 48)		
IV/IM CS prescriptions (yes/no)	N (% not missing)	1926 (100.0)	642 (100.0)	0.071	0.003
	No, n (%)	917 (47.6)	283 (44.1)		
	Yes, n (%)	1009 (52.4)	359 (55.9)		
	N (% not missing)	1926 (100.0)	642 (100.0)	0.082	0.014
	0, n (%)	917 (47.6)	283 (44.1)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
IV/IM CS prescriptions (categorised)	1-3, n (%)	682 (35.4)	237 (36.9)		
	4-8, n (%)	232 (12.0)	82 (12.8)		
	9-13, n (%)	51 (2.6)	19 (3.0)		
	≥13, n (%)	44 (2.3)	21 (3.3)		
SABA prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)	0.005	0.004
	Mean (SD)	3.1 (5.9)	3.0 (6.0)		
	Median (IQR)	1 (0, 4)	1 (0, 3)		
	Min, Max	(0, 93)	(0, 61)		
SABA prescriptions (yes/no)	N (% not missing)	1926 (100.0)	642 (100.0)	0.052	0.001
	No, n (%)	769 (39.9)	240 (37.4)		
	Yes, n (%)	1157 (60.1)	402 (62.6)		
SABA prescriptions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.015	0.018
	0, n (%)	769 (39.9)	240 (37.4)		
	1-3, n (%)	660 (34.3)	255 (39.7)		
	4-6, n (%)	219 (11.4)	61 (9.5)		
	7-9, n (%)	108 (5.6)	31 (4.8)		
	10-12, n (%)	71 (3.7)	24 (3.7)		
	≥13, n (%)	99 (5.1)	31 (4.8)		
SABA inhaler prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)	0.009	0.000
	Mean (SD)	1.5 (3.3)	1.6 (3.3)		
	Median (IQR)	0 (0, 2)	0 (0, 1)		
	Min, Max	(0, 49)	(0, 28)		
SABA inhaler prescriptions (yes/no)	N (% not missing)	1926 (100.0)	642 (100.0)	0.000	0.000
	No, n (%)	1086 (56.4)	362 (56.4)		
	Yes, n (%)	840 (43.6)	280 (43.6)		
SABA inhaler prescriptions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.016	0.000
	0, n (%)	1086 (56.4)	362 (56.4)		
	1-3, n (%)	597 (31.0)	192 (29.9)		
	4-6, n (%)	111 (5.8)	43 (6.7)		
	7-9, n (%)	59 (3.1)	20 (3.1)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
	10-12, n (%)	41 (2.1)	12 (1.9)		
	≥13, n (%)	32 (1.7)	13 (2.0)		
SABA inhaler average daily dose	N (% not missing)	1926 (100.0)	642 (100.0)	0.013	0.000
	Mean (SD)	121.1 (323.4)	116.9 (300.4)		
	Median (IQR)	0 (0, 110)	0 (0, 55)		
	Min, Max	(0, 5534)	(0, 3123)		
SABA inhaler average daily dose (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.000	0.000
	0, n (%)	1086 (56.4)	362 (56.4)		
	>0-200, n (%)	561 (29.1)	187 (29.1)		
	>200-400, n (%)	117 (6.1)	39 (6.1)		
	>400-800, n (%)	96 (5.0)	32 (5.0)		
	≥800, n (%)	66 (3.4)	22 (3.4)		
SABA nebuliser prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)	0.019	0.000
	Mean (SD)	0.9 (3.7)	1.0 (3.2)		
	Median (IQR)	0 (0, 1)	0 (0, 1)		
	Min, Max	(0, 92)	(0, 44)		
SABA nebuliser prescriptions (yes/no)	N (% not missing)	1926 (100.0)	642 (100.0)	0.121	0.012
	No, n (%)	1354 (70.3)	415 (64.6)		
	Yes, n (%)	572 (29.7)	227 (35.4)		
SABA nebuliser prescriptions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.074	0.004
	0, n (%)	1354 (70.3)	415 (64.6)		
	1-3, n (%)	458 (23.8)	190 (29.6)		
	4-6, n (%)	59 (3.1)	20 (3.1)		
	7-9, n (%)	26 (1.3)	4 (0.6)		
	10-12, n (%)	9 (0.5)	5 (0.8)		
	≥13, n (%)	20 (1.0)	8 (1.2)		
SABA oral prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)	0.054	0.010
	Mean (SD)	0.6 (2.6)	0.5 (2.1)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 46)	(0, 24)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
SABA oral prescriptions (yes/no)	N (% not missing)	1926 (100.0)	642 (100.0)	0.015	0.001
	No, n (%)	1670 (86.7)	560 (87.2)		
	Yes, n (%)	256 (13.3)	82 (12.8)		
SABA oral prescriptions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.057	0.012
	0, n (%)	1670 (86.7)	560 (87.2)		
	1-3, n (%)	154 (8.0)	61 (9.5)		
	4-6, n (%)	57 (3.0)	9 (1.4)		
	7-9, n (%)	15 (0.8)	5 (0.8)		
	10-12, n (%)	12 (0.6)	4 (0.6)		
	≥13, n (%)	18 (0.9)	3 (0.5)		
FDC SABA/SAMA prescriptions (yes/no)	N (% not missing)	1926 (100.0)	642 (100.0)	0.014	0.001
	Mean (SD)	0.0 (0.0)	0.0 (0.0)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 1)	(0, 1)		
SAMA prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)	0.118	0.006
	Mean (SD)	0.3 (2.0)	0.6 (2.7)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 72)	(0, 44)		
SAMA prescriptions (yes/no)	N (% not missing)	1926 (100.0)	642 (100.0)	0.103	0.009
	No, n (%)	1604 (83.3)	509 (79.3)		
	Yes, n (%)	322 (16.7)	133 (20.7)		
SAMA prescriptions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.148	0.028
	0, n (%)	1604 (83.3)	509 (79.3)		
	1, n (%)	221 (11.5)	80 (12.5)		
	2, n (%)	57 (3.0)	22 (3.4)		
	3, n (%)	20 (1.0)	9 (1.4)		
	≥4, n (%)	24 (1.2)	22 (3.4)		
LAMA prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)	0.028	0.007
	Mean (SD)	1.4 (3.0)	1.5 (3.1)		
	Median (IQR)	0 (0, 0)	0 (0, 1)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
	Min, Max	(0, 15)	(0, 14)		
LAMA prescriptions (yes/no)	N (% not missing)	1926 (100.0)	642 (100.0)	0.045	0.007
	No, n (%)	1477 (76.7)	480 (74.8)		
	Yes, n (%)	449 (23.3)	162 (25.2)		
LAMA prescriptions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.013	0.009
	0, n (%)	1477 (76.7)	480 (74.8)		
	1-2, n (%)	56 (2.9)	24 (3.7)		
	3-4, n (%)	99 (5.1)	50 (7.8)		
	≥5, n (%)	294 (15.3)	88 (13.7)		
LABA inhaler prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)	0.147	0.003
	Mean (SD)	0.0 (0.1)	0.1 (0.6)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 3)	(0, 10)		
LABA inhaler prescriptions (yes/no)	N (% not missing)	1926 (100.0)	642 (100.0)	0.186	0.013
	No, n (%)	1920 (99.7)	626 (97.5)		
	Yes, n (%)	6 (0.3)	16 (2.5)		
LABA inhaler prescriptions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.164	0.010
	0, n (%)	1920 (99.7)	626 (97.5)		
	1, n (%)	3 (0.2)	9 (1.4)		
	2, n (%)	2 (0.1)	2 (0.3)		
	3, n (%)	1 (0.1)	1 (0.2)		
	≥4, n (%)	0 (0.0)	4 (0.6)		
LABA oral prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)	0.071	0.003
	Mean (SD)	1.6 (3.9)	1.3 (3.2)		
	Median (IQR)	0 (0, 1)	0 (0, 1)		
	Min, Max	(0, 41)	(0, 34)		
LABA oral prescriptions (yes/no)	N (% not missing)	1926 (100.0)	642 (100.0)	0.003	0.001
	No, n (%)	1350 (70.1)	449 (69.9)		
	Yes, n (%)	576 (29.9)	193 (30.1)		
	N (% not missing)	1926 (100.0)	642 (100.0)	0.051	0.002

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
LABA oral prescriptions (categorised)	0, n (%)	1350 (70.1)	449 (69.9)		
	1-3, n (%)	316 (16.4)	117 (18.2)		
	4-6, n (%)	100 (5.2)	35 (5.5)		
	7-11, n (%)	83 (4.3)	26 (4.0)		
	≥12, n (%)	77 (4.0)	15 (2.3)		
LABA patch prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)	0.005	0.004
	Mean (SD)	0.3 (1.4)	0.3 (1.3)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 20)	(0, 12)		
LABA patch prescriptions (yes/no)	N (% not missing)	1926 (100.0)	642 (100.0)	0.062	0.008
	No, n (%)	1782 (92.5)	583 (90.8)		
	Yes, n (%)	144 (7.5)	59 (9.2)		
LABA patch prescriptions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.029	0.002
	0, n (%)	1782 (92.5)	583 (90.8)		
	1-2, n (%)	74 (3.8)	37 (5.8)		
	3-4, n (%)	31 (1.6)	9 (1.4)		
	5-6, n (%)	14 (0.7)	3 (0.5)		
	≥7, n (%)	25 (1.3)	10 (1.6)		
LTRA prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)	0.246	0.030
	Mean (SD)	3.7 (4.8)	4.9 (5.5)		
	Median (IQR)	2 (0, 6)	4 (0, 7)		
	Min, Max	(0, 42)	(0, 58)		
LTRA prescriptions (yes/no)	N (% not missing)	1926 (100.0)	642 (100.0)	0.276	0.020
	No, n (%)	781 (40.6)	177 (27.6)		
	Yes, n (%)	1145 (59.4)	465 (72.4)		
LTRA prescriptions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.279	0.026
	0, n (%)	781 (40.6)	177 (27.6)		
	1-3, n (%)	387 (20.1)	129 (20.1)		
	4-6, n (%)	330 (17.1)	146 (22.7)		
	7-11, n (%)	273 (14.2)	110 (17.1)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
	≥12, n (%)	155 (8.0)	80 (12.5)		
Theophylline or other methylxanthines prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)	0.033	0.008
	Mean (SD)	4.8 (6.6)	4.6 (5.8)		
	Median (IQR)	3 (0, 7)	3 (0, 7)		
	Min, Max	(0, 90)	(0, 65)		
Theophylline or other methylxanthines prescriptions (yes/no)	N (% not missing)	1926 (100.0)	642 (100.0)	0.089	0.001
	No, n (%)	656 (34.1)	192 (29.9)		
	Yes, n (%)	1270 (65.9)	450 (70.1)		
Theophylline or other methylxanthines prescriptions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.015	0.014
	0, n (%)	656 (34.1)	192 (29.9)		
	1-3, n (%)	418 (21.7)	163 (25.4)		
	4-6, n (%)	289 (15.0)	112 (17.4)		
	7-11, n (%)	326 (16.9)	100 (15.6)		
	≥12, n (%)	237 (12.3)	75 (11.7)		
ASTHMA RELATED COST DURING BASELINE YEAR					
	Measure	**DPI Repeat Cohort**	**pMDI Change Cohort**	**SMD**	**RCC**
FDC ICS/LABA cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.219	0.017
	Mean (SD)	378887.3 (221267.5)	330670.1 (218664.9)		
	Min, Max	(74658, 2176464)	(86950, 3437952)		
ICS only cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.074	0.003
	Mean (SD)	5164.1 (23375.5)	6897.6 (23787.3)		
	Min, Max	(0, 461849)	(0, 248624)		
IV/IM CS cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.059	0.015
	Mean (SD)	3835.5 (15215.2)	4727.7 (15076.6)		
	Min, Max	(0, 283017)	(0, 186724)		
SABA inhaler cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.019	0.000
	Mean (SD)	9065.6 (24145.6)	8627.7 (22334.5)		
	Min, Max	(0, 420527)	(0, 237234)		
	N (% not missing)	1926 (100.0)	642 (100.0)	0.056	0.003

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
SABA oral cost (KRW)	Mean (SD)	1487.2 (13168.9)	810.4 (10918.9)		
	Min, Max	(0, 283416)	(0, 266640)		
SABA nebuliser cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	1710.1 (10353.8)	2050.9 (11228.2)	0.032	0.006
	Min, Max	(0, 231609)	(0, 193129)		
FDC SABA/SAMA cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	14.0 (456.9)	12.0 (304.4)	0.005	0.001
	Min, Max	(0, 17938)	(0, 7713)		
SAMA cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	2117.0 (12398.2)	2385.9 (10210.0)	0.024	0.006
	Min, Max	(0, 346740)	(0, 174540)		
LAMA cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	95415.5 (203721.7)	85281.5 (177227.7)	0.053	0.001
	Min, Max	(0, 1721882)	(0, 811740)		
LABA inhaler cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	201.9 (3957.9)	2609.4 (22790.2)	0.147	0.003
	Min, Max	(0, 116640)	(0, 388800)		
LABA oral cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	7755.1 (27824.8)	5250.0 (19544.9)	0.104	0.001
	Min, Max	(0, 374820)	(0, 218400)		
LABA patch cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	2803.6 (22785.6)	2210.1 (14601.6)	0.031	0.003
	Min, Max	(0, 473287)	(0, 205920)		
LTRA cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	122012.9 (180989.6)	114401.3 (131995.2)	0.048	0.003
	Min, Max	(0, 1245896)	(0, 554140)		
Theophylline or other methylxanthine cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	29165.5 (45331.9)	23698.4 (34812.1)	0.135	0.017
	Min, Max	(0, 400303)	(0, 159642)		
	N (% not missing)	1926 (100.0)	642 (100.0)	0.007	0.008

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
Acute OCS cost (KRW)	Mean (SD)	2021.7 (10166.0)	1950.9 (10021.4)		
	Min, Max	(0, 278100)	(0, 209562)		
Non-acute OCS cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	608.6 (5436.9)	395.4 (1789.0)	0.053	0.006
	Min, Max	(0, 225408)	(0, 36360)		
Antibiotics cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	44220.0 (162117.4)	50776.9 (240245.1)	0.032	0.003
	Min, Max	(0, 2388553)	(0, 5092382)		
All inpatient admissions cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	1080756.8 (2981392.0	1413734.3 (4009021.2	0.094	0.000
	Min, Max	(0, 42545150)	(0, 53905540)		
LRTI-related inpatient admissions cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	400329.1 (1384010.9)	556818.8 (2333827.1)	0.082	0.008
	Min, Max	(0, 17986500)	(0, 43951550)		
Asthma-related inpatient admissions cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	231313.7 (894824.1)	310212.2 (999326.8)	0.083	0.009
	Min, Max	(0, 17986500)	(0, 9598590)		
Asthma exacerbation-related inpatient admissions cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	80620.4 (525353.4)	126415.0 (662497.1)	0.077	0.011
	Min, Max	(0, 9824000)	(0, 6845720)		
All outpatient attendances cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	849514.9 (1323000.9)	948336.6 (1314429.2)	0.075	0.006
	Min, Max	(34630, 24945790)	(66520, 24875180)		
LRTI-related outpatient attendances cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	849514.9 (1323000.9)	948336.6 (1314429.2)	0.075	0.006
	Min, Max	(34630, 24945790)	(66520, 24875180)		
Asthma-related outpatient attendances cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	161057.6 (203547.9)	173403.4 (180851.7)	0.064	0.001
	Min, Max	(0, 2503440)	(0, 1662900)		
	N (% not missing)	1926 (100.0)	642 (100.0)	0.072	0.001

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
All emergency attendances cost (KRW)	Mean (SD)	409354.5 (1665530.6)	557420.3 (2401452.0)		
	Min, Max	(0, 38557320)	(0, 42381850)		
LRTI-related emergency attendances cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	409354.5 (1665530.6)	557420.3 (2401452.0)	0.072	0.001
	Min, Max	(0, 38557320)	(0, 42381850)		
Asthma-related emergency attendances cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	100572.5 (508245.2)	138370.1 (700243.9)	0.062	0.008
	Min, Max	(0, 6275700)	(0, 9598590)		
All hospitalisation costs (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	2339626.2 (4670337.0)	2919491.2 (6423627.0)	0.103	0.004
	Min, Max	(34630, 81897370)	(66520, 97633700)		
All asthma-related hospitalisation costs (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	1339489.7 (2316099.3)	1632171.9 (3035750.1)	0.108	0.012
	Min, Max	(34630, 39352220)	(66520, 43728160)		
Drug costs (without ICS) (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	330440.9 (392849.1)	314898.9 (380439.4)	0.040	0.002
	Min, Max	(0, 4045468)	(0, 5260946)		
Drug costs (with ICS) (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	714492.2 (532256.0)	652466.5 (494072.0)	0.121	0.020
	Min, Max	(75807, 4686823)	(100040, 5584425)		
Total costs (without ICS) (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	1669930.6 (2480644.4)	1947070.7 (3259219.6)	0.096	0.013
	Min, Max	(42150, 39881473)	(72455, 48989106)		
Total costs (with ICS) (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	2053981.9 (2531746.3)	2284638.4 (3289058.6)	0.079	0.012
	Min, Max	(149974, 40056081)	(220157, 49312585)		

* RCC based on primary outcome of no exacerbations

Table A9: Detailed results outcome 3

	Measure	DPI Repeat Cohort	pMDI Change Cohort	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Adjusted p-value
Severe exacerbations (ATS/ERS)	N (% not missing)	1926 (100.0)	642 (100.0)	0.88 (0.731, 1.06)†	0.788 (0.651, 0.954)†	0.015†
	Mean (SD)	1.1 (2.4)	1.0 (2.3)			
	Median (IQR)	0 (0, 1)	0 (0, 1)			
	Min, Max	(0, 26)	(0, 39)			
Severe exacerbations (ATS/ERS) (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	Data visualisation only		
	0, n (%)	1144 (59.4)	379 (59.0)			
	1, n (%)	347 (18.0)	121 (18.8)			
	2, n (%)	154 (8.0)	68 (10.6)			
	3, n (%)	91 (4.7)	23 (3.6)			
	≥4, n (%)	190 (9.9)	51 (7.9)			
Acute respiratory events	N (% not missing)	1926 (100.0)	642 (100.0)	0.919 (0.795, 1.063)†	0.84 (0.728, 0.971)†	0.018†
	Mean (SD)	1.7 (2.8)	1.6 (2.7)			
	Median (IQR)	1 (0, 2)	1 (0, 2)			
	Min, Max	(0, 27)	(0, 39)			
Acute respiratory events (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	Data visualisation only		
	0, n (%)	885 (46.0)	297 (46.3)			
	1, n (%)	401 (20.8)	133 (20.7)			
	2, n (%)	199 (10.3)	74 (11.5)			
	3, n (%)	136 (7.1)	46 (7.2)			
	≥4, n (%)	305 (15.8)	92 (14.3)			
Risk domain asthma control	N (% not missing)	1926 (100.0)	642 (100.0)	0.959 (0.761, 1.209)Δ	1.157 (0.9, 1.487)Δ	0.255Δ
	No, n (%)	1095 (56.9)	369 (57.5)			
	Yes, n (%)	831 (43.1)	273 (42.5)			
Overall asthma control	N (% not missing)	1926 (100.0)	642 (100.0)	1.041 (0.822, 1.317)Δ	1.221 (0.95, 1.57)Δ	0.120Δ
	No, n (%)	1178 (61.2)	389 (60.6)			
	Yes, n (%)	748 (38.8)	253 (39.4)			
Asthma exacerbation-related	N (% not missing)	1926 (100.0)	642 (100.0)	1.737 (0.902, 3.345)†	1.033 (0.596, 1.788)†	0.909†
	Mean (SD)	0.0 (0.3)	0.1 (0.5)			
	Median (IQR)	0 (0, 0)	0 (0, 0)			

	Measure	DPI Repeat Cohort	pMDI Change Cohort	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Adjusted p-value
inpatient admissions	Min, Max	(0, 6)	(0, 10)			
Asthma exacerbation-related inpatient admissions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	Data visualisation only		
	0, n (%)	1878 (97.5)	616 (96.0)			
	1, n (%)	35 (1.8)	19 (3.0)			
	2, n (%)	4 (0.2)	4 (0.6)			
	3, n (%)	5 (0.3)	1 (0.2)			
	≥4, n (%)	4 (0.2)	2 (0.3)			
SABA inhaler average daily dose, µg (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.781 (0.671, 0.909)‡	0.713 (0.606, 0.840)‡	<0.001‡
	0, n (%)	1302 (67.6)	466 (72.6)			
	>0-200, n (%)	358 (18.6)	108 (16.8)			
	>200-400, n (%)	127 (6.6)	30 (4.7)			
	>400-800, n (%)	77 (4.0)	27 (4.2)			
	>800, n (%)	62 (3.2)	11 (1.7)			
Oral thrush	N (% not missing)	1926 (100.0)	642 (100.0)	0.75 (0.251, 2.243)Δ	0.768 (0.252, 2.343)Δ	0.215Δ
	No, n (%)	1910 (99.2)	638 (99.4)			
	Yes, n (%)	16 (0.8)	4 (0.6)			
ICS average daily dose, µg (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	1.565 (1.353, 1.809)‡	1.41 (1.212, 1.641)‡	<0.001‡
	>0-250, n (%)	901 (46.8)	251 (39.1)			
	>250-500, n (%)	728 (37.8)	220 (34.3)			
	>500, n (%)	297 (15.4)	171 (26.6)			
Treatment stability	N (% not missing)	1926 (100.0)	642 (100.0)	0.947 (0.753, 1.191)Δ	1.1 (0.861, 1.404)Δ	0.580Δ
	No, n (%)	1106 (57.4)	374 (58.3)			
	Yes, n (%)	820 (42.6)	268 (41.7)			

Δ Conditional binary logistic regression; ‡ Conditional ordinal logistic regression; † Conditional Poisson regression; N/A, not applicable; Severe exacerbations adjusted for LTRA prescriptions (categorised) and SAMA prescriptions (categorised); Acute respiratory events adjusted for LTRA prescriptions (categorised) and antibiotic prescriptions (categorised); Risk domain asthma control and overall asthma control both adjusted for LTRA prescriptions (categorised), antibiotic prescriptions (categorised) and other lung diseases ever; Asthma exacerbation-related inpatient admissions adjusted for SAMA prescriptions (categorised), LABA inhaler prescriptions, LTRA prescriptions and ICS prescriptions (yes/no indicator); SABA inhaler average daily dose adjusted for SAMA prescriptions (categorised), COPD diagnosis ever, LABA inhaler prescriptions (categorised); Oral thrush adjusted for influenza diagnosis ever, ICS prescriptions (yes/no indicator) and SAMA prescriptions (categorised); ICS average daily dose adjusted for LTRA prescriptions, SAMA prescriptions (categorised) and

LABA inhaler prescriptions (yes/no indicator); Treatment stability adjusted for antibiotic prescriptions, LTRA prescriptions (yes/no indicator) and other lung diseases (ever)

Appendix Transfform HIRA

Appendix 1: Outcome specific inclusion criteria

[TABLE A1]

Appendix 2: Clinical effectiveness outcomes

i. Severe asthma exacerbation rate (ATS/ERS statement definition 2015), defined as an occurrence[1] of the following:

- Asthma exacerbation -related hospital admission OR
- LRTI-related A&E attendance OR
- LRTI-related acute oral corticosteroid course

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

- Asthma exacerbation-related hospital admission OR
- LRTI-related A&E attendance OR
- LRTI-related acute oral corticosteroid course OR
- LRTI-related antibiotics

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

- Asthma exacerbation-related hospital admissions AND
- LRTI-related A&E attendance AND
- LRTI-related acute oral corticosteroid course AND
- LRTI-related antibiotics

iv. Overall asthma control (OAC)

- RDAC as defined above AND
- ≤200µg salbutamol/≤500µg 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 LTRA or LABA

vi. Asthma exacerbation-related hospitalisation rate, defined as:

- Rate of asthma exacerbation-related 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 (µg) calculated by

[1] 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).

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

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

ix. Incidence of oral thrush:

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

Appendix 3: Statistical tests used

[TABLE A2]

Appendix 4: Detailed statistical and analyses plan

Sample size calculations

Outcome 1: Persistence of change

A previous study conducted by RiRL UK on the persistence of change from one ICS/LABA pMDI to a different 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.

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".

Outcome 2: Non-inferiority of no exacerbations pre vs post change

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 0.0, assuming that the proportion of discordant pairs is 0.242 (based on previous RiRL UK research).

Outcome 3: Non-inferiority of no exacerbations pMDI vs DPI

When the sample sizes in the groups are 208 and 208, a two-group large-sample normal approximation test of proportions with a one-sided 0.025 significance level has a 90% power to reject the null hypothesis that the proportions are non-inferior (the difference in proportions, ICS/LABA pMDI - ICS/LABA DPI is -0.10 or farther from zero in the same direction) in favour of the alternative hypothesis that the proportions in the two groups are equivalent, assuming that the expected difference in proportions is 0.033 and the proportion in the standard group is 0.758 (based on RiRL UK study).

Superiority

A two-group continuity corrected $\chi 2$ test with a 0.05 one-sided significance level has 90% power to detect the difference between a ICS/LABA pMDI proportion, $\pi 1$, of 0.791 and a ICS/LABA DPI proportion, $\pi 2$, of 0.758 (odds ratio of 0.590) when the sample sizes are 1062 and 1062, respectively (a total sample size of 2123). These numbers were also based on the RiRL UK study (79.1% exacerbation free on FLUTIFORM® vs 75.8% exacerbation-free on SERETIDE®).

Non-inferiority versus superiority

Following successful testing of non-inferiority, we also planned to examine superiority. Numbers were therefore calculated so as to be sufficient to allow for both non-inferiority and superiority testing.

Baseline characterisation

A characterisation of all baseline demographics, co-morbidities, indicators of disease severity and other patient characteristic variables was carried out and is presented for each arm. The following definitions were used:

Demographics (at index date)

- Age (years)
- Gender (male/female)
- Type of insurance (medical insurance, medical aid, veterans cover)

Comorbidities (1-year baseline and ever)

- COPD (KCD-6: J43-J44)
- Tuberculosis (KCD-6: A15-A16)
- Bronchiectasis (KCD-6: J47)
- Diffuse panbronchiolitis (KCD-6: J21.9)
- Interstitial lung disease (KCD-6: J84)
- Lung cancer (KCD-6: C34)
- 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[2] (CCI) score

[2] 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

Disease severity and control (1-year baseline)

- Number of all/LRTI-related[3]/asthma-related[4]/asthma exacerbation-related[5] hospitalisations
- Number of all/LRTI-related[d]/asthma-related[e] hospital outpatient attendances
- Number of all/LRTI-related[d]/asthma-related[e] emergency attendances
- LRTI-related[d] acute[6]/non-acute oral corticosteroid course
- LRTI-related[d] antibiotics[7]
- Average SABA inhaler daily dose
- Average SABA nebuliser daily dose
- Average ICS daily dose
- Number of severe asthma exacerbations
- Number of acute respiratory events

Medication (1-year baseline)

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

Health care costs (1-year baseline)

- Prescriptions for asthma medication (specified under 'Medication (1-year baseline)
- Respiratory-related hospital costs: inpatient hospitalisation costs; outpatient attendance costs; and Accident & Emergency attendance costs

The difference between the arms is quantified using the Standardised Mean Difference (SMD). This measure is not affected by the number of observations, and thus a better way to judge imbalance than a p-value of a hypothesis test of difference. The SMD was calculated

[3] LRTI-related defined as: A lower respiratory tract infection (LRTI) diagnosis [whooping cough (A37), influenza (J09-J12), pneumonia (J13-J18), bronchitis (J20-22, J40)], OR asthma (J45– J46, J82) OR respiratory diagnosis [respiratory failure (J96), disorders of breathing (R06)]
[4] Asthma-related defined as: a diagnosis of asthma (J45– J46, J82) AND a prescription of any asthma medication (inhalers, OCS, Theophylline or LTRA) during visit/hospitalisation
[5] Asthma exacerbation-related defined as: a diagnosis of asthma (J45– J46, J82) AND a prescription of OCS or antibiotics during the visit/hospitalisation
[6] Acute oral corticosteroid use associated with asthma exacerbation treatment defined as: oral corticosteroid prescription of >10mg Prednisolone-equivalence with a duration of prescription ≥3 days
[7] Antibiotics use associated with asthma exacerbation treatment defined as: antibiotics prescription ≥7 days

for both continuous and categorical variables as described below: an SMD ≤0.1 indicates sufficient balance between the treatment and the reference (control) groups.

[TABLE A3]

Bias potential

Bias potential assesses the degree to which the observed association between the exposure of interest and the outcome is affected by conditioning on the variable. Bias potential was measured using the relative change in co-efficient (RCC) of the exposure when the covariate is added into the model predicting outcome.

[TABLE A4]

It is called *bias potential* since the bias was estimated without other covariates in the model. To what extent a variable introduces bias into a model will depend on the total model. The baseline variables with the highest bias potential, that were also sufficiently imbalanced (SMD > 0.10) were presented to the steering committee for the final selection of variables that were used for matching.

Matching process

Exact matching for categorical variables and matching within a maximum caliper (maximum distance allowed between a case and a control) for continuous variables was used to match patients using nearest neighbour variable mixed matching, with a match maximum of 3:1 without replacement. Mixed matching is a process that helps utilise more of the data by matching varying numbers of control arm patients to a treatment arm patient. In other words, a cohort of unique patients was matched 1:1, another cohort of unique patients was matched 1:2, and a third cohort of unique patients was matched 1:3. The analysis was then conducted using all matched patients, even though some patients had 1 match while other patients may have had 3 matches.

In cases of repeated measurements for a patient, only one record could contribute to the matching. Matching was repeated several times using a different patient sequence to select the run that resulted in the highest number of patients and/or the best baseline balance. The actual number of variables used for matching depended upon the degree of restriction caused by the matching process.

Missing data was treated as missing completely at random and not imputed. If a selected confounder had more than 20% of missing data, it was not used for matching. If missingness was below 20%, the variable was encoded into a categorical variable, adding a category for

the observations with missing values, enabling this variable to be used for matching.

Based on the standardised mean difference (SMD) and clinical judgement, patients were matched based on baseline variables of age, gender, COPD diagnosis, categorised SABA inhaler average daily dose, categorised ICS inhaler average daily dose and categorised ATS exacerbation. Patients were then randomly picked with a maximum of 1:3 matching. The final cohort consisted of 642 FDC ICS/LABA pMDI patients and 1926 FDC ICS/LABA DPI patients.

Post-matching evaluation

Matching variables and confounder identification was conducted using the standardised mean difference (SMD) as a better measure of difference between cohorts instead of correlation measures. Bias potential in terms of relative change in co-efficient (RCC) of the exposure was also used in modelling and confounder identification to provide a measure of extent a variable introduces bias into a model. In order to not only rely on statistical differences, we also asked a panel of experienced clinicians to judge whether there remained any clinical relevant differences after SMD assessment.

Statistical analyses

Conditional regression analysis was performed on the matched dataset, taking into account the matched pairs. The type of regression used was dependent upon the outcome, linear regression for a continuous outcome, logistic regression for a binary outcome, Poisson regression for rates and proportional hazards regression for a time-to-event outcome. Adjustment for variables with residual confounding was made.

Since it can be expected that these variables have similar associations with exposure and/or outcome their conditional bias on the variables already in the model was assessed. Starting with a model with exposure as the only explanatory variable, the variables were added one by one in order of their individual bias potential, highest first. After a variable was added to the model it was kept in if it caused the largest change-in-estimate (at least 2%) and a maximum change-in-standard error (less than 2%) relative to the prior model. The variable that caused the largest change-in-estimate was kept.

Persistence of change

The percentage of ICS/LABA pMDI patients who received ≥1 prescription of ICS/LABA pMDI (in addition to that issued at their prescription date) and no ICS/LABA DPI at 6 months was used to evaluate ICS/LABA pMDI “persistence of change”. Sub-analyses were performed to assess the number of patients remaining on the same drug and pMDI device. One-sided 90% confidence intervals for binomial proportions were calculated for all Phase 1 analyses.

Non-inferiority of no exacerbations pre vs post change (Outcome 2)

Conditional linear regression 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.

Conditional logistic regression was used to compare the proportion of patients with "no exacerbations" for within cohort (baseline vs outcome of persistence of change cohort) comparisons.

Non-inferiority of no exacerbations pMDI vs DPI (Outcome 3)

Conditional linear regression 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, pMDI change cohort – DPI repeat cohort ≥ -0.10.

Conditional logistic regression was used to compare the proportion of patients with "no exacerbations" for cohort (persistence of change cohort vs DPI continuation cohort) comparisons.

Secondary outcomes

Conditional logistic regression, conditional Poisson regression and conditional ordinal logistic regression were used, as appropriate, to analyse the secondary effectiveness outcomes in outcome 2 and 3.

Cost outcomes

Cost outcomes were conducted for outcome 3 with comparisons made for asthma-related costs during the outcome year for the pMDI change cohort versus the DPI continuation cohort. Summary costs were compared between the matched pMDI change and continuation cohorts (outcome periods) using conditional linear regression.

Appendix 5: Outcome 1 detailed results

[FIGURE A1]

[TABLE A5]

Appendix 6: Outcome 2 detailed results

[FIGURE A2]

[TABLE A6]

[TABLE A7]

Appendix 7: Outcome 3 detailed results

[FIGURE A3]

[TABLE A8]

[TABLE A9]

Figure legends

[FIGURE A1]

Figure A1: Consort diagram outcome 1

[FIGURE A2]

Figure A2: Consort diagram outcome 2

[FIGURE A3]

Figure A3: Consort diagram outcome 3


All patients with FDC ICS/LABA pMDI prescriptions n = 167,789
Not aged between 12 and 80 years; n = 13,234
Aged from 12 to 80 years at date of change n = 154,555
Patients with exclusion diagnosis; n= 10,583 (lung cancer = 399, tuberculous =1417, interstitial lung disease = 1450, bronchiectasis = 9836)
Patients with no exclusion diagnosis n = 143,972
No asthma diagnosis; n = 11,526
Patients with asthma diagnosis n = 132,446
Patients with pMDI prescribed at baseline; n = 36
Patients with no pMDI prescribed at baseline n = 132,410
Patients with <2 DPIs prescribed at baseline; n = 117,848
Patients with ≥2 DPIs prescribed at baseline n = 14,562
Patients with maintenance OCS prescribed; n = 2847
Patients with no maintenance OCS prescribed n = 11,715
Patients with multiple FDC at switch date n = 426
Patients with no multiple FDC at change date n = 11,289
Patients with ICS at change date; n = 730
Patients with no ICS at change date n = 10,559
Patients with LABA at change date; n = 40
Patients with no LABA at change date n =10,519
Different ICS GINA category (last-recorded baseline vs index date); n = 7337
Same ICS GINA category (last-recorded baseline vs index date) n = 3182
Patients with less than 1 –year baseline data; n = 315
Patients with 1-year baseline data n = 2867
Patients with less than 6-months outcome data; n = 481
Patients with 6-months outcome data n= 2386
Patients with <1 FDC ICS/LABA in outcome; n = 395
Patients with ≥1 FDC ICS/LABA in outcome n = 1991
First possible repeat date within study period n = 1991
Patients in pMDI change cohort n = 1991


All patients with FDC ICS/LABA pMDI prescriptions n = 167,789
Not aged between 12 and 80 years; n = 13,234
Aged from 12 to 80 years at date of change n = 154,555
Patients with exclusion diagnosis; n= 10,583 (lung cancer = 359, tuberculous =1417, interstitial lung disease = 1450, bronchiectasis = 9836)
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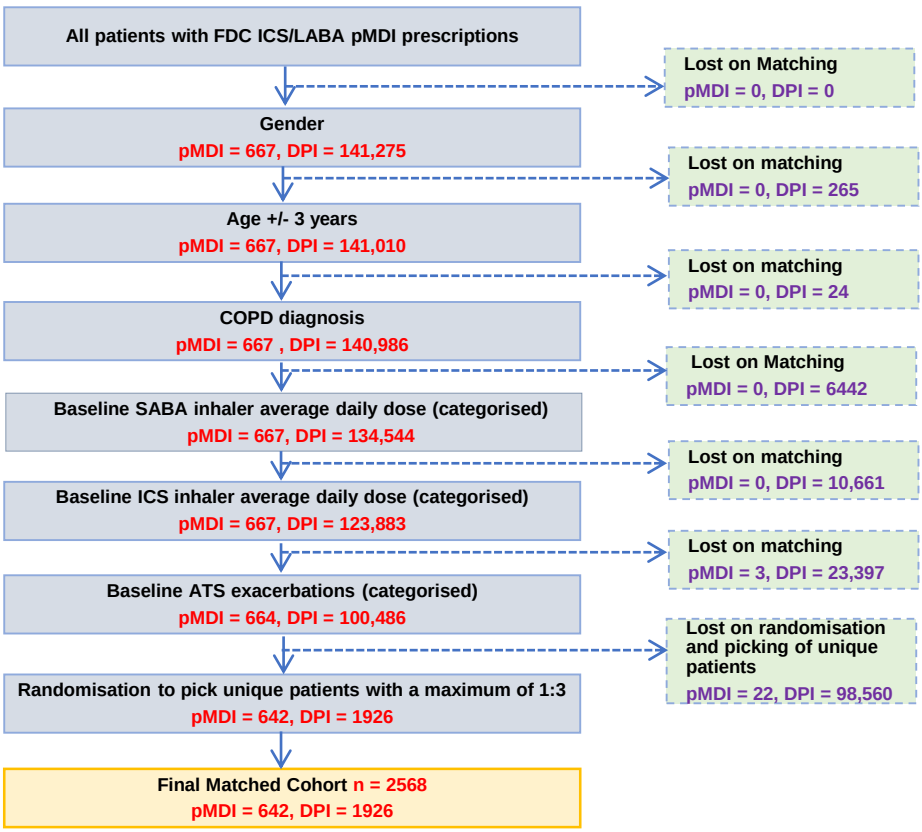
Patients with no multiple FDC at change date n = 11,289
Patients with ICS at change date; n = 730
Patients with no ICS at change date n = 10,559
Patients with LABA at switch date; n = 40
Patients with no LABA at change date n =10,519
Different ICS GINA category (last-recorded baseline vs index date); n = 7337
Same ICS GINA category (last-recorded baseline vs index date) n = 3182
Patients with less than 1-year baseline data; n = 315
Patients with 1-year baseline data n = 2867
Patients with less than 1- year outcome data; n = 1023
Patients with 1-year outcome data n= 1844
Patients with <1 FDC ICS/LABA in outcome; n = 1177
Patients with ≥1 FDC ICS/LABA in outcome n = 667
First possible repeat date not within study period; n = 0
First possible repeat date within study period n = 667
Patients in pMDI change cohort n = 667


All patients with FDC ICS/LABA pMDI prescriptions
Lost on Matching
pMDI = 0, DPI = 0
Gender
pMDI = 667, DPI = 141,275
Lost on matching
pMDI = 0, DPI = 265
Age +/- 3 years
pMDI = 667, DPI = 141,010
Lost on matching
pMDI = 0, DPI = 24
COPD diagnosis
pMDI = 667 , DPI = 140,986
Lost on Matching
pMDI = 0, DPI = 6442
Baseline SABA inhaler average daily dose (categorised)
pMDI = 667, DPI = 134,544
Lost on matching
pMDI = 0, DPI = 10,661
Baseline ICS inhaler average daily dose (categorised)
pMDI = 667, DPI = 123,883
Lost on matching
pMDI = 3, DPI = 23,397
Baseline ATS exacerbations (categorised)
pMDI = 664, DPI = 100,486
Lost on randomisation and picking of unique patients
pMDI = 22, DPI = 98,560
Randomisation to pick unique patients with a maximum of 1:3
pMDI = 642, DPI = 1926
Final Matched Cohort n = 2568
pMDI = 642, DPI = 1926