Final report

Real-life effectiveness evaluation of changing inhaler device for asthma treatment in Korea

A historical, observational study to evaluate the real-life effectiveness and cost-effectiveness of asthma treatment using the Health Insurance Review and Assessment (HIRA) Service database, Korea

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Title	Real-life effectiveness evaluation of changing inhaler device for asthma treatment in Korea
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Study aim and objectives	The study aims to characterise asthma treatment and outcomes surrounding the change from DPI to pMDI inhaler device for FDC ICS/LABA treatment using data from the Korean Health Insurance Review and Assessment (HIRA) Service database. The objectives of this study were: • To compare multiple clinical and economic outcomes between a cohort of patients that change from a DPI to a pMDI and those that remain on a DPI, during the 1 year following the change of inhaler (or matched date) • To compare multiple clinical and economic outcomes within the cohort of patients that change from a DPI to a pMDI, during the 1 year following the change of inhaler device compared to the 1 year prior • To evaluate the 'persistence of change' after 6 months for patients that change inhaler device from a DPI to a pMDI, for FDC ICS/LABA asthma therapy, in a real-life population in Korea
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List of abbreviations

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

1 Executive summary

1.1 Introduction

Asthma is a chronic inflammatory airway disease with increasing global prevalence and significant morbidity and mortality worldwide. In Korea, asthma is increasingly recognised as an economic burden, with an estimated prevalence of 3.9%. Inhaled therapy is the mainstay of asthma treatment and the Global Initiative for Asthma (GINA) and Korean Asthma Guideline recommend inhaled corticosteroids (ICS) and ICS/long-acting β_2-agonist (LABA) combination therapy, dependent upon the treatment step required. Incorrect inhaler technique is common among patients and associated with poor asthma control and reduced adherence.

In Korea, current prescribing patterns for ICS/LABA therapy are dominated by dry powder inhalers (DPI). However, pressurised metered dose inhalers (pMDI) are cost-effective, 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. Change of device, from a DPI to a pMDI, for FDC ICS/LABA therapy may therefore improve clinical and economic outcomes.

1.2 Study aims and objectives

This study aims to characterise clinical and economic outcomes surrounding the change from a DPI to a pMDI inhaler device for FDC ICS/LABA asthma treatment using data from the Korean Health Insurance Review and Assessment (HIRA) Service database.

The objectives of this study were:

- To compare clinical and economic outcomes between the cohort of patients that change from a DPI to a pMDI, and those that remain on a DPI, during the 1 year following the change of inhaler (or matched date)
- To compare clinical outcomes within the cohort of patients that change from a DPI to a pMDI, during the 1 year following the change of inhaler device compared to the 1 year prior
- To evaluate the ‘persistence of change’ after 6 months for patients that change inhaler device from a DPI to a pMDI, for FDC ICS/LABA asthma therapy, in a real-life population in Korea

1.3 Methods

A historical cohort database study using data extracted from the Health Insurance and Review (HIRA) service database. The HIRA database covers the complete medical healthcare utilisation data for the entire population of South Korea of over 50 million people. For this

study, HIRA data from January 2010 to December 2015 were accessed. The index date for all study phases was defined as the date at which patients received a first prescription for a FDC ICS/LABA pMDI (or matched date for phase 3 DPI continuation cohort patients). Patients with ≥2 separate prescriptions for FDC ICS/LABA DPI during the baseline year were studied.

Phase 1

For this exploratory phase, baseline and outcome periods of 1 year and 6 months respectively were designed to evaluate the proportion of asthma patients, prescribed ICS/LABA DPI treatment in the baseline period, that continued to collect prescriptions for ICS/LABA pMDI after the initial prescription for change in treatment to a pMDI. All patients were characterised during the baseline year. The exploratory outcome was persistence of change, defined as receiving ≥1 additional prescription for FDC ICS/LABA pMDI treatment (post-index date), and no prescription for a FDC ICS/LABA DPI, within 6 months after the initial change in therapy.

Phase 2

In phase 2, the outcome period was one year; outcomes during the year following the change from a DPI to a pMDI for FDC ICS/LABA therapy were compared to the those during the baseline year. Patients who changed to a pMDI (i.e. those with ≥2 separate FDC ICS/LABA pMDI prescriptions, in addition to that at index date, and no prescription for a DPI during the outcome year) were studied. Non-inferiority of asthma effectiveness, namely the proportion of patients who remained free from severe exacerbations, and exploratory clinical outcomes were investigated.

Phase 3

Phase 3 was a non-inferiority comparison of asthma effectiveness (primary outcome) and a descriptive comparison of respiratory-related costs during the outcome year between patients that changed to a pMDI for FDC ICS/LABA therapy and those that continued with a DPI inhaler. Patients were matched on baseline variables using clinical judgement after review of the data. In the pMDI change arm, patients with ≥2 separate FDC ICS/LABA pMDI prescriptions (in addition to that at index date) and no prescription for a DPI during the outcome year were studied. Patients in the DPI repeat arm had ≥2 separate FDC ICS/LABA DPI prescriptions (in addition to that at index date) during the outcome year.

1.4 Results

In exploratory phase 1, 58% of patients (95%CI 56, 60) persisted with the change from a DPI to a pMDI for FDC ICS/LABA therapy during the 6-months outcome period. During the baseline year, patients that persisted with the change to a pMDI were shown to have less inpatient admissions (p=0.022), outpatient visits (p<0.001) and emergency visits (p=0.027)

than non-persistent patients.

In phase 2, the change to a pMDI inhaler for FDC ICS/LABA therapy was associated with non-inferior asthma effectiveness, in terms of the proportion of patients that remained free from severe asthma exacerbations, compared to prior to the change. During the year following the change in therapy, an increased proportion of patients remained free from severe exacerbations (58.3%, p<0.001) or acute respiratory events (45.3%, p<0.001) compared to the year prior (47.4% and 32.8% respectively). More patients achieved overall asthma control during the year following the change from a DPI to pMDI (p=0.024, OR [95%CI] 1.18 [1.02, 1.37]).

In phase 3, changing to a pMDI was associated with non-inferior asthma effectiveness, in terms of the proportion of patients that remained free from severe asthma exacerbations, compared to those remaining on a DPI. During the year following the change of inhaler, pMDI patients were found to have significantly less severe exacerbations (p=0.015, RR [95%CI] 0.788 [0.651, 0.954]) and acute respiratory events (p=0.018, RR [95%CI] 0.84 [0.73, 0.97]), and lower SABA inhaler average daily dose (p<0.001, OR [95%CI] 0.71 [0.61, 0.84]) compared to patients remaining on a DPI. However, patients that changed to a pMDI had increased ICS average daily dose (p<0.001, OR [95%CI] 1.57 [1.35, 1.81]) during the outcome year.

Total treatment and hospital attendance costs over the outcome year were found to be similar between patients that changed to pMDI therapy compared to those remaining on a DPI (n=1926) (KRW 2,073,305 vs KRW 1,927,458 respectively, p=0.451). However, patients that changed to a pMDI incurred lower costs for FDC ICS/LABA (p=0.027), oral (p=0.014) and inhaled (p<0.001) SABA and oral LABA (p=0.002) treatment and higher costs for leukotriene receptor antagonist treatment (p<0.001) compared to those that continued with DPI therapy. A descriptive assessment showed that changing from a DPI to a pMDI for FDC ICS/LABA therapy is associated with neutral cost-effectiveness.

1.5 Conclusion

The results show that changing from a DPI to a pMDI inhaler for FDC ICS/LABA asthma treatment is as effective as remaining on a DPI in terms of exacerbation prevention. 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. 58% of patients that changed inhaler from a DPI to a pMDI persisted with the change over 6 months. Changing to a pMDI for ICS/LABA therapy in patients with asthma was also found to be associated with similar costs as remaining on a DPI.

1 Background

Asthma is a chronic inflammatory airway disease with increasing global prevalence and significant morbidity and mortality worldwide[1,2]. In Korea, asthma is increasingly recognised as an economic burden, with an estimated prevalence of 3.9%[3]. Guidelines reflecting the updates in asthma treatment result in better asthma control[4]. The international Global Initiative for Asthma (GINA) provides an evidence-based approach to asthma management in recognition of increasing prevalence[5], while national Korean guidelines have also been introduced to improve the clinical management of asthma[6]. Inhaled therapy to deliver corticosteroids is the mainstay of treatment for patients; however, incorrect inhaler technique is common and associated with poor asthma control and reduced adherence[7,8].

The GINA and Korean Asthma Guideline recommend inhaled corticosteroids (ICS) and ICS/long-acting β_2-agonist (LABA) combination therapy, dependent upon the treatment step required[5,6]. Effective delivery is important if guideline practice is to be followed and current inhaler devices available for ICS/LABA combination therapy include dry powder inhalers (DPIs) and pressurised metered-dose inhalers (pMDIs). Optimal delivery to the lung requires a different inhalation technique and breathing pattern for each device-type[9]. DPIs are breath-activated, requiring deep and forceful inhalation, while pMDIs require coordination of inhalation with actuation of the inhaler. Incorrect inhaler technique is common among patients and is associated with poor asthma control and reduced adherence[7,8].

In Korea, current prescribing patterns for ICS/LABA therapy are dominated by DPIs[a]. However, pMDIs are cost-effective[10], 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[9]. Since the use of pMDI short-acting β_2-agonist (SABA) relievers are common among patients with asthma, changing to a pMDI preventer might improve health and economic outcomes by simplifying the process of learning inhaler technique.

A universal health coverage system exists in South Korea, with all healthcare utilisation and cost data for 90% of the entire population of 50 million people captured within the Health Insurance Review and Assessment Service (HIRA) database[12]. The longitudinal electronic medical records within the HIRA database are suitable for real-life research and have been

[a] 83% of the population prescribed FDC ICS/LABA were prescribed a DPI (phase 1 consort diagram)

used in numerous published, peer-reviewed studies[13-16]. Using data extracted from this database, the aim of this study is therefore to evaluate the treatment effectiveness and cost outcomes of changing from a DPI to a pMDI for FDC ICS/LABA therapy for asthma patients in South Korea.

2 Study aims and objectives

2.1 Study aims

The study aims to characterise clinical and cost outcomes surrounding the change from a DPI to a pMDI inhaler device for FDC ICS/LABA asthma treatment, using data from the Korean Health Insurance Review and Assessment (HIRA) Service database.

2.2 Study objectives

The objectives of this study were:

- To compare clinical and economic outcomes between the cohort of patients that change from a DPI to a pMDI, and those that remain on a DPI, during the 1 year following the change of inhaler (or matched date)
- To compare clinical outcomes within the cohort of patients that change from a DPI to a pMDI, during the 1 year following the change of inhaler device compared to the 1 year prior
- To evaluate the 'persistence of change' after 6 months for patients that change inhaler device from a DPI to a pMDI, for FDC ICS/LABA asthma therapy, in a real-life population in Korea

3 Study design

3.1 Products studied

All FDC ICS/LABA pMDI and DPI therapies prescribed in the Korean Health Insurance Review and Assessment (HIRA) Service database.

3.2 Study design

This was a historical cohort database study. Exploratory phase 1 consisted of 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 after their initial prescription for change to this inhaler device-type from a DPI (Figure 1).

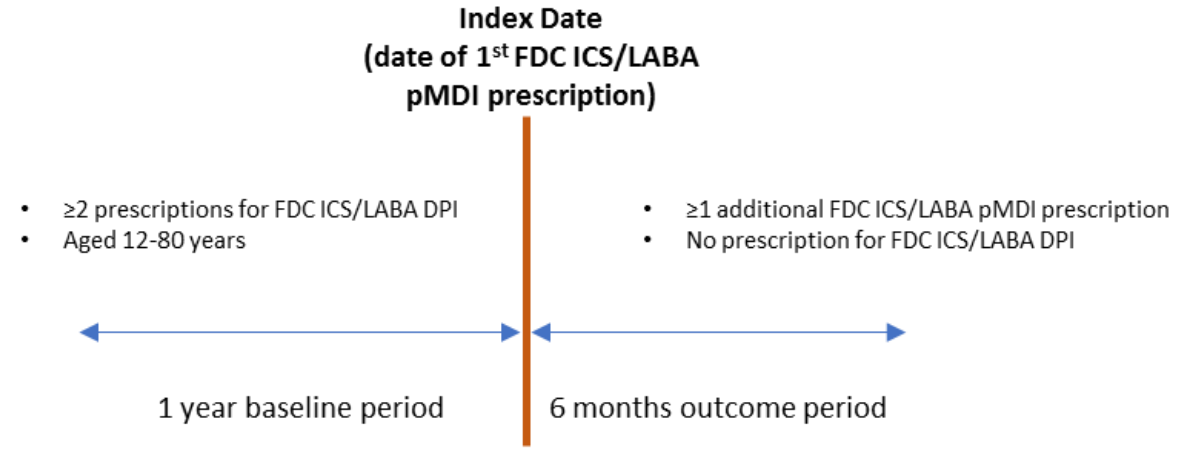

Figure 1: Phase 1 study design

Phase 2 consisted of 1 year baseline characterisation and followed 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 effectiveness and exploratory clinical outcomes during the 1 year outcome period were compared to those during the baseline year (Figure 2).

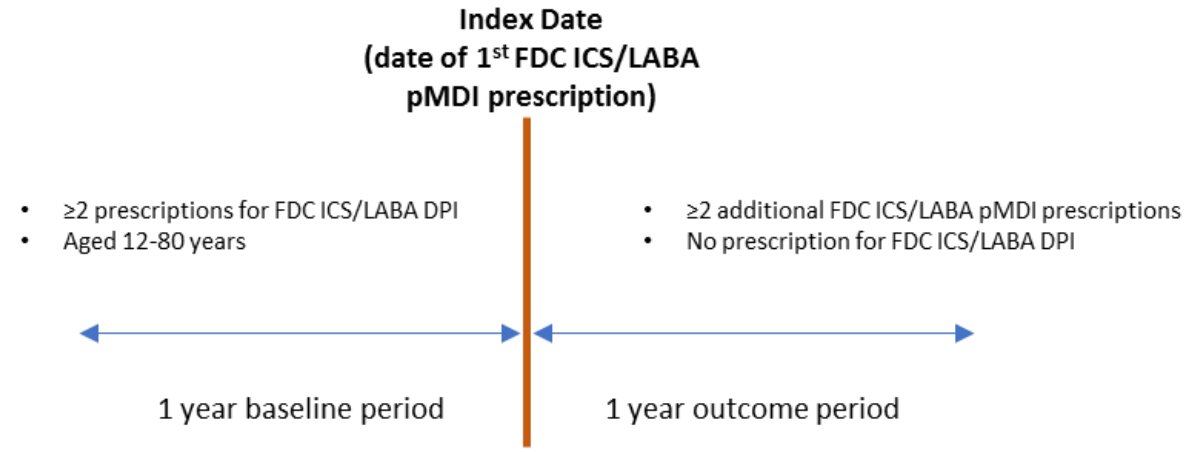

Figure 2: Phase 2 study design

Phase 3 consisted of a 1 year baseline characterisation and a 1 year outcome period (Figure 3). Asthma effectiveness and economic outcomes were compared between patients that changed to FDC ICS/LABA pMDI asthma treatment and those that remained on FDC ICS/LABA DPI treatment.

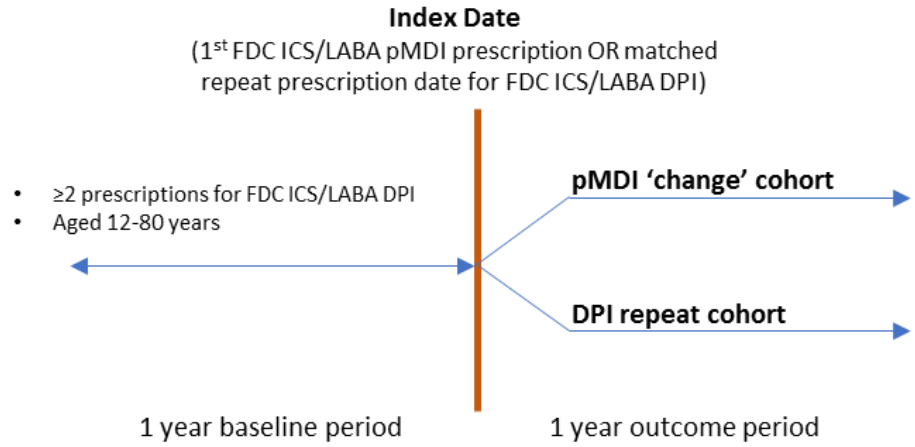

Figure 3: Phase 3 study design

4 Study population

4.1 Inclusion and exclusion criteria

Table 1: General inclusion and exclusion criteria

Inclusion criteria
➢ Aged 12-80 years at date of first prescription for FDC ICS/LABA pMDI ➢ At least 1 year baseline electronic medical records ➢ Actively treated asthma, defined as ≥ 2 prescriptions (prescribed on different dates) for FDC ICS/LABA DPI at baseline ➢ Same ICS daily FP 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
Exclusion criteria
➢ Prescription of FDC ICS/LABA pMDI prior to study period ➢ Received maintenance oral corticosteroids[b] during the baseline year ➢ Received multiple FDC ICS/LABA or separate ICS or LABA prescriptions at index date

4.1.1 Phase 1-specific inclusion criteria

Table 2: Phase 1-specific inclusion criteria

Inclusion criteria
➢ ≥1 prescription of FDC ICS/LABA during outcome period ➢ Index date pMDI prescription between January 2010 to December 2015 (1 year baseline, 6 months outcome)

[b] "Maintenance therapy" is defined as ≥5 prescriptions of ≤10mg Prednisolone-equivalent oral corticosteroids

4.1.2 Phase 2-specific inclusion and exclusion criteria

Table 3: Phase 2-specific inclusion criteria

Inclusion criteria
➢ ≥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
➢ Prescription of FDC ICS/LABA DPI during outcome period

4.1.3 Phase 3-specific inclusion and exclusion criteria

Table 4: Phase 3-specific inclusion criteria

Inclusion criteria
➢ ≥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
➢ Change of FDC ICS/LABA inhaler-type during outcome period

4.2 Data source

For this study, data from the Korean Health Insurance Review and Assessment (HIRA) Service database was used. In South Korea, all patients have a compulsory and universal health plan. The HIRA database covers the complete medical healthcare utilisation data for the entire population of South Korea, over 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[12] and has been used in several previous studies including respiratory research[17]. For this study, HIRA data from January 2010 to December 2015 was accessed.

5 Study variables and study outcomes

5.1 Exposures

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

5.2 Demographic and baseline variables

5.2.1 Demographics (at index date)

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

5.2.2 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[c] (CCI) score

5.2.3 Disease severity and control (1-year baseline)

- Number of all/LRTI-related[d]/asthma-related[e]/asthma exacerbation-related[f] 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[g]/non-acute oral corticosteroid course
- LRTI-related[d] antibiotics[h]
- Average SABA inhaler daily dose
- Average SABA nebuliser daily dose
- Average ICS daily dose

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[c] 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

[d] 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)]

[e] 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

[f] Asthma exacerbation-related defined as: a diagnosis of asthma (J45– J46, J82) AND a prescription of OCS or antibiotics during the visit/hospitalisation

[g] 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

[h] Antibiotics use associated with asthma exacerbation treatment defined as: antibiotics prescription ≥7 days

- Number of severe asthma exacerbations (section 5.6.1)
- Number of acute respiratory events (section 5.6.1)

5.2.4 Medication (1-year baseline)

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

5.2.5 Health care costs (1-year baseline)

- Prescriptions for asthma medication (listed in section 5.2.4)
- Respiratory-related hospital costs: inpatient hospitalisation costs; outpatient attendance costs; and Accident & Emergency attendance costs

5.3 **Study outcomes**

5.3.1 Primary outcome (Phase 3)

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

- 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 inhaler device, compared to the continuation cohort that remained on FDC ICS/LABA DPI treatment. Non-inferiority was claimed if the lower limit of the 95% CI of the mean difference in patient proportions with no severe exacerbations, outcome - baseline ≥-0.10

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

- Asthma-related[4] hospital admissions AND A&E attendance; AND
- An acute course of oral corticosteroids[6]

5.3.2 Secondary outcome (Phase 2)

The secondary outcome of this study was a non-inferiority assessment powered on the "no-exacerbation" endpoint, as defined in section 5.3.1:

- 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 inhaler device, compared to the baseline year. Non-inferiority was claimed if the lower limit of the 95% CI of the mean difference in patient proportions with no severe exacerbations, outcome - baseline ≥ -0.125

5.3.3 Tertiary outcome (Phase 1)

The tertiary outcome of this study 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.

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

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

5.3.4 Exploratory effectiveness outcomes (Phases 2 and 3)

The following exploratory effectiveness outcomes were investigated for phases 2 and 3:

5.3.4.1 Clinical effectiveness outcomes

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

- Asthma exacerbation -related[5] hospital admission OR
- LRTI-related[d] A&E attendance OR
- LRTI-related[d] acute[6] oral corticosteroid course

ii. Acute respiratory event, defined as an occurrence[8] of the following:

- Asthma exacerbation-related[5] hospital admission OR
- LRTI-related[d] A&E attendance OR
- LRTI-related[d] acute[6] oral corticosteroid course OR
- LRTI-related[d] antibiotics[7]

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

- Asthma exacerbation-related[5] hospital admissions AND
- LRTI-related[d] A&E attendance AND
- LRTI-related[d] acute[6] oral corticosteroid course AND

[i] Where ≥1 oral corticosteroid course/hospital inpatient/hospital outpatient/hospital emergency occurs within 7 days of each other, these events will be considered the result of the same exacerbation (and will only be counted once). Index date exacerbations will be included in the baseline count.

- LRTI-related[d] antibiotics[7]

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[5] hospitalisation[8] rate, defined as:

- Rate of asthma exacerbation-related[5] 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

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

- 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

5.3.4.2 Cost effectiveness outcomes

i. Asthma-related costs

Change in asthma-related costs (per patient per year) for each of the categories below, individually and in total, including:

- Asthma medication prescriptions, including ICS/LABA, ICS, LABA, SABA/SAMA, LABA/LAMA, SABA, SAMA, LAMA, LTRA, theophylline, omalizumab, acute oral corticosteroids and antibiotics for LRTIs
- Respiratory-related hospital costs: inpatient hospitalisation costs; outpatient hospitalisation costs; and Accident & Emergency hospitalisation costs

ii. Cost-effectiveness of treatment

Cost-effectiveness of treatment using both exacerbation prevention and RDAC as measures of effectiveness, with a main focus on exacerbation prevention, was conducted for Phase 3.

6 Statistical analysis

6.1 Software

All statistical analyses were conducted using SAS Enterprise Guide 6.1 (SAS Institute, Cary, North Carolina, USA). Statistically significant results are defined as $p<0.05$. The statistical tests used in the analysis are summarized in appendix section 11.2.

6.2 Sample size calculations

6.2.1 Primary outcome: non-inferiority of no exacerbations (Phase 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 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 Flutiform stage 2 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 Flutiform UK study (79.1% exacerbation free on Flutiform vs 75.8% exacerbation-free on Seretide[18]).

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.

6.2.2 Secondary outcome: non-inferiority of no exacerbations (Phase 2)

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 Mundipharma R03212b-Effectiveness of Flutiform® Stage 2).

6.2.3 Exploratory outcome: persistence of change

A previous study conducted by RiRL UK (Mundipharma R03212b-Effectiveness of Flutiform® Stage 2) 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[18].

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

6.2.4 Multiplicity

Although more than one sample size calculation, the primary endpoint was non-inferiority of effectiveness, in terms of the proportion of patients in the change cohort that remain free from severe exacerbations during the outcome year, as compared to the continuation cohort. This was the primary focus of the study.

The power calculation for 'persistence of change' was provided to give an indication of how much data was needed to demonstrate sufficient persistence of change.

The analyses were performed in a hierarchical approach, in that persistence of change was only considered with evidence non-inferiority of asthma effectiveness.

6.3 **Baseline characterisation**

6.3.1 Baseline balance

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

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 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 5: 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 $\hat{p}_{jk} = P(category\ k | treatment\ arm\ j)$, $j = 1,2$, $k = 2,3, \dots, k$

6.3.2 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 6: 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.

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.

6.4 Matching and confounding

6.4.1 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 (**Error! Reference source not found.**).

6.4.2 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.

6.5 Analysis

6.5.1 General

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 (see section 6.4.2) 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.

6.5.2 Primary outcome: non-inferiority of no exacerbations (Phase 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.

6.5.3 Secondary outcome: non-inferiority of no exacerbations (Phase 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.

6.5.4 Exploratory outcome: persistence of change (Phase 1)

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.

6.5.5 Exploratory clinical effectiveness outcomes (Phases 2 and 3)

Conditional logistic regression, conditional Poisson regression and conditional ordinal logistic regression were used, as appropriate, to analyse the exploratory clinical effectiveness outcomes (section 5.3.4.1, i-ix).

6.5.6 Exploratory cost effectiveness outcomes (Phase 3)

Cost outcomes were conducted for phase 3 with comparisons made for asthma-related costs during the outcome year for the pMDI change cohort versus the DPI continuation cohort.

a) Change in asthma-related costs

The following asthma-related healthcare costs were calculated for each treatment group for the baseline and outcome periods:

- Costs for asthma drugs:
  - ICS
  - FDC ICS/LABA
  - SABA
  - SAMA
  - FDC SABA/SAMA
  - LABA
  - LAMA
  - FDC LABA/LAMA
  - LTRA
  - Theophylline
  - Acute oral corticosteroids
  - LRTI-related[d] antibiotics
- LRTI-related[d] inpatient hospitalisation costs
- LRTI-related[d] A&E attendance costs
- LRTI-related[d] outpatient attendance costs

These costs are summarised as total costs (including and excluding ICS), disaggregated as:

- Asthma drug costs including/excluding ICS

- LRTI-related[d] consultation costs
- LRTI-related[d] hospital costs

Summary costs were compared between the matched pMDI change and continuation cohorts (outcome periods) using conditional linear regression.

The main outcome of interest for policy makers and providers is the total cost associated with implementing a particular treatment. The arithmetic mean asthma-related health care cost is therefore the preferred statistic (even though distributions are likely to be skewed) as it can be multiplied by a target population to estimate total costs.

b) Cost-effectiveness of treatment, using both exacerbation prevention and Risk Domain Asthma Control (RDAC) as measures of effectiveness

The economic evaluation compared the cost effectiveness of ICS/LABA pMDI therapy with ICS/LABA DPI therapy in terms of the cost of exacerbation prevention and RDAC (between the persistence of change and continuation cohorts). Exacerbation prevention was the main focus.

Incremental cost-effectiveness provides information on the combined effectiveness and cost of therapies. If a treatment is both *less costly* and *more effective*, it is deemed to be "dominant" and constitutes the "preferred treatment strategy". If an intervention is *more costly* and *more effective* then there is a "trade-off" and decision-makers are required to decide whether the additional cost is worth the additional effect.

Generalised estimating equations with a log link and gamma distribution (to account for correlations between matched pairs i.e. generalised linear model with cluster robust standard errors) was used to estimate mean asthma-related health care costs per year during the outcome period. This model can be used for both unadjusted and adjusted analyses. Equivalent adjustments were made using the confounders from the clinical effectiveness analysis. Mean costs are reported with 95% confidence intervals found by bootstrapping methods, using 1000 random samples taken, with replacement, from the dataset.

The costs of treatments were compared via the differences in mean asthma-related health care costs (per patient per year) during the outcome period, adjusted for potential confounders, with the continuation cohort as the reference treatment. Differences in mean costs are reported with 95% confidence intervals found by bootstrapping methods, using the 1000 random samples taken, with replacement, from the dataset.

The effectiveness of treatments was compared via the difference in the proportion of patients controlled during the outcome period, adjusted for potential confounders, with the continuation cohort as the reference treatment. Adjusted proportions were estimated using generalised

estimating equations with a logit link and binomial distribution. Proportions and differences in proportions of patients controlled were reported with 95% confidence intervals found by bootstrapping methods, using the 1000 random samples taken, with replacement, from the dataset. The comparison of effectiveness of treatments was repeated comparing the proportion and difference in proportion of patients with no exacerbations during the outcome period, using the same method as above.

The differences between the persistence of changes and the continuation cohort in costs and proportions of patients controlled as well as for patients with no exacerbations for the 1000 random samples will be displayed graphically on a cost-effectiveness plane. The four quadrants of the cost-effectiveness plane (see figure 4) represent ICS/LABA pMDI treatment being:

- Quadrant I: more costly and more effective (a trade-off)
- Quadrant II: more costly and less effective (ICS/LABA DPI dominant)
- Quadrant III: less costly and less effective (a trade-off)
- Quadrant IV: less costly and more effective (ICS/LABA pMDI dominant)

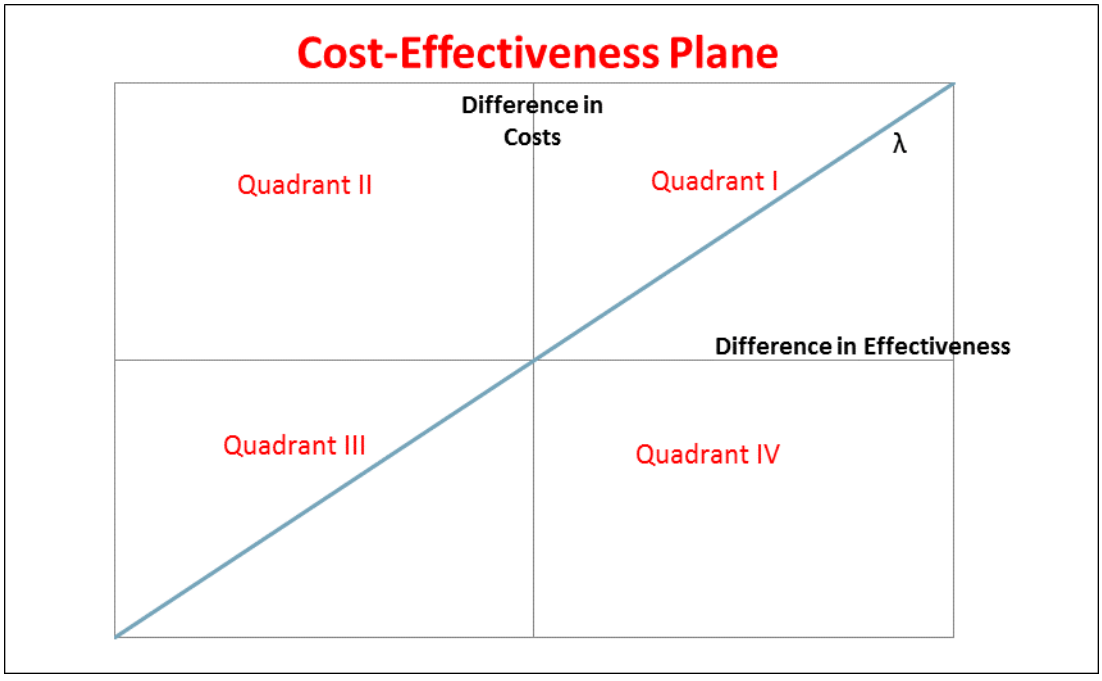

Figure 4: The cost-effectiveness plane

Cost-effectiveness Acceptability Curves (CEAC)

The resampled data covered all four quadrants and therefore Cost-effectiveness Acceptability Curves (CEAC) were produced. These graphically show the proportion of the distribution of cost and effect differences (based on the bootstrap samples) that lie below a given price line, as the price line varies from 0 to infinity[19]. This price line (λ) is a measure of a decision-maker's

“willingness to pay” for increased effectiveness and is represented by the straight line through the origin in figure 4, of gradient λ, as it is rotated from λ = 0 to λ -> infinity.

7 Results

7.1 Phase 1

7.1.1 Patient population

Patients changing from FDC ICS/LABA DPI to pMDI, with ≥1 additional prescription of FDC ICS/LABA during the 6-month outcome period, were investigated in exploratory Phase 1 (see Figure 5).

7.1.2 Phase 1 outcomes

7.1.2.1 Exploratory outcome: persistence of change

During the 6-month outcome period, 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 7: Phase 1 - persistence of change at 6 months

Persistence of change	N	% (one-sided 95% CI)
N not missing	1991	100
No	839	42.14 (39.97, 44.31)
Yes	1152	57.86 (55.69, 60.03)

7.1.2.2 Subanalysis: remaining on the same device

Patients were deemed remaining on the same device at 6-months post-index date if they were prescribed ≥1 of the FDC ICS/LABA drug of the same device, and no prescriptions for other FDC ICS/LABA regardless of device-type. 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 8: Phase 1 – patients remaining on the same device at 6 months

	Total	
	N	% (one-sided 95% CI)
N not missing	1991	100
No	863	43.35 (41.17, 45.52)
Yes	1128	56.65 (54.48, 58.83)

7.1.3 Patient characteristics

Patients were stratified by persistence of change to investigate differences in demographics, comorbidities, disease severity, medication prescribed and clinical measurements during the 1 year baseline period. A description of the main differences and the data tables are presented in the appendix, section 11.4.

7.2 Phase 2

7.2.1 Patient population

Patients changing from FDC ICS/LABA DPI to pMDI, with ≥1 additional prescription of FDC ICS/LABA pMDI (and no prescription of FDC ICS/LABA DPI) during the 1-year outcome period, were investigated (see Figure 6).

7.2.2 Baseline characterisation

Demographics, comorbidities, disease severity, medication prescribed and clinical measurements were described for patients in Phase 2; the data is presented in tables in the appendix, section 11.6.

7.2.3 Phase 2 outcome

7.2.3.1 Secondary outcome: non-inferiority of no exacerbations

The secondary outcome was non-inferiority of effectiveness, with regards the proportion of patients that remain free from severe exacerbations before and after the change of inhaler device. Non-inferiority was claimed if the lower limit of the 95% CI of the mean difference in the proportions of patients with no exacerbations, outcome year – baseline year ≥ -0.125.

Non-inferiority of effectiveness during the outcome year was determined for the population that changed from a DPI to a pMDI for FDC ICS/LABA therapy, as compared to the year prior to the change.

Table 9: Phase 2 – secondary outcome: non-inferiority of effectiveness (proportion of patients with no exacerbations)

Exacerbations (ATS/ERS[#])	**Patients changing from FDC ICS/LABA DPI to FDC ICS/LABA pMDI (n = 667)**	
	Baseline	**Outcome**
N (% not missing)	667 (100.0)	667 (100.0)
No n (%)	351 (52.6)	278 (41.7)
Yes n (%)	316 (47.4)	389 (58.3)
Odds ratio (95% CI)	1	1.554 (1.296, 1.863)[Δ]
Mean difference in proportion of patients with 'no exacerbations' (95% CI)	N/A	0.109 (0.065, 0.154)*
Non-inferiority met? (Lower 95% CI >-0.125)		YES

[#]Exacerbations defined as: asthma-related[j] hospital admission AND asthma-related[9] A&E attendance AND a prescription for an acute course of oral corticosteroids[k]; *Conditional linear regression; [Δ]Conditional binary logistic regression (unadjusted)

[j] 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
[k] 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

7.2.3.2 Exploratory effectiveness outcomes

Other clinical effectiveness measures during the outcome period (listed in section 5.6.1) were compared against the equivalent measures during the baseline year; the data is presented in appendix section 11.7.

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]) was found 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 (Table 22). Statistical significance for both outcomes were 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=0.024, OR [95%CI] 1.18 [1.02, 1.37]), reflecting the decreased average SABA daily dose following change of inhaler device (p<0.001, 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. 41% of patients that changed to FDC ICS/LABA pMDI attained treatment stability.

7.3 **Phase 3**

7.3.1 Patient population (unmatched)

Patients changing from FDC ICS/LABA DPI to pMDI, with ≥2 additional FDC ICS/LABA pMDI prescriptions (and no prescription of FDC ICS/LABA DPI) during the 1-year outcome period were investigated (Figure 6). These patients were compared to DPI patients who had ≥ 2 repeat FDC ICS/LABA DPI prescriptions (and no prescription of FDC ICS/LABA pMDI) during the 1-year outcome period (see Figure 7).

7.3.2 Unmatched patient characteristics

Unmatched patients in the DPI continuation cohort were found to differ significantly from those in the pMDI change cohort in terms of medical insurance (Table 23), comorbidities (Table 24), disease severity (Table 25), medication during the baseline year (Table 26) and asthma-related costs (Table 27). The data is summarised and presented in tables in the appendix, section 11.9.

7.3.3 Patient population (matched)

Based on standardised difference (SMD) and clinical judgement, patients were matched 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 (**Error! Reference source not found.**).

7.3.4 Matched patient characteristics

Patient demographics, comorbidities, disease severity, prescribed medication and clinical measurements were described for matched patients during the baseline year; data is presented in tables in the appendix, section 11.10.

Following matching, patients in the DPI continuation and pMDI change cohorts were similar in age and gender (Table 28). Comorbidities were also matched between cohorts, with the exception of COPD (ever), oral thrush (ever), GERD, influenza, other respiratory disease and rhinitis having a high SMD (Table 29). 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 (Table 30). 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 (Table 31). SAMA and LTRA prescriptions were deemed candidates for adjustment.

Asthma-related costs during the baseline year for the matched pMDI change and DPI continuation cohorts were similar and no cost variables were candidates for adjustment (Table 32).

7.3.5 Phase 3 outcomes

7.3.5.1 Primary outcome: non-inferiority of no exacerbations

Non-inferiority of effectiveness, with regards the proportion of patients that remain free from severe exacerbations during the outcome year, was investigated for the matched cohorts. Non-inferiority was claimed if the lower limit of the 95% CI of the mean difference in the proportions of patients with no exacerbations, pMDI change cohort – DPI repeat cohort ≥ -0.10.

Non-inferiority of effectiveness was determined for the population that changed from FDC ICS/LABA DPI to FDC ICS/LABA pMDI as compared to patients that remained on FDC ICS/LABA DPI therapy (Table 10).

Superiority was not met and the sample size requirements to enable demonstration of superiority were not achieved.

Table 10: Phase 3 – primary outcome: non-inferiority of no exacerbations

Exacerbations (ATS/ERS)	DPI Repeat Cohort	pMDI Change Cohort
N (% not missing)	1926 (100.0)	642 (100.0)
No, n (%)	782 (40.6)	263 (41.0)
Yes, n (%)	1144 (59.4)	379 (59.0)
Unadjusted mean difference in proportion of 'no exacerbations' (95% CI)	-0.004 (-0.045, 0.038)*	
Adjusted mean difference in proportion of 'no exacerbations' (95% CI)	0.013 (-0.028, 0.055)*	
Non-inferiority met? (Lower 95% CI >-0.10)		YES
Unadjusted odds ratio (95% CI)	1	0.983 (0.811, 1.192)Δ
Adjusted odds ratio (95% CI)	1	1.037 (0.852, 1.261)Δ
Superiority met? (OR, lower 95% CI > 1)		NO

ΔConditional binary logistic regression; *Conditional linear regression; N/A, not applicable; No exacerbation models adjusted for antibiotics (categorised) and SAMA prescriptions (categorised)

7.3.5.2 Exploratory clinical effectiveness outcomes

Other clinical effectiveness outcomes, as listed in section 5.3.4.1, were compared between patients changing to a pMDI and those that continued with a DPI during the outcome year (Table 33). Patients changing to FDC ICS/LABA pMDI had significantly less severe exacerbations (p=0.015, RR [95%CI] 0.79 [0.65, 0.95]) and acute respiratory events (p=0.018, RR [95%CI] 0.84 [0.73, 0.97]), lower SABA inhaler average daily dose (p<0.001, OR [95%CI] 0.71 [0.61, 0.84]) and higher ICS average daily dose category (based on GINA guidelines, p<0.001, OR [95%CI] 1.57 [1.35, 1.81]) as compared to patients continuing with FDC ICS/LABA DPI treatment.

7.3.5.3 Exploratory cost outcome: changes in asthma-related costs

Asthma-related cost outcomes during the year following index date were described (Table 34). Total treatment and hospital attendance 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 vs KRW 1,927,458 respectively, p = 0.451). Patients that changed to a pMDI incurred lower costs for FDC ICS/LABA (p=0.027), oral (p=0.014) and inhaled (p<0.001) short-

acting β_2 agonist and oral LABA (p=0.002) treatment and higher costs for leukotriene receptor antagonist treatment (p<0.001) compared to those that continued with a DPI inhaler.

7.3.5.4 Exploratory cost-effectiveness outcome: cost-effectiveness of treatment

Cost-effectiveness was compared between the pMDI change cohort and the DPI continuation cohort with exacerbation-prevention and risk domain asthma control as measures of treatment effectiveness. For this phase, descriptive analyses only were performed (with p-values from the Wilcoxon signed rank test with continuity correction).

7.3.5.4.1 Exploratory cost-effectiveness of treatment: no exacerbations

With respect to the clinical outcome of no exacerbations, there was no clear indication of cost-effectiveness of switching to a pMDI, as compared to staying on a DPI, for FDC ICS/LABA treatment (bootstrapped differences in mean costs and mean proportion of no exacerbations falling in all quadrants, Figure 9). At a willingness to pay (WTP) of KRW 0, there was a 62% probability that switching to pMDI would be cost-effective (Figure 10). As the WTP increases up to KRW 24,100,000, the probability of cost-effectiveness decreases to 26.4% (Figure 11). Beyond this value, there is little change in probability of cost-effectiveness as WTP increases.

7.3.5.4.2 Exploratory cost effectiveness of treatment: risk domain asthma control

With respect to the clinical outcome of risk domain asthma control, there was no clear indication of cost effectiveness of switching to a pMDI, as compared to staying on a DPI, for FDC ICS/LABA treatment (bootstrapped differences in mean costs and mean proportion of RDAC falling in all quadrants, Figure 12). The probability that switching to pMDI would be cost-effective is relatively unchanged (62.0% to 62.2%) as WTP increases from KRW 0 to KRW 60,000 (Figure 13).

8 Conclusions

This study aimed to characterise clinical asthma outcomes and assess the economic effect of changing inhaler from a DPI to a pMDI for ICS/LABA treatment in real-life Korean practice. A historical cohort study was performed using data extracted from the HIRA database.

1991 patients were studied in phase 1. Analysis of baseline patient characteristics showed that a high proportion of the total population experienced asthma-related exacerbations (46%) and/or acute respiratory events (43%) during the baseline year. The exploratory outcome for this study phase was persistence of change over 6 months; 58% of patients (95%CI 56, 60) were determined to have persisted with the change from a DPI to a pMDI for FDC ICS/LABA therapy. A subanalysis revealed that 57% of patients also persisted with the same device-type at 6 months post-index date. The analysis of patient characteristics during the baseline year was split by persistence groups. Patients that persisted with the change to a pMDI were shown to have less inpatient admissions (p=0.022), outpatient visits (p<0.001) and emergency visits (p=0.027) than non-persistent patients during the baseline year.

In phase 2, asthma effectiveness outcomes during the year following the change in therapy from a DPI to a pMDI for FDC ICS/LABA treatment were compared to those during the baseline year. Non-inferior asthma effectiveness, in terms of the proportion of patients that remained free from severe asthma exacerbations, was determined for patients that changed to a pMDI. During the year following the change in therapy, an increased proportion of patients remained free from severe exacerbations (58.3%, p<0.001) or acute respiratory events (45.3%, p<0.001) compared to the year prior (47.4% and 32.8% respectively). The proportion of patients that achieved overall asthma control during the year following the change from DPI to pMDI was also increased (p=0.024, OR [95%CI] 1.18 [1.02, 1.37]) compared to the baseline year, with 41% of patients attaining treatment stability.

Phase 3 compared outcomes during the year following index date for patients changing to FDC ICS/LABA pMDI (n=642) versus matched patients continuing with DPI treatment (n=1926). The primary outcome, non-inferiority of asthma effectiveness, in terms of the proportion of patients that remained free from severe asthma exacerbations, was determined for patients that changed to a pMDI for FDC ICS/LABA therapy. During the year following the change of inhaler, pMDI patients were found to have significantly less severe exacerbations (p=0.015, RR [95%CI] 0.79 [0.65, 0.95]) and acute respiratory events (p=0.018, RR [95%CI] 0.84 [0.73, 0.97]), and lower SABA inhaler average daily dose (p<0.001, OR [95%CI] 0.71 [0.61, 0.84]) compared to patients remaining on a DPI. However, during the outcome year, patients that changed to a pMDI were shown to have increased ICS average daily dose

(p<0.001, OR [95%CI] 1.57 [1.35, 1.81]) as compared to those remaining on DPI treatment.

Phase 3 also examined the health economic effect of changing inhaler device for ICS/LABA asthma treatment in Korea. Total treatment and hospital attendance costs over the outcome year were found to be similar between patients that changed to pMDI therapy compared to those remaining on a DPI (n=1926) (KRW 2,073,305 vs KRW 1,927,458 respectively, p=0.451). However, patients that changed to a pMDI incurred lower costs for FDC ICS/LABA (p=0.027), oral (p=0.014) and inhaled (p<0.001) SABA and oral LABA (p=0.002) treatment and higher costs for leukotriene receptor antagonist treatment (p<0.001) compared to those that continued with DPI therapy. A descriptive assessment showed that changing from a DPI to a pMDI for FDC ICS/LABA therapy is associated with neutral cost-effectiveness.

In summary, the above results show 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. 58% of patients that changed inhaler from a DPI to a pMDI persisted with the change over 6 months. 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 also found to be associated with similar costs as remaining on a DPI.

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[12]. The retrospective nature of this study means that patients were not influenced in any way. The datasets represent information collected for clinical and routine use however, rather than specifically for research purposes. The validity and completeness of individual patient records cannot be assessed; as such there may be omissions or errors.

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 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. It is also noted that some asthma drugs are prescribed with COPD as a diagnosis due to strict reimbursement criteria in Korea. Having COPD as an exclusion criterion would unnecessarily exclude asthma patients who are prescribed drugs affected by this reimbursement criteria.

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11 Appendix

11.1 Definitions

Original definitions were based on UK read codes prior to accessing the HIRA database. Definitions were updated based on direct access to the type of variables available and clinical relevance following discussions with the steering committee. The definition for 'asthma-related' was changed, since it is more common to code asthma-related conditions as 'asthma' in Korea than it is in the UK. Oral corticosteroid definitions were altered in line with local prescribing practices. The changes made to the definitions used are summarised below in Table 11.

Table 11: Definitions

Term	Old definition	New definition
Asthma-related	Principal or secondary diagnosis of asthma (KCD-6 codes: J45– J46, J82) OR lower respiratory tract infection (LRTI) diagnosis [whooping cough (A37), influenza (J09-J12), pneumonia (J13-J18), bronchitis (J40), bronchitis (J20-22)], OR respiratory diagnosis [respiratory failure (J96), disorders of breathing (R06)] on the same day as a hospitalization event of interest	A diagnosis of asthma (J45–J46, J82) AND a prescription of any asthma medication (inhalers, OCS, Theophylline or LTRA) during the hospitalization
Asthma exacerbation-related	-	A diagnosis of asthma (J45–J46, J82) AND a prescription of OCS or antibiotics during the visit
LRTI-related	-	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)]
Maintenance oral corticosteroids	"Maintenance therapy" is defined as: daily dosing instructions of ≤10mg Prednisolone (or equivalent) or prescriptions for 1mg or 2.5mg Prednisolone (or equivalent) tablets where daily dosing instructions are not available	≥5 prescriptions of ≤10mg Prednisolone equivalent oral corticosteroids AND no prescription of >10mg Prednisolone equivalent oral corticosteroids during an inpatient admission
LRTI-related acute course of oral corticosteroid	Asthma-related acute oral steroid use associated with asthma exacerbation treatment will be defined as: • all courses that are definitely not maintenance therapy, and/or • all courses where dosing instructions suggest exacerbation treatment (e.g. 30mg as directed)	LRTI-related oral corticosteroid prescription of ≥15mg AND duration ≥3 days

	where “maintenance therapy” is defined as: daily dosing instructions of ≤10mg Prednisolone or prescriptions for 1mg or 2.5mg Prednisolone tablets where daily dosing instructions are not available.	
LRTI- related antibiotics prescription	An antibiotic prescription with principal or secondary diagnosis of asthma (KCD-6 codes: J45– J46, J82) OR lower respiratory tract infection (LRTI) diagnosis [whooping cough (A37), influenza (J09-J12), pneumonia (J13-J18), bronchitis (J40), bronchitis (J20-22)], OR respiratory diagnosis [respiratory failure (J96), disorders of breathing (R06)]	LRTI-related antibiotics prescription of duration ≥7 days

11.2 Statistical tests

Table 12: Summary of statistical tests used

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

11.3 Phase 1: Patient population

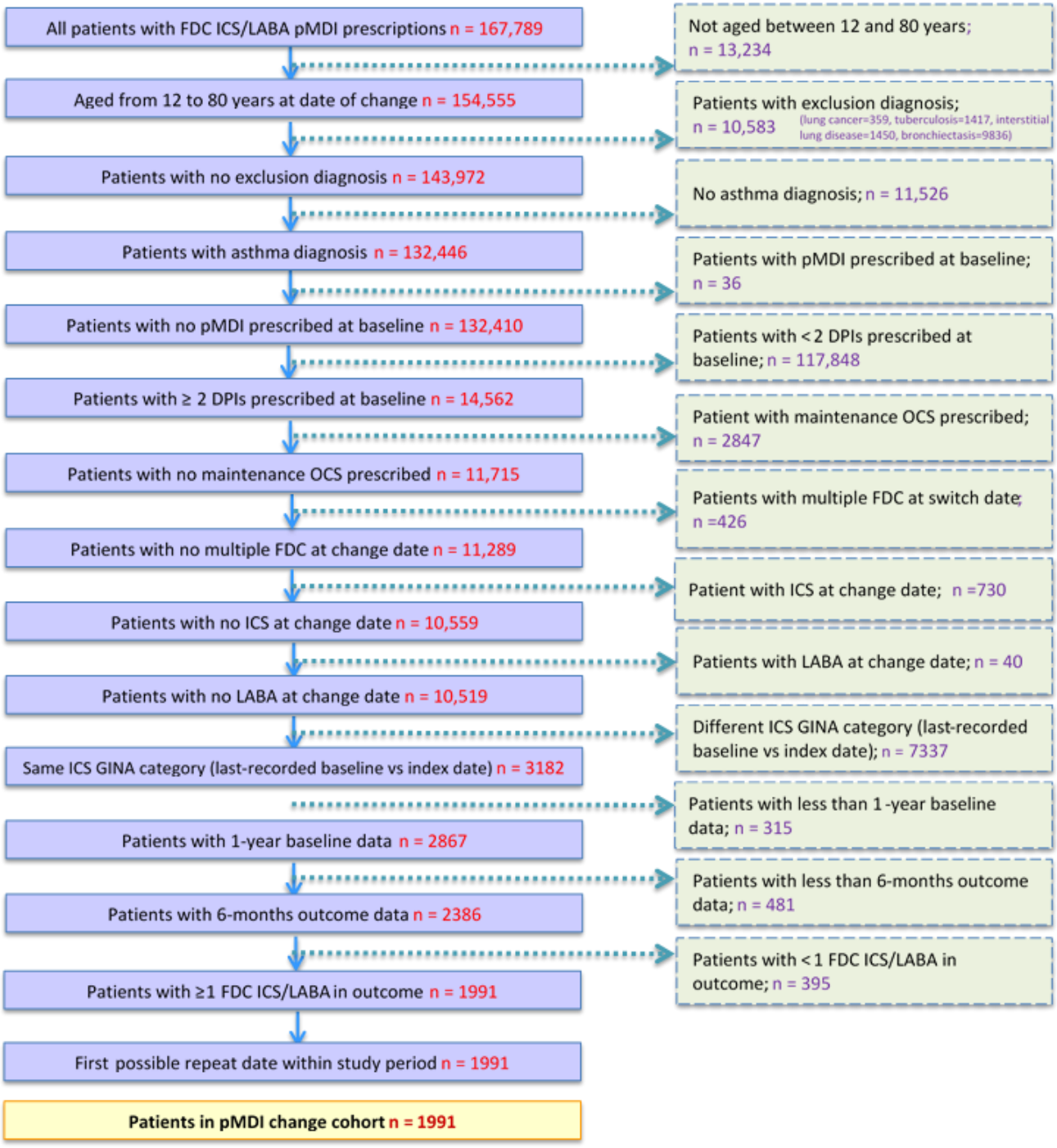

Figure 5: Phase 1 consort diagram

11.4 Phase 1: Patient characteristics

Patients within the persistence of change group were younger in age and had a different distribution of insurance-type compared to those who did not persist with the change to FDC ICS/LABA pMDI (Table 13). The distribution of comorbidities during the baseline year and ever prior to the index date (ever) were 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 (Table 14). 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 (Table 15). Persistent patients also had less severe exacerbations and acute respiratory events compared to those that failed with the change in therapy.

Medications prescribed during the baseline year were compared between patients that persisted with the change to FDC ICS/LABA pMDI and those that failed (Table 16). 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.

11.4.1 Demographics

Table 13: Phase 1 - demographics

	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)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
	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)	

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

11.4.2 Comorbidities

Table 14: Phase 1 - 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
	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)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
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)	
Comorbid nasal polyps	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.817
	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)	0.582
	No, n (%)	1098 (95.3)	804 (95.8)	1902 (95.5)	
	Yes, n (%)	54 (4.7)	35 (4.2)	89 (4.5)	
Pneumonia	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.129
	No, n (%)	1043 (90.5)	742 (88.4)	1785 (89.7)	
	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)	0.737
	No, n (%)	950 (82.5)	687 (81.9)	1637 (82.2)	
	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)	0.179
	No, n (%)	411 (35.7)	324 (38.6)	735 (36.9)	
	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)	0.874
	No, n (%)	226 (19.6)	167 (19.9)	393 (19.7)	
	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)	0.058
	Mean (SD)	1.4 (0.9)	1.5 (0.9)	1.4 (0.9)	
	Median (IQR)	1 (1, 1)	1 (1, 1)	1 (1, 1)	
	Min, Max	(0, 7)	(0, 6)	(0, 7)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value*
Charlson Comorbidity Index (CCI) (categorised)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.152
	0-1, n (%)	920 (79.9)	641 (76.4)	1561 (78.4)	
	2-5, n (%)	228 (19.8)	193 (23.0)	421 (21.1)	
	6-10 n (%)	4 (0.3)	5 (0.6)	9 (0.5)	

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

11.4.3 Disease severity

Table 15: Phase 1 – disease severity

	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)	0.022
	Mean (SD)	0.9 (1.9)	1.1 (2.3)	1.0 (2.1)	
	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)	For visualisation of data 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)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value
LRTI-related inpatient admissions days	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)	
	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-related inpatient admissions	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)	
	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)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value
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)	
LRTI-related outpatient attendances	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)	
	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)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value
	≥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)	
LRTI-related 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)	
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)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value
	10-12, n (%)	5 (0.4)	8 (1.0)	13 (0.7)	
	≥13, n (%)	4 (0.3)	6 (0.7)	10 (0.5)	
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)	
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)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value
	3, n (%)	58 (5.0)	61 (7.3)	119 (6.0)	
	≥4, n (%)	78 (6.8)	74 (8.8)	152 (7.6)	

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

11.4.4 Medication during the baseline year

Table 16: Phase 1 – medication during the baseline year

	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)	
	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)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value
	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)	
SABA prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.003
	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)	0.001
	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)	
	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)	0.011
	Mean (SD)	1.7 (3.8)	2.1 (4.0)	1.8 (3.9)	
	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)	0.055
	No, n (%)	650 (56.4)	437 (52.1)	1087 (54.6)	
	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)	0.166
	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)	
	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)	0.011
	Mean (SD)	127.4 (362.9)	157.3 (358.3)	140.0 (361.2)	
	Median (IQR)	0 (0, 110)	0 (0, 110)	0 (0, 110)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value
	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)	0.060
	0, n (%)	650 (56.4)	437 (52.1)	1087 (54.6)	
	>0-200, n (%)	327 (28.4)	235 (28.0)	562 (28.2)	
	>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)	
	≥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)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value
	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)	
	No, n (%)	915 (79.4)	634 (75.6)	1549 (77.8)	0.041
	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, 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)	0.169
	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)	
	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)	0.219
	Min, Max	(0, 14)	(0, 15)	(0, 15)	
LAMA prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	No, n (%)	864 (75.0)	611 (72.8)	1475 (74.1)	0.274
	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, n (%)	864 (75.0)	611 (72.8)	1475 (74.1)	
	1-2, n (%)	62 (5.4)	63 (7.5)	125 (6.3)	<0.001
	3-4, n (%)	90 (7.8)	31 (3.7)	121 (6.1)	
	≥5, n (%)	136 (11.8)	134 (16.0)	270 (13.6)	
FDC LABA/LAMA prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	
	No, n (%)	1151 (99.9)	839 (100.0)	1990 (99.9)	0.393
	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)	
	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)	0.785
	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)	
	No, n (%)	1128 (97.9)	823 (98.1)	1951 (98.0)	0.782
	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, 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)	0.904
	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)	
	Mean (SD)	1.4 (3.3)	1.7 (4.4)	1.5 (3.8)	0.136

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value
	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)	
LABA patch prescriptions	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.660
	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)	0.650
	No, n (%)	1041 (90.4)	753 (89.7)	1794 (90.1)	
	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)	0.484
	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)	
	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)	0.378
	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)	
	Min, Max	(0, 77)	(0, 123)	(0, 123)	
LTRA prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.331
	No, n (%)	268 (23.3)	211 (25.1)	479 (24.1)	
	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)	0.176
	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)	
	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)	0.001
	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)	
	Min, Max	(0, 76)	(0, 73)	(0, 76)	

	Measure	Persistent Cohort	Non-Persistent Cohort	Total Cohort	p-value
Theophylline or other methylxanthine prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	0.061
	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)	
Omalizumab prescriptions (yes/no)	N (% not missing)	1152 (100.0)	839 (100.0)	1991 (100.0)	N/A
	No, n (%)	1152 (100.0)	839 (100.0)	1991 (100.0)	

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

11.5 Phase 2: Patient population

Figure 6: Phase 2 and Phase 3 (pMDI group) consort diagram

11.6 Phase 2: Baseline characterisation

11.6.1 Demographics

Table 17: Phase 2 - demographics

	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)

11.6.2 Comorbidities

Table 18: Phase 2 - 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)
	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)

	Measure	Patients changing from DPI to pMDI
	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)
	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)

	Measure	Patients changing from DPI to pMDI
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)

11.6.3 Disease severity

Table 19: Phase 2 – disease severity

	Measure	Patients changing from DPI to pMDI
All inpatient admissions	N (% not missing)	667 (100.0)
	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)

	Measure	Patients changing from DPI to pMDI
	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)
	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)
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)

	Measure	Patients changing from DPI to pMDI
	≥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)
LRTI-related outpatient attendances (categorised)	N (% not missing)	667(100)
	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)

	Measure	Patients changing from DPI to pMDI
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)
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)

	Measure	Patients changing from DPI to pMDI
Acute OCS	N (% not missing)	667 (100.0)
	Mean (SD)	1.2 (2.4)
	Median (IQR)	0 (0, 1)
	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)

11.6.4 Medication during the baseline year

Table 20: Phase 2 – medication during the 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)
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)

	Measure	Patients changing from DPI to pMDI
	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)
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)

	Measure	Patients changing from DPI to pMDI
	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)
	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)
	N (% not missing)	667(100)

	Measure	Patients changing from DPI to pMDI
SABA oral prescriptions (yes/no)	No, n (%)	579 (86.8)
	Yes, n (%)	88 (13.2)
SABA oral prescriptions (categorised)	N (% not missing)	667(100)
	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)
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)

	Measure	Patients changing from DPI to pMDI
	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)
	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)

	Measure	Patients changing from DPI to pMDI
	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)
Theophylline or other methylxanthine prescriptions	N (% not missing)	667 (100.0)
	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)
Omalizumab prescriptions (yes/no)	N (% not missing)	667(100)
	No, n (%)	667 (100.0)

11.6.5 Asthma-related costs during the baseline year

Table 21: Phase 2 – asthma-related costs during the baseline year

	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)

	Measure	Patients changing from DPI to pMDI
	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)
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)
Omalizumab cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	0.0 (0.0)
	Min, Max	(0, 0)
Acute OCS cost (KRW)	N (% not missing)	667 (100.0)
	Mean (SD)	1913.7 (9842.8)
	Min, Max	(0, 209562)

	Measure	Patients changing from DPI to pMDI
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)
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)

	Measure	Patients changing from DPI to pMDI
	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)
Secondary outcTotal 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)

11.7 Phase 2: Exploratory effectiveness outcomes

Table 22: Phase 2 – exploratory effectiveness outcomes

	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)		
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)		

	Measure	Baseline	Outcome	OR (95%CI)	p-value
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.

11.8 Phase 3: Patient population

Figure 7: Phase 3 (DPI group) consort diagram

11.9 Phase 3: Unmatched patient characteristics

Unmatched patients in the cohort that continued with FDC ICS/LABA DPI therapy were similar to those in the pMDI change cohort in terms of age and gender, but differed significantly with respect to type of medical insurance (p=0.046) (Table 23). Unmatched patients in the DPI continuation cohort had significantly less diagnoses of COPD (p<0.001), oral thrush (p=0.017 and p<0.001), rhinitis (p=0.001 and p<0.001), GERD (p=0.005 and p<0.001) and other chronic lung disease (p=0.001 and p<0.001) during the baseline year and ever prior to the index date, as compared to patients that changed to pMDI therapy (Table 24). Patients in the DPI cohort also had less incidence of ischaemic heart disease (p=0.025), influenza (p=0.021) and comorbid nasal polyps (p=0.039) ever prior to index date. In terms of disease severity, unmatched patients in the DPI cohort had less severe disease during the baseline year for all variables studied (excluding prescriptions for non-acute oral corticosteroids) compared to patients in the pMDI change cohort (Table 25). Patients within the DPI continuation cohort also had fewer inpatient hospital admissions, hospital admission days, outpatient and emergency department attendance, asthma exacerbations, acute respiratory events and prescriptions for acute oral corticosteroids and antibiotics (all p<0.001).

Medication during the baseline year was compared for unmatched patients in both cohorts (Table 26). Patients that continued with a DPI were prescribed fewer FDC ICS/LABA, ICS only, LTRA, LABA (inhaler and patch), SAMA, theophylline and SABA prescriptions and had a lower ICS average daily dose compared to patients in the pMDI change cohort (all p<0.001 except for LABA patch [p=0.002]). Asthma-related costs during the baseline year were higher for unmatched patients that changed from DPI to pMDI for FDC ICS/LABA therapy as compared to patients that continued with a DPI inhaler (Table 27). Costs were found to be increased for the pMDI change cohort for all asthma-related medications (except for oral SABA, FDC SABA/SAMA, oral LABA and non-acute oral corticosteroids) and for all in- and out- patient hospital attendance (all p<0.001, except for LABA patch [p=0.002]).

11.9.1 Demographics

Table 23: Phase 3 – demographics (unmatched)

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
Age at IPD (years)	N (% not missing)	141275 (100.0)	667 (100.0)	0.003	0.925
	Mean (SD)	58.2 (15.1)	58.1 (15.1)		
	Median (IQR)	61 (49, 70)	60 (49, 70)		
	Min, Max	(12, 80)	(12, 80)		
	N (% not missing)	141275 (100.0)	667 (100.0)	0.009	0.159

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
Age at IPD (years) (categorised)	12-18, n (%)	1613 (1.1)	2 (0.3)		
	19-35, n (%)	11734 (8.3)	63 (9.4)		
	36-65, n (%)	73929 (52.3)	347 (52.0)		
	66-80, n (%)	53999 (38.2)	255 (38.2)		
Gender	N (% not missing)	141275 (100.0)	667 (100.0)		
	Male, n (%)	77464 (54.8)	366 (54.9)	0.001	0.983
	Female, n (%)	63811 (45.2)	301 (45.1)		
Insurance	N (% not missing)	141275 (100.0)	667 (100.0)		
	Medical insurance, n (%)	126516 (89.6)	586 (87.9)		
	Medical aid, n (%)	13544 (9.6)	79 (11.8)	0.015	0.046
	Veterans cover, n (%)	1215 (0.9)	2 (0.3)		

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

11.9.2 Comorbidities

Table 24: Phase 3 – comorbidities (unmatched)

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
COPD	N (% not missing)	141275 (100.0)	667 (100.0)		
	No, n (%)	64114 (45.4)	247 (37.0)	0.170	<0.001
	Yes, n (%)	77161 (54.6)	420 (63.0)		
COPD (ever)	N (% not missing)	141275 (100.0)	667 (100.0)		
	No, n (%)	55324 (39.2)	170 (25.5)	0.295	<0.001
	Yes, n (%)	85951 (60.8)	497 (74.5)		
Oral thrush	N (% not missing)	141275 (100.0)	667 (100.0)		
	No, n (%)	140531 (99.5)	659 (98.8)	0.073	0.017
	Yes, n (%)	744 (0.5)	8 (1.2)		
Oral thrush (ever)	N (% not missing)	141275 (100.0)	667 (100.0)		
	No, n (%)	140250 (99.3)	653 (97.9)	0.117	<0.001
	Yes, n (%)	1025 (0.7)	14 (2.1)		
Comorbid eczema	N (% not missing)	141275 (100.0)	667 (100.0)		
	No, n (%)	134054 (94.9)	638 (95.7)	0.036	0.372
	Yes, n (%)	7221 (5.1)	29 (4.3)		
Comorbid eczema (ever)	N (% not missing)	141275 (100.0)	667 (100.0)		
	No, n (%)	130098 (92.1)	601 (90.1)	0.070	0.058
	Yes, n (%)	11177 (7.9)	66 (9.9)		
Comorbid GERD	N (% not missing)	141275 (100.0)	667 (100.0)		
	No, n (%)	106153 (75.1)	470 (70.5)	0.105	0.005
	Yes, n (%)	35122 (24.9)	197 (29.5)		
Comorbid GERD (ever)	N (% not missing)	141275 (100.0)	667 (100.0)		
	No, n (%)	95397 (67.5)	367 (55.0)	0.259	<0.001

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
	Yes, n (%)	45878 (32.5)	300 (45.0)		
Ischaemic heart disease	N (% not missing)	141275 (100.0)	667 (100.0)	0.001	0.988
	No, n (%)	129859 (91.9)	613 (91.9)		
	Yes, n (%)	11416 (8.1)	54 (8.1)		
Ischaemic heart disease (ever)	N (% not missing)	141275 (100.0)	667 (100.0)	0.083	0.025
	No, n (%)	127362 (90.2)	584 (87.6)		
	Yes, n (%)	13913 (9.8)	83 (12.4)		
Influenza	N (% not missing)	141275 (100.0)	667 (100.0)	0.057	0.094
	No, n (%)	139536 (98.8)	654 (98.1)		
	Yes, n (%)	1739 (1.2)	13 (1.9)		
Influenza (ever)	N (% not missing)	141275 (100.0)	667 (100.0)	0.079	0.021
	No, n (%)	138404 (98.0)	645 (96.7)		
	Yes, n (%)	2871 (2.0)	22 (3.3)		
Other chronic lung diseases	N (% not missing)	141275 (100.0)	667 (100.0)	0.124	0.001
	No, n (%)	94570 (66.9)	407 (61.0)		
	Yes, n (%)	46705 (33.1)	260 (39.0)		
Other chronic lung diseases (ever)	N (% not missing)	141275 (100.0)	667 (100.0)	0.306	<0.001
	No, n (%)	83247 (58.9)	292 (43.8)		
	Yes, n (%)	58028 (41.1)	375 (56.2)		
Comorbid nasal polyps	N (% not missing)	141275 (100.0)	667 (100.0)	0.012	0.744
	No, n (%)	138556 (98.1)	653 (97.9)		
	Yes, n (%)	2719 (1.9)	14 (2.1)		
Comorbid nasal polyps (ever)	N (% not missing)	141275 (100.0)	667 (100.0)	0.072	0.039
	No, n (%)	137409 (97.3)	640 (96.0)		
	Yes, n (%)	3866 (2.7)	27 (4.0)		
Pneumonia	N (% not missing)	141275 (100.0)	667 (100.0)	0.081	0.026
	No, n (%)	131462 (93.1)	606 (90.9)		
	Yes, n (%)	9813 (6.9)	61 (9.1)		
Pneumonia (ever)	N (% not missing)	141275 (100.0)	667 (100.0)	0.186	<0.001
	No, n (%)	127742 (90.4)	562 (84.3)		
	Yes, n (%)	13533 (9.6)	105 (15.7)		
Comorbid rhinitis (active)	N (% not missing)	141275 (100.0)	667 (100.0)	0.125	0.001
	No, n (%)	59685 (42.2)	241 (36.1)		
	Yes, n (%)	81590 (57.8)	426 (63.9)		
Comorbid rhinitis (ever)	N (% not missing)	141275 (100.0)	667 (100.0)	0.272	<0.001
	No, n (%)	47982 (34.0)	146 (21.9)		
	Yes, n (%)	93293 (66.0)	521 (78.1)		
Charlson Comorbidity Index (CCI)	N (% not missing)	141275 (100.0)	667 (100.0)	0.041	0.340
	Mean (SD)	1.4 (0.8)	1.4 (0.9)		
	Median (IQR)	1 (1, 1)	1 (1, 1)		
	Min, Max	(0, 9)	(0, 7)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
Charlson Comorbidity Index (CCI) (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.038	0.550
	0-1, n (%)	114497 (81.0)	531 (79.6)		
	2-5, n (%)	26343 (18.6)	133 (19.9)		
	6-10 n (%)	435 (0.3)	3 (0.4)		

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

11.9.3 Disease severity

Table 25: Phase 3 – disease severity (unmatched)

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
All inpatient admissions	N (% not missing)	141275 (100.0)	667 (100.0)	0.143	<0.001
	Mean (SD)	0.6 (1.5)	0.9 (1.8)		
	Median (IQR)	0 (0, 1)	0 (0, 1)		
	Min, Max	(0, 46)	(0, 24)		
All inpatient admissions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.180	<0.001
	0, n (%)	99491 (70.4)	414 (62.1)		
	1, n (%)	23959 (17.0)	125 (18.7)		
	2, n (%)	9168 (6.5)	68 (10.2)		
	3, n (%)	3636 (2.6)	29 (4.3)		
	≥4, n (%)	5021 (3.6)	31 (4.6)		
All inpatient admissions days	N (% not missing)	141275 (100.0)	667 (100.0)	0.110	<0.001
	Mean (SD)	5.7 (21.9)	8.3 (23.8)		
	Median (IQR)	0 (0, 3)	0 (0, 7)		
	Min, Max	(0, 424)	(0, 312)		
All inpatient admissions days (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	Data visualisation only	
	0, n (%)	99491 (70.4)	414 (62.1)		
	1-3, n (%)	8659 (6.1)	44 (6.6)		
	4-6, n (%)	7337 (5.2)	38 (5.7)		
	7-13, n (%)	10746 (7.6)	58 (8.7)		
	≥14, n (%)	15042 (10.6)	113 (16.9)		
LRTI-related inpatient admissions	N (% not missing)	141275 (100.0)	667 (100.0)	0.145	<0.001
	Mean (SD)	0.2 (0.5)	0.3 (0.6)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 14)	(0, 5)		
LRTI-related inpatient admissions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.155	<0.001
	0, n (%)	123113 (87.1)	543 (81.4)		
	1, n (%)	14431 (10.2)	93 (13.9)		
	2, n (%)	2596 (1.8)	22 (3.3)		
	3, n (%)	687 (0.5)	5 (0.7)		
	≥4, n (%)	448 (0.3)	4 (0.6)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
LRTI-related inpatient admissions days	N (% not missing)	141275 (100.0)	667 (100.0)	0.116	<0.001
	Mean (SD)	1.9 (8.9)	3.0 (10.9)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 424)	(0, 161)		
LRTI-related inpatient admissions days (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	Data visualisation only	
	0, n (%)	123113 (87.1)	543 (81.4)		
	1-3, n (%)	2103 (1.5)	14 (2.1)		
	4-6, n (%)	3879 (2.7)	22 (3.3)		
	7-13, n (%)	6487 (4.6)	43 (6.4)		
	≥14, n (%)	5693 (4.0)	45 (6.7)		
Asthma-related inpatient admissions	N (% not missing)	141275 (100.0)	667 (100.0)	0.152	<0.001
	Mean (SD)	0.1 (0.5)	0.2 (0.7)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 19)	(0, 5)		
Asthma-related inpatient admissions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.169	<0.001
	0, n (%)	128331 (90.8)	567 (85.0)		
	1, n (%)	9807 (6.9)	72 (10.8)		
	2, n (%)	2045 (1.4)	18 (2.7)		
	3, n (%)	563 (0.4)	4 (0.6)		
	≥4, n (%)	529 (0.4)	6 (0.9)		
Asthma-related inpatient admissions days	N (% not missing)	141275 (100.0)	667 (100.0)	0.117	<0.001
	Mean (SD)	1.2 (7.1)	2.1 (7.6)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 366)	(0, 99)		
Asthma-related inpatient admissions days (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	Data visualisation only	
	0, n (%)	128331 (90.8)	567 (85.0)		
	1-3, n (%)	1789 (1.3)	13 (1.9)		
	4-6, n (%)	3186 (2.3)	20 (3.0)		
	7-13, n (%)	4486 (3.2)	35 (5.2)		
	≥14, n (%)	3483 (2.5)	32 (4.8)		
Asthma exacerbation-related inpatient admissions	N (% not missing)	141275 (100.0)	667 (100.0)	0.137	<0.001
	Mean (SD)	0.0 (0.3)	0.1 (0.4)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 16)	(0, 5)		
Asthma exacerbation-related inpatient admissions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.151	<0.001
	0, n (%)	138038 (97.7)	629 (94.3)		
	1, n (%)	2262 (1.6)	26 (3.9)		
	2, n (%)	606 (0.4)	8 (1.2)		
	3, n (%)	165 (0.1)	2 (0.3)		
	≥4, n (%)	204 (0.1)	2 (0.3)		
	N (% not missing)	141275 (100.0)	667 (100.0)	0.112	<0.001

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
Asthma exacerbation-related inpatient admissions days	Mean (SD)	0.3 (3.9)	0.9 (5.3)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 353)	(0, 78)		
Asthma exacerbation-related inpatient admissions days (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	Data visualisation only	
	0, n (%)	138038 (97.7)	629 (94.3)		
	1-3, n (%)	365 (0.3)	8 (1.2)		
	4-6, n (%)	759 (0.5)	5 (0.7)		
	7-13, n (%)	1082 (0.8)	11 (1.6)		
	≥14, n (%)	1031 (0.7)	14 (2.1)		
All outpatient attendances	N (% not missing)	141275 (100.0)	667 (100.0)		
	Mean (SD)	30.5 (25.6)	33.7 (26.9)	0.120	<0.001
	Median (IQR)	24 (14, 38)	27 (16, 41)		
	Min, Max	(0, 367)	(2, 220)		
All outpatient attendances (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)		
	0, n (%)	25 (0.0)	0 (0.0)		
	1-12, n (%)	27451 (19.4)	88 (13.2)		
	13-24, n (%)	45910 (32.5)	221 (33.1)	0.140	0.002
	25-36, n (%)	29798 (21.1)	149 (22.3)		
	37-48, n (%)	16181 (11.5)	91 (13.6)		
	≥48, n (%)	21910 (15.5)	118 (17.7)		
LRTI-related outpatient attendances	N (% not missing)	141275 (100.0)	667 (100.0)		
	Mean (SD)	26.4 (22.6)	28.9 (23.9)	0.111	<0.001
	Median (IQR)	20 (13, 33)	22 (14, 35)		
	Min, Max	(0, 361)	(2, 216)		
LRTI-related outpatient attendances (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)		
	0, n (%)	25 (0.0)	0 (0.0)		
	1-12, n (%)	34640 (24.5)	120 (18.0)		
	13-24, n (%)	50535 (35.8)	251 (37.6)	0.128	0.006
	25-36, n (%)	27711 (19.6)	141 (21.1)		
	37-48, n (%)	12993 (9.2)	72 (10.8)		
	≥48, n (%)	15371 (10.9)	83 (12.4)		
Asthma-related outpatient attendances	N (% not missing)	141275 (100.0)	667 (100.0)		
	Mean (SD)	6.7 (7.3)	7.3 (7.6)	0.080	0.004
	Median (IQR)	5 (3, 9)	6 (3, 9)		
	Min, Max	(0, 266)	(0, 85)		
Asthma-related outpatient attendances (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)		
	0, n (%)	10829 (7.7)	47 (7.0)		
	1-3, n (%)	36522 (25.9)	146 (21.9)		
	4-6, n (%)	41355 (29.3)	184 (27.6)	0.113	0.026
	7-9, n (%)	22516 (15.9)	129 (19.3)		
	10-12, n (%)	12818 (9.1)	65 (9.7)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
	≥13, n (%)	17235 (12.2)	96 (14.4)		
All emergency attendances	N (% not missing)	141275 (100.0)	667 (100.0)	0.154	<0.001
	Mean (SD)	0.3 (0.7)	0.4 (0.9)		
	Median (IQR)	0 (0, 0)	0 (0, 1)		
	Min, Max	(0, 54)	(0, 11)		
All emergency attendances (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.168	<0.001
	0, n (%)	116330 (82.3)	497 (74.5)		
	1, n (%)	18215 (12.9)	119 (17.8)		
	2, n (%)	4335 (3.1)	38 (5.7)		
	3, n (%)	1343 (1.0)	5 (0.7)		
	≥4, n (%)	1052 (0.7)	8 (1.2)		
LRTI-related emergency attendances	N (% not missing)	141275 (100.0)	667 (100.0)	0.157	<0.001
	Mean (SD)	0.3 (0.7)	0.4 (0.8)		
	Median (IQR)	0 (0, 0)	0 (0, 1)		
	Min, Max	(0, 54)	(0, 9)		
LRTI-related emergency attendances (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.168	<0.001
	0, n (%)	116330 (82.3)	497 (74.5)		
	1, n (%)	18673 (13.2)	123 (18.4)		
	2, n (%)	4112 (2.9)	35 (5.2)		
	3, n (%)	1244 (0.9)	5 (0.7)		
	≥4, n (%)	916 (0.6)	7 (1.0)		
Asthma-related emergency attendances	N (% not missing)	141275 (100.0)	667 (100.0)	0.134	<0.001
	Mean (SD)	0.1 (0.4)	0.1 (0.4)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 40)	(0, 4)		
Asthma-related emergency attendances (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.146	<0.001
	0, n (%)	133515 (94.5)	603 (90.4)		
	1, n (%)	6463 (4.6)	51 (7.6)		
	2, n (%)	919 (0.7)	10 (1.5)		
	3, n (%)	238 (0.2)	2 (0.3)		
	≥4, n (%)	140 (0.1)	1 (0.1)		
Antibiotics	N (% not missing)	141275 (100.0)	667 (100.0)	0.229	<0.001
	Mean (SD)	0.7 (1.7)	1.2 (2.1)		
	Median (IQR)	0 (0, 1)	0 (0, 2)		
	Min, Max	(0, 50)	(0, 15)		
Antibiotics (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.255	<0.001
	0, n (%)	96323 (68.2)	375 (56.2)		
	1-3, n (%)	37301 (26.4)	224 (33.6)		
	4-6, n (%)	5462 (3.9)	43 (6.4)		
	7-9, n (%)	1332 (0.9)	19 (2.8)		
	10-12, n (%)	472 (0.3)	3 (0.4)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
	≥13, n (%)	385 (0.3)	3 (0.4)		
Acute OCS	N (% not missing)	141275 (100.0)	667 (100.0)	0.172	<0.001
	Mean (SD)	0.8 (2.0)	1.2 (2.4)		
	Median (IQR)	0 (0, 1)	0 (0, 1)		
	Min, Max	(0, 48)	(0, 18)		
Acute OCS (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.189	<0.001
	0, n (%)	97569 (69.1)	408 (61.2)		
	1, n (%)	20423 (14.5)	107 (16.0)		
	2, n (%)	9343 (6.6)	47 (7.0)		
	3, n (%)	4817 (3.4)	38 (5.7)		
	≥4, n (%)	9123 (6.5)	67 (10.0)		
Non-acute OCS	N (% not missing)	141275 (100.0)	667 (100.0)	0.012	0.951
	Mean (SD)	0.7 (1.3)	0.6 (1.2)		
	Median (IQR)	0 (0, 1)	0 (0, 1)		
	Min, Max	(0, 55)	(0, 9)		
Non-acute OCS (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.008	0.780
	0, n (%)	95355 (67.5)	450 (67.5)		
	1, n (%)	22002 (15.6)	107 (16.0)		
	2, n (%)	11218 (7.9)	49 (7.3)		
	3, n (%)	6765 (4.8)	37 (5.5)		
	≥4, n (%)	5935 (4.2)	24 (3.6)		
Severe exacerbations (ATS/ERS)	N (% not missing)	141275 (100.0)	667 (100.0)	0.207	<0.001
	Mean (SD)	0.5 (0.7)	0.6 (0.8)		
	Median (IQR)	0 (0, 1)	1 (0, 1)		
	Min, Max	(0, 18)	(0, 6)		
Severe exacerbations (ATS/ERS) (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.214	<0.001
	0, n (%)	82149 (58.1)	316 (47.4)		
	1, n (%)	51443 (36.4)	295 (44.2)		
	2, n (%)	5751 (4.1)	42 (6.3)		
	3, n (%)	1238 (0.9)	7 (1.0)		
	≥4, n (%)	694 (0.5)	7 (1.0)		
Acute respiratory event	N (% not missing)	141275 (100.0)	667 (100.0)	0.199	<0.001
	Mean (SD)	0.9 (1.4)	1.2 (1.5)		
	Median (IQR)	1 (0, 1)	1 (0, 1)		
	Min, Max	(0, 50)	(0, 12)		
Acute respiratory event (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.245	<0.001
	0, n (%)	63939 (45.3)	219 (32.8)		
	1, n (%)	53867 (38.1)	291 (43.6)		
	2, n (%)	12620 (8.9)	83 (12.4)		
	3, n (%)	5100 (3.6)	24 (3.6)		
	≥4, n (%)	5749 (4.1)	50 (7.5)		

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

11.9.4 Medication during the baseline year

Table 26: Phase 3 – medication during the baseline year (unmatched)

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
FDC ICS/LABA prescriptions	N (% not missing)	141275 (100.0)	667 (100.0)	0.325	<0.001
	Mean (SD)	3.8 (2.6)	4.7 (2.7)		
	Median (IQR)	3 (2, 5)	4 (3, 6)		
	Min, Max	(2, 43)	(2, 14)		
FDC ICS/LABA prescriptions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.352	<0.001
	2-3, n (%)	85514 (60.5)	288 (43.2)		
	≥4, n (%)	55761 (39.5)	379 (56.8)		
ICS only prescriptions	N (% not missing)	141275 (100.0)	667 (100.0)	0.062	<0.001
	Mean (SD)	0.4 (1.9)	0.5 (1.4)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 146)	(0, 18)		
ICS only prescriptions (yes/no)	N (% not missing)	141275 (100.0)	667 (100.0)	0.207	<0.001
	No, n (%)	118474 (83.9)	504 (75.6)		
	Yes, n (%)	22801 (16.1)	163 (24.4)		
ICS only prescriptions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.143	<0.001
	0, n (%)	118474 (83.9)	504 (75.6)		
	1, n (%)	12084 (8.6)	90 (13.5)		
	2, n (%)	4447 (3.1)	40 (6.0)		
	3, n (%)	2181 (1.5)	10 (1.5)		
	≥4, n (%)	4089 (2.9)	23 (3.4)		
ICS average daily dose	N (% not missing)	141275 (100.0)	667 (100.0)	0.563	<0.001
	Mean (SD)	262.7 (206.0)	400.8 (279.3)		
	Median (IQR)	205.5 (123.3, 328.8)	328.8 (205.5, 498.1)		
	Min, Max	(19.7, 4602.7)	(65.8, 2219.2)		
ICS average daily dose (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.605	<0.001
	>0-250, n (%)	91912 (65.1)	243 (36.4)		
	>250-500, n (%)	35651 (25.2)	259 (38.8)		
	>500, n (%)	13712 (9.7)	165 (24.7)		
IV/IM CS prescriptions	N (% not missing)	141275 (100.0)	667 (100.0)	0.112	<0.001
	Mean (SD)	1.8 (4.0)	2.3 (4.5)		
	Median (IQR)	1 (0, 2)	1 (0, 3)		
	Min, Max	(0, 180)	(0, 48)		
IV/IM CS prescriptions (yes/no)	N (% not missing)	141275 (100.0)	667 (100.0)	0.115	0.003
	No, n (%)	70388 (49.8)	294 (44.1)		
	Yes, n (%)	70887 (50.2)	373 (55.9)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
IV/IM CS prescriptions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.138	0.008
	0, n (%)	70388 (49.8)	294 (44.1)		
	1-3, n (%)	49287 (34.9)	244 (36.6)		
	4-8, n (%)	15451 (10.9)	87 (13.0)		
	9-13, n (%)	3202 (2.3)	20 (3.0)		
	≥13, n (%)	2947 (2.1)	22 (3.3)		
SABA prescriptions	N (% not missing)	141275 (100.0)	667 (100.0)	0.128	<0.001
	Mean (SD)	2.5 (5.4)	3.3 (6.5)		
	Median (IQR)	1 (0, 3)	1 (0, 3)		
	Min, Max	(0, 287)	(0, 64)		
SABA prescriptions (yes/no)	N (% not missing)	141275 (100.0)	667 (100.0)	0.217	<0.001
	No, n (%)	66975 (47.4)	245 (36.7)		
	Yes, n (%)	74300 (52.6)	422 (63.3)		
SABA prescriptions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.166	<0.001
	0, n (%)	66975 (47.4)	245 (36.7)		
	1-3, n (%)	44933 (31.8)	260 (39.0)		
	4-6, n (%)	13692 (9.7)	65 (9.7)		
	7-9, n (%)	6312 (4.5)	34 (5.1)		
	10-12, n (%)	3635 (2.6)	26 (3.9)		
	≥13, n (%)	5728 (4.1)	37 (5.5)		
SABA inhaler prescriptions	N (% not missing)	141275 (100.0)	667 (100.0)	0.158	<0.001
	Mean (SD)	1.2 (3.0)	1.8 (4.2)		
	Median (IQR)	0 (0, 1)	0 (0, 1)		
	Min, Max	(0, 113)	(0, 64)		
SABA inhaler prescriptions (yes/no)	N (% not missing)	141275 (100.0)	667 (100.0)	0.212	<0.001
	No, n (%)	92542 (65.5)	368 (55.2)		
	Yes, n (%)	48733 (34.5)	299 (44.8)		
SABA inhaler prescriptions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.199	<0.001
	0, n (%)	92542 (65.5)	368 (55.2)		
	1-3, n (%)	34360 (24.3)	201 (30.1)		
	4-6, n (%)	7305 (5.2)	44 (6.6)		
	7-9, n (%)	3272 (2.3)	24 (3.6)		
	10-12, n (%)	1919 (1.4)	14 (2.1)		
	≥13, n (%)	1877 (1.3)	16 (2.4)		
SABA inhaler average daily dose	N (% not missing)	141275 (100.0)	667 (100.0)	0.137	<0.001
	Mean (SD)	90.7 (273.4)	138.0 (405.5)		
	Median (IQR)	0 (0, 55)	0 (0, 110)		
	Min, Max	(0, 13315)	(0, 6630)		
SABA inhaler average daily dose (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.196	<0.001
	0, n (%)	92542 (65.5)	368 (55.2)		
	>0-200, n (%)	32157 (22.8)	193 (28.9)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
	>200-400, n (%)	7913 (5.6)	43 (6.4)		
	>400-800, n (%)	5206 (3.7)	34 (5.1)		
	≥800, n (%)	3457 (2.4)	29 (4.3)		
SABA nebuliser prescriptions	N (% not missing)	141275 (100.0)	667 (100.0)		
	Mean (SD)	0.7 (3.1)	1.0 (3.2)	0.087	<0.001
	Median (IQR)	0 (0, 1)	0 (0, 1)		
	Min, Max	(0, 274)	(0, 44)		
SABA nebuliser prescriptions (yes/no)	N (% not missing)	141275 (100.0)	667 (100.0)		
	No, n (%)	105281 (74.5)	427 (64.0)	0.229	<0.001
	Yes, n (%)	35994 (25.5)	240 (36.0)		
SABA nebuliser prescriptions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)		
	0, n (%)	105281 (74.5)	427 (64.0)		
	1-3, n (%)	29165 (20.6)	200 (30.0)		
	4-6, n (%)	3810 (2.7)	23 (3.4)	0.169	<0.001
	7-9, n (%)	1272 (0.9)	4 (0.6)		
	10-12, n (%)	680 (0.5)	5 (0.7)		
	≥13, n (%)	1067 (0.8)	8 (1.2)		
SABA oral prescriptions	N (% not missing)	141275 (100.0)	667 (100.0)		
	Mean (SD)	0.6 (2.4)	0.5 (2.0)	0.038	0.728
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 126)	(0, 24)		
SABA oral prescriptions (yes/no)	N (% not missing)	141275 (100.0)	667 (100.0)		
	No, n (%)	122104 (86.4)	579 (86.8)	0.011	0.777
	Yes, n (%)	19171 (13.6)	88 (13.2)		
SABA oral prescriptions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)		
	0, n (%)	122104 (86.4)	579 (86.8)		
	1-3, n (%)	12239 (8.7)	66 (9.9)		
	4-6, n (%)	3414 (2.4)	10 (1.5)	0.050	0.416
	7-9, n (%)	1487 (1.1)	5 (0.7)		
	10-12, n (%)	944 (0.7)	4 (0.6)		
	≥13, n (%)	1087 (0.8)	3 (0.4)		
FDC SABA/SAMA prescriptions (yes/no)	N (% not missing)	141275 (100.0)	667 (100.0)		
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.017	0.694
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 1)	(0, 1)		
SAMA prescriptions	N (% not missing)	141275 (100.0)	667 (100.0)		
	Mean (SD)	0.3 (1.5)	0.7 (2.8)	0.179	<0.001
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 141)	(0, 44)		
	N (% not missing)	141275 (100.0)	667 (100.0)		
	No, n (%)	123204 (87.2)	524 (78.6)	0.231	<0.001

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
SAMA prescriptions (yes/no)	Yes, n (%)	18071 (12.8)	143 (21.4)		
SAMA prescriptions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.244	<0.001
	0, n (%)	123204 (87.2)	524 (78.6)		
	1, n (%)	12118 (8.6)	83 (12.4)		
	2, n (%)	3192 (2.3)	26 (3.9)		
	3, n (%)	1170 (0.8)	9 (1.3)		
	≥4, n (%)	1591 (1.1)	25 (3.7)		
LAMA prescriptions	N (% not missing)	141275 (100.0)	667 (100.0)	0.167	<0.001
	Mean (SD)	1.0 (2.5)	1.5 (3.1)		
	Median (IQR)	0 (0, 0)	0 (0, 1)		
	Min, Max	(0, 41)	(0, 14)		
LAMA prescriptions (yes/no)	N (% not missing)	141275 (100.0)	667 (100.0)	0.148	<0.001
	No, n (%)	114143 (80.8)	498 (74.7)		
	Yes, n (%)	27132 (19.2)	169 (25.3)		
LAMA prescriptions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.148	<0.001
	0, n (%)	114143 (80.8)	498 (74.7)		
	1-2, n (%)	4853 (3.4)	28 (4.2)		
	3-4, n (%)	8473 (6.0)	50 (7.5)		
	≥5, n (%)	13806 (9.8)	91 (13.6)		
FDC LABA/LAMA prescriptions (yes/no)	N (% not missing)	141275 (100.0)	667 (100.0)	-	N/A
	No, n (%)	141275 (100.0)	667 (100.0)		
LABA inhaler prescriptions	N (% not missing)	141275 (100.0)	667 (100.0)	0.132	<0.001
	Mean (SD)	0.0 (0.2)	0.1 (0.6)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 14)	(0, 10)		
LABA inhaler prescriptions (yes/no)	N (% not missing)	141275 (100.0)	667 (100.0)	0.182	<0.001
	No, n (%)	140846 (99.7)	651 (97.6)		
	Yes, n (%)	429 (0.3)	16 (2.4)		
LABA inhaler prescriptions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.150	<0.001
	0, n (%)	140846 (99.7)	651 (97.6)		
	1, n (%)	180 (0.1)	9 (1.3)		
	2, n (%)	89 (0.1)	2 (0.3)		
	3, n (%)	56 (0.0)	1 (0.1)		
	≥4, n (%)	104 (0.1)	4 (0.6)		
LABA oral prescriptions	N (% not missing)	141275 (100.0)	667 (100.0)	0.016	0.287
	Mean (SD)	1.3 (3.5)	1.3 (3.2)		
	Median (IQR)	0 (0, 1)	0 (0, 1)		
	Min, Max	(0, 90)	(0, 34)		
	N (% not missing)	141275 (100.0)	667 (100.0)	0.051	0.180

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
LABA oral prescriptions (yes/no)	No, n (%)	101378 (71.8)	463 (69.4)		
	Yes, n (%)	39897 (28.2)	204 (30.6)		
LABA oral prescriptions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.006	0.289
	0, n (%)	101378 (71.8)	463 (69.4)		
	1-3, n (%)	22342 (15.8)	126 (18.9)		
	4-6, n (%)	8042 (5.7)	37 (5.5)		
	7-11, n (%)	5749 (4.1)	26 (3.9)		
	≥12, n (%)	3764 (2.7)	15 (2.2)		
LABA patch prescriptions	N (% not missing)	141275 (100.0)	667 (100.0)	0.072	0.002
	Mean (SD)	0.2 (1.4)	0.3 (1.3)		
	Median (IQR)	0 (0, 0)	0 (0, 0)		
	Min, Max	(0, 111)	(0, 12)		
LABA patch prescriptions (yes/no)	N (% not missing)	141275 (100.0)	667 (100.0)	0.112	0.002
	No, n (%)	132375 (93.7)	605 (90.7)		
	Yes, n (%)	8900 (6.3)	62 (9.3)		
LABA patch prescriptions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.107	0.006
	0, n (%)	132375 (93.7)	605 (90.7)		
	1-2, n (%)	5474 (3.9)	38 (5.7)		
	3-4, n (%)	1639 (1.2)	9 (1.3)		
	5-6, n (%)	760 (0.5)	4 (0.6)		
	≥7, n (%)	1027 (0.7)	11 (1.6)		
LTRA prescriptions	N (% not missing)	141275 (100.0)	667 (100.0)	0.349	<0.001
	Mean (SD)	3.2 (4.6)	5.0 (5.5)		
	Median (IQR)	1 (0, 5)	4 (0, 8)		
	Min, Max	(0, 97)	(0, 58)		
LTRA prescriptions (yes/no)	N (% not missing)	141275 (100.0)	667 (100.0)	0.338	<0.001
	No, n (%)	60567 (42.9)	180 (27.0)		
	Yes, n (%)	80708 (57.1)	487 (73.0)		
LTRA prescriptions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.409	<0.001
	0, n (%)	60567 (42.9)	180 (27.0)		
	1-3, n (%)	31876 (22.6)	132 (19.8)		
	4-6, n (%)	24027 (17.0)	153 (22.9)		
	7-11, n (%)	16197 (11.5)	119 (17.8)		
	≥12, n (%)	8608 (6.1)	83 (12.4)		
Theophylline or other methylxanthines prescriptions	N (% not missing)	141275 (100.0)	667 (100.0)	0.089	<0.001
	Mean (SD)	4.0 (6.3)	4.6 (5.7)		
	Median (IQR)	2 (0, 6)	3 (0, 7)		
	Min, Max	(0, 273)	(0, 65)		
Theophylline or other	N (% not missing)	141275 (100.0)	667 (100.0)	0.197	<0.001
	No, n (%)	55064 (39.0)	198 (29.7)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
methylxanthines prescriptions (yes/no)	Yes, n (%)	86211 (61.0)	469 (70.3)		
Theophylline or other methylxanthines prescriptions (categorised)	N (% not missing)	141275 (100.0)	667 (100.0)	0.168	<0.001
	0, n (%)	55064 (39.0)	198 (29.7)		
	1-3, n (%)	32759 (23.2)	170 (25.5)		
	4-6, n (%)	21439 (15.2)	115 (17.2)		
	7-11, n (%)	18113 (12.8)	107 (16.0)		
	≥12, n (%)	13900 (9.8)	77 (11.5)		
Omalizumab prescriptions (yes/no)	N (% not missing)	141275 (100.0)	667 (100.0)	-	N/A
	No, n (%)	141275 (100.0)	667 (100.0)		

* Mann-Whitney test for continuous variables and Chi-squared test for categorical variables; N/A – not applicable.

11.9.5 Asthma-related costs during the baseline year

Table 27: Phase 3 – asthma-related costs during the baseline year

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
FDC ICS/LABA cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.234	<0.001
	Mean (SD)	283710.8 (190459.7)	331480.1 (216955.7)		
	Min, Max	(0, 16503960)	(86950, 3437952)		
ICS only cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.141	<0.001
	Mean (SD)	3818.0 (20875.7)	6992.5 (24096.8)		
	Min, Max	(0, 1512780)	(0, 248624)		
IV/IM CS cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.153	<0.001
	Mean (SD)	2868.9 (12232.9)	5056.9 (16060.6)		
	Min, Max	(0, 707405)	(0, 186724)		
SABA inhaler cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.128	<0.001
	Mean (SD)	6825.6 (21050.7)	10143.6 (29869.2)		
	Min, Max	(0, 1868047)	(0, 487378)		
SABA oral cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.026	0.736
	Mean (SD)	1067.8 (10425.2)	788.7 (10713.3)		
	Min, Max	(0, 391320)	(0, 266640)		
SABA nebuliser cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.096	<0.001
	Mean (SD)	1152.6 (8357.7)	2094.3 (11049.5)		
	Min, Max	(0, 556650)	(0, 193129)		
FDC SABA/SAMA cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.036	0.693
	Mean (SD)	51.9 (1550.5)	11.6 (298.6)		
	Min, Max	(0, 213372)	(0, 7713)		
SAMA cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.101	<0.001
	Mean (SD)	1480.3 (10214.1)	2525.8 (10455.3)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
	Min, Max	(0, 1050615)	(0, 174540)		
LAMA cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.059	<0.001
	Mean (SD)	68007.9 (348072.0)	84249.3 (176232.2)		
	Min, Max	(0, 97670070)	(0, 811740)		
LABA/LAMA cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	-	N/A
	Mean (SD)	0.0 (0.0)	0.0 (0.0)		
	Min, Max	(0, 0)	(0, 0)		
LABA inhaler cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.130	<0.001
	Mean (SD)	328.4 (7878.2)	2511.6 (22363.8)		
	Min, Max	(0, 703560)	(0, 388800)		
LABA oral cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.039	0.199
	Mean (SD)	5980.5 (24722.1)	5113.2 (19197.3)		
	Min, Max	(0, 713856)	(0, 218400)		
LABA patch cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.047	0.002
	Mean (SD)	1579.9 (15576.3)	2294.2 (14596.3)		
	Min, Max	(0, 1136800)	(0, 205920)		
LTRA cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.155	<0.001
	Mean (SD)	93622.8 (156375.4)	116117.7 (132790.5)		
	Min, Max	(0, 8059931)	(0, 554140)		
Theophylline or other methylxanthine cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.080	<0.001
	Mean (SD)	20550.5 (39227.8)	23493.8 (34530.8)		
	Min, Max	(0, 3137778)	(0, 159642)		
Omalizumab cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	-	N/A
	Mean (SD)	0.0 (0.0)	0.0 (0.0)		
	Min, Max	(0, 0)	(0, 0)		
Acute OCS cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.096	<0.001
	Mean (SD)	1112.8 (6592.3)	1913.7 (9842.8)		
	Min, Max	(0, 605208)	(0, 209562)		
Non-acute OCS cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.012	0.846
	Mean (SD)	425.1 (2336.9)	399.7 (1768.2)		
	Min, Max	(0, 225900)	(0, 36360)		
Antibiotics cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.102	<0.001
	Mean (SD)	32074.2 (132470.1)	51814.0 (238078.8)		
	Min, Max	(0, 5665178)	(0, 5092382)		
All inpatient admissions cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.135	<0.001
	Mean (SD)	1009959.3 (3110966.2)	1499861.0 (4097685.5)		
	Min, Max	(0, 116690120)	(0, 53905540)		
LRTI-related inpatient admissions cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.145	<0.001
	Mean (SD)	307611.2 (1296225.7)	581952.0 (2343977.4)		
	Min, Max	(0, 66019610)	(0, 43951550)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
Asthma-related inpatient admissions cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.152	<0.001
	Mean (SD)	184953.5 (899464.5)	338353.1 (1104294.1)		
	Min, Max	(0, 40603890)	(0, 11255030)		
Asthma exacerbation-related inpatient admissions cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.143	<0.001
	Mean (SD)	52322.4 (511203.7)	147886.4 (796022.2)		
	Min, Max	(0, 40603890)	(0, 11255030)		
All outpatient attendances cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.096	<0.001
	Mean (SD)	816756.7 (1812292.1)	969568.8 (1331032.1)		
	Min, Max	(0, 327434830)	(66520, 24875180)		
LRTI-related outpatient attendances cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.096	<0.001
	Mean (SD)	816756.7 (1812292.1)	969568.8 (1331032.1)		
	Min, Max	(0, 327434830)	(66520, 24875180)		
Asthma-related outpatient attendances cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.153	<0.001
	Mean (SD)	142744.7 (265287.8)	177838.8 (185737.7)		
	Min, Max	(0, 24167720)	(0, 1662900)		
All emergency attendances cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.139	<0.001
	Mean (SD)	301866.8 (1375927.4)	572961.8 (2386341.7)		
	Min, Max	(0, 72369870)	(0, 42381850)		
LRTI-related emergency attendances cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.139	<0.001
	Mean (SD)	301866.8 (1375927.4)	572961.8 (2386341.7)		
	Min, Max	(0, 72369870)	(0, 42381850)		
Asthma-related emergency attendances cost (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.127	<0.001
	Mean (SD)	66496.3 (477860.5)	142548.1 (701601.2)		
	Min, Max	(0, 26816330)	(0, 9598590)		
All hospitalisation costs (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.161	<0.001
	Mean (SD)	2128582.8 (4703002.1)	3042391.5 (6501754.7)		
	Min, Max	(0, 328667830)	(66520, 97633700)		
All asthma-related hospitalisation costs (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.185	<0.001
	Mean (SD)	1170945.9 (2471460.3)	1690417.0 (3115036.8)		
	Min, Max	(0, 327434830)	(66520, 43728160)		
Drug costs (without ICS) (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.178	<0.001
	Mean (SD)	244208.9 (447716.5)	318297.8 (380091.2)		
	Min, Max	(0, 97671642)	(0, 5260946)		
Drug costs (with ICS) (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.242	<0.001
	Mean (SD)	531737.7 (536517.9)	656770.4 (494364.0)		
	Min, Max	(1583, 98034945)	(100040, 5584425)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	p-value
Total costs (without ICS) (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.199	<0.001
	Mean (SD)	1415154.8 (2583388.4)	2008714.8 (3330415.6)		
	Min, Max	(0, 328118400)	(72455, 48989106)		
Total costs (with ICS) (KRW)	N (% not missing)	141275 (100.0)	667 (100.0)	0.214	<0.001
	Mean (SD)	1702683.6 (2609765.1)	2347187.3 (3361235.4)		
	Min, Max	(97511, 328534616)	(220157, 49312585)		

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

11.10 Phase 3: Matched Patient characteristics

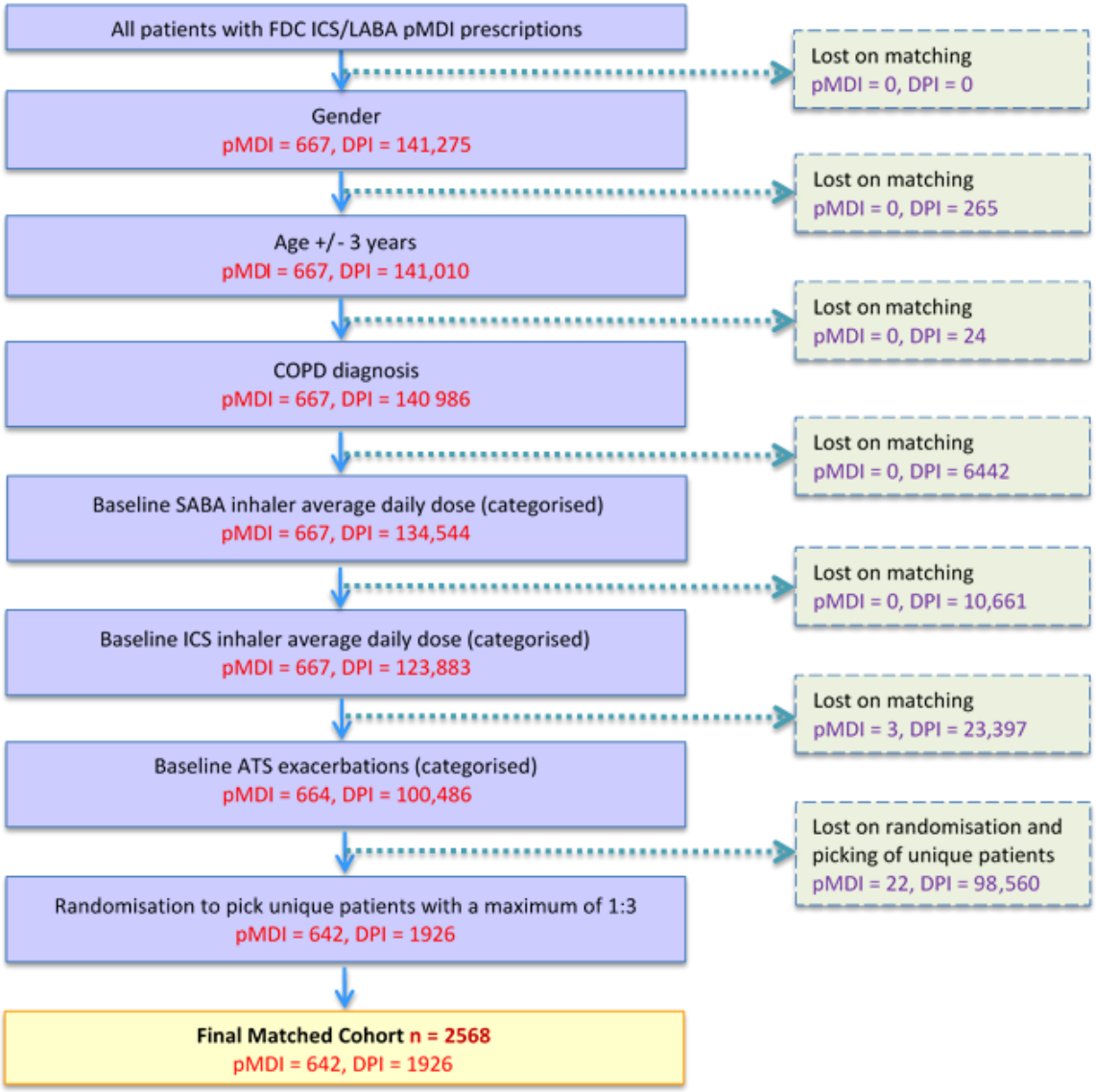

Figure 8: Phase 3 matched patient population consort diagram

11.10.1 Demographics

Table 28: Phase 3 – demographics (matched)

	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)		

* RCC based on primary outcome of no exacerbations

11.10.2 Comorbidities

Table 29: Phase 3 – comorbidities (matched)

	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)		
	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)		
	N (% not missing)	1926 (100.0)	642 (100.0)	0.060	0.004

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
Comorbid eczema (ever)	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)		
	No, n (%)	1459 (75.8)	457 (71.2)	0.104	0.006
	Yes, n (%)	467 (24.2)	185 (28.8)		
Comorbid GERD (ever)	N (% not missing)	1926 (100.0)	642 (100.0)		
	No, n (%)	1319 (68.5)	358 (55.8)	0.264	0.008
	Yes, n (%)	607 (31.5)	284 (44.2)		
Ischaemic heart disease	N (% not missing)	1926 (100.0)	642 (100.0)		
	No, n (%)	1774 (92.1)	591 (92.1)	0.002	0.000
	Yes, n (%)	152 (7.9)	51 (7.9)		
Ischaemic heart disease (ever)	N (% not missing)	1926 (100.0)	642 (100.0)		
	No, n (%)	1745 (90.6)	562 (87.5)	0.098	0.003
	Yes, n (%)	181 (9.4)	80 (12.5)		
Influenza	N (% not missing)	1926 (100.0)	642 (100.0)		
	No, n (%)	1909 (99.1)	629 (98.0)	0.095	0.003
	Yes, n (%)	17 (0.9)	13 (2.0)		
Influenza (ever)	N (% not missing)	1926 (100.0)	642 (100.0)		
	No, n (%)	1891 (98.2)	620 (96.6)	0.101	0.004
	Yes, n (%)	35 (1.8)	22 (3.4)		
Other chronic lung diseases	N (% not missing)	1926 (100.0)	642 (100.0)		
	No, n (%)	1210 (62.8)	396 (61.7)	0.024	0.001
	Yes, n (%)	716 (37.2)	246 (38.3)		
Other chronic lung diseases (ever)	N (% not missing)	1926 (100.0)	642 (100.0)		
	No, n (%)	1064 (55.2)	286 (44.5)	0.215	0.010
	Yes, n (%)	862 (44.8)	356 (55.5)		
Comorbid nasal polyps	N (% not missing)	1926 (100.0)	642 (100.0)		
	No, n (%)	1888 (98.0)	629 (98.0)	0.004	0.000
	Yes, n (%)	38 (2.0)	13 (2.0)		
Comorbid nasal polyps (ever)	N (% not missing)	1926 (100.0)	642 (100.0)		
	No, n (%)	1876 (97.4)	617 (96.1)	0.073	0.002
	Yes, n (%)	50 (2.6)	25 (3.9)		
Pneumonia	N (% not missing)	1926 (100.0)	642 (100.0)		
	No, n (%)	1674 (86.9)	552 (86.0)	0.027	0.005
	Yes, n (%)	252 (13.1)	90 (14.0)		
Pneumonia (ever)	N (% not missing)	1926 (100.0)	642 (100.0)		
	No, n (%)	1591 (82.6)	506 (78.8)	0.096	0.016
	Yes, n (%)	335 (17.4)	136 (21.2)		
Comorbid rhinitis (active)	N (% not missing)	1926 (100.0)	642 (100.0)		
	No, n (%)	821 (42.6)	232 (36.1)	0.133	0.000
	Yes, n (%)	1105 (57.4)	410 (63.9)		
	N (% not missing)	1926 (100.0)	642 (100.0)	0.315	0.010

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
Comorbid rhinitis (ever)	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)		

* RCC based on primary outcome of no exacerbations

11.10.3 Disease severity

Table 30: Phase 3 – disease severity (matched)

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
All inpatient admissions	N (% not missing)	1926 (100.0)	642 (100.0)	0.075	0.006
	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)		
	N (% not missing)	1926 (100.0)	642 (100.0)	0.033	0.005

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
LRTI-related inpatient admissions (categorised)	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)		
LRTI-related inpatient admissions days	N (% not missing)	1926 (100.0)	642 (100.0)	0.049	0.002
	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)		
Asthma exacerbation-related inpatient admissions	N (% not missing)	1926 (100.0)	642 (100.0)	0.068	0.009
	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-	N (% not missing)	1926 (100.0)	642 (100.0)	0.065	0.006
	0, n (%)	1849 (96.0)	608 (94.7)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
related inpatient admissions (categorised)	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)		
LRTI-related outpatient attendances	N (% not missing)	1926 (100.0)	642 (100.0)	0.092	0.020
	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)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
	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)		
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)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
	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)		
	≥13, n (%)	7 (0.4)	3 (0.5)		
Acute OCS	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	1.1 (2.3)	1.2 (2.4)	0.030	0.015
	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, n (%)	1189 (61.7)	394 (61.4)		
	1, n (%)	297 (15.4)	103 (16.0)	0.007	0.001
	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)		
	Mean (SD)	0.7 (1.4)	0.6 (1.2)	0.086	0.021
	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, n (%)	1251 (65.0)	435 (67.8)		
	1, n (%)	306 (15.9)	104 (16.2)	0.090	0.029
	2, n (%)	150 (7.8)	45 (7.0)		
	3, n (%)	115 (6.0)	35 (5.5)		
	≥4, n (%)	104 (5.4)	23 (3.6)		

* RCC based on primary outcome of no exacerbations

11.10.4 Medication during the baseline year

Table 31: Phase 3 – medication during the baseline year (matched)

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
FDC ICS/LABA prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	4.8 (2.9)	4.7 (2.7)	0.035	0.003
	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)		
	2-3, n (%)	829 (43.0)	278 (43.3)	0.005	0.000
	≥4, n (%)	1097 (57.0)	364 (56.7)		
ICS only prescriptions	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	0.6 (2.0)	0.5 (1.2)	0.036	0.006
	Median (IQR)	0 (0, 0)	0 (0, 0)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
	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)		
IV/IM CS prescriptions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.082	0.014
	0, n (%)	917 (47.6)	283 (44.1)		
	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)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
	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)		
	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)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
	≥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)		
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)		
	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)		
	N (% not missing)	1926 (100.0)	642 (100.0)	0.013	0.009
	0, n (%)	1477 (76.7)	480 (74.8)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
LAMA prescriptions (categorised)	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)		
LABA oral prescriptions (categorised)	N (% not missing)	1926 (100.0)	642 (100.0)	0.051	0.002
	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)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
	≥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)		
	≥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)		

* RCC based on primary outcome of no exacerbations

11.10.5 Asthma-related costs during the baseline year

Table 32: Phase 3 – asthma-related costs during the 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)		
	N (% not missing)	1926 (100.0)	642 (100.0)	0.059	0.015

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
IV/IM CS cost (KRW)	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)		
	Mean (SD)	9065.6 (24145.6)	8627.7 (22334.5)	0.019	0.000
	Min, Max	(0, 420527)	(0, 237234)		
SABA oral cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	1487.2 (13168.9)	810.4 (10918.9)	0.056	0.003
	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)		
Acute OCS cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)		
	Mean (SD)	2021.7 (10166.0)	1950.9 (10021.4)	0.007	0.008
	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)		

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
Antibiotics cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.032	0.003
	Mean (SD)	44220.0 (162117.4)	50776.9 (240245.1)		
	Min, Max	(0, 2388553)	(0, 5092382)		
All inpatient admissions cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.094	0.000
	Mean (SD)	1080756.8 (2981392.0	1413734.3 (4009021.2		
	Min, Max	(0, 42545150)	(0, 53905540)		
LRTI-related inpatient admissions cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.082	0.008
	Mean (SD)	400329.1 (1384010.9)	556818.8 (2333827.1)		
	Min, Max	(0, 17986500)	(0, 43951550)		
Asthma-related inpatient admissions cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.083	0.009
	Mean (SD)	231313.7 (894824.1)	310212.2 (999326.8)		
	Min, Max	(0, 17986500)	(0, 9598590)		
Asthma exacerbation-related inpatient admissions cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.077	0.011
	Mean (SD)	80620.4 (525353.4)	126415.0 (662497.1)		
	Min, Max	(0, 9824000)	(0, 6845720)		
All outpatient attendances cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.075	0.006
	Mean (SD)	849514.9 (1323000.9)	948336.6 (1314429.2)		
	Min, Max	(34630, 24945790)	(66520, 24875180)		
LRTI-related outpatient attendances cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.075	0.006
	Mean (SD)	849514.9 (1323000.9)	948336.6 (1314429.2)		
	Min, Max	(34630, 24945790)	(66520, 24875180)		
Asthma-related outpatient attendances cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.064	0.001
	Mean (SD)	161057.6 (203547.9)	173403.4 (180851.7)		
	Min, Max	(0, 2503440)	(0, 1662900)		
All emergency attendances cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.072	0.001
	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)	0.072	0.001
	Mean (SD)	409354.5 (1665530.6)	557420.3 (2401452.0)		
	Min, Max	(0, 38557320)	(0, 42381850)		
Asthma-related emergency attendances cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.062	0.008
	Mean (SD)	100572.5 (508245.2)	138370.1 (700243.9)		
	Min, Max	(0, 6275700)	(0, 9598590)		
All hospitalisation costs (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.103	0.004
	Mean (SD)	2339626.2 (4670337.0)	2919491.2 (6423627.0)		
	Min, Max	(34630, 81897370)	(66520, 97633700)		
All asthma-related hospitalisation costs (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.108	0.012
	Mean (SD)	1339489.7 (2316099.3)	1632171.9 (3035750.1)		
	Min, Max	(34630, 39352220)	(66520, 43728160)		
	N (% not missing)	1926 (100.0)	642 (100.0)	0.040	0.002

	Measure	DPI Repeat Cohort	pMDI Change Cohort	SMD	RCC
Drug costs (without ICS) (KRW)	Mean (SD)	330440.9 (392849.1)	314898.9 (380439.4)		
	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

11.11 Phase 3: Exploratory clinical effectiveness outcomes

Table 33: Phase 3 – exploratory effectiveness outcomes

	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 inpatient admissions	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)			
	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)			

	Measure	DPI Repeat Cohort	pMDI Change Cohort	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Adjusted p-value
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]	0.215[Δ]
	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]	0.580[Δ]
	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)

11.12 Phase 3: Exploratory cost outcome

Table 34: Phase 3 – exploratory asthma-related cost outcomes

	Measure	DPI Repeat Cohort	pMDI Change Cohort	p-value*
FDC ICS/LABA cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.027
	Mean (SD)	320457.6 (179916.7)	300146.7 (227263.3)	
	Min, Max	(41512, 2127028)	(59000, 3680622)	
ICS only cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.394
	Mean (SD)	4021.8 (21291.7)	4901.4 (23837.5)	
	Min, Max	(0, 430075)	(0, 385167)	
IV/IM CS cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.684
	Mean (SD)	3338.8 (13179.9)	3122.8 (11752.1)	
	Min, Max	(0, 240562)	(0, 190368)	
SABA inhaler cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	<0.001
	Mean (SD)	7423.4 (21235.7)	4673.8 (14280.2)	
	Min, Max	(0, 324636)	(0, 166480)	
SABA oral cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.014
	Mean (SD)	1039.9 (9089.6)	371.7 (3904.9)	
	Min, Max	(0, 159060)	(0, 80976)	
SABA nebuliser cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.631
	Mean (SD)	1662.1 (10555.2)	1927.4 (13573.5)	
	Min, Max	(0, 192973)	(0, 233599)	
FDC SABA/SAMA cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	N/A
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	
	Min, Max	(0, 0)	(0, 0)	
SAMA cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.572
	Mean (SD)	2016.3 (11406.3)	2348.0 (13879.7)	
	Min, Max	(0, 237568)	(0, 175511)	
LAMA cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.384
	Mean (SD)	89412.5 (191958.1)	79810.9 (283763.7)	
	Min, Max	(0, 3108592)	(0, 6124080)	
LABA/LAMA cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.238
	Mean (SD)	23.7 (1040.3)	213.4 (4026.7)	
	Min, Max	(0, 45657)	(0, 91314)	
LABA inhaler cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.166
	Mean (SD)	615.6 (8148.5)	1849.9 (22070.5)	
	Min, Max	(0, 194400)	(0, 427680)	
LABA oral cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.002
	Mean (SD)	5643.7 (20054.3)	3470.2 (13051.1)	
	Min, Max	(0, 256680)	(0, 104006)	
LABA patch cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.536
	Mean (SD)	1911.5 (15469.4)	1535.4 (11768.5)	
	Min, Max	(0, 227900)	(0, 189360)	

	Measure	DPI Repeat Cohort	pMDI Change Cohort	p-value*
LTRA cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	<0.001
	Mean (SD)	95133.1 (127009.4)	114998.0 (121257.9)	
	Min, Max	(0, 742360)	(0, 441840)	
Theophylline or other methylxanthine cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.222
	Mean (SD)	20315.9 (30160.8)	18826.3 (28877.3)	
	Min, Max	(0, 167256)	(0, 168456)	
Omalizumab cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	N/A
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	
	Min, Max	(0, 0)	(0, 0)	
Acute OCS cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.876
	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)	0.135
	Mean (SD)	608.6 (5436.9)	395.4 (1789.0)	
	Min, Max	(0, 225408)	(0, 36360)	
Antibiotics cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.155
	Mean (SD)	41987.3 (159284.8)	32702.4 (142388.3)	
	Min, Max	(0, 2314830)	(0, 2342901)	
All inpatient admissions cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.440
	Mean (SD)	1266237.9 (3688602.1	1450238.1 (5999555.5	
	Min, Max	(0, 40710970)	(0, 104061330)	
LRTI-related inpatient admissions cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.464
	Mean (SD)	420914.3 (1606850.6)	369323.0 (1700074.8)	
	Min, Max	(0, 24869720)	(0, 30124150)	
Asthma-related inpatient admissions cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.511
	Mean (SD)	209391.0 (955495.0)	239031.4 (1100480.3)	
	Min, Max	(0, 13550410)	(0, 16235780)	
Asthma exacerbation-related inpatient admissions cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.177
	Mean (SD)	65599.0 (604656.1)	114932.6 (858563.8)	
	Min, Max	(0, 13550410)	(0, 16235780)	
All outpatient attendances cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.800
	Mean (SD)	840344.7 (1578834.6)	856345.5 (1309633.9)	
	Min, Max	(0, 30106520)	(15680, 23995580)	
LRTI-related outpatient attendances cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.800
	Mean (SD)	840344.7 (1578834.6)	856345.5 (1309633.9)	
	Min, Max	(0, 30106520)	(15680, 23995580)	
Asthma-related outpatient attendances cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.237
	Mean (SD)	131621.7 (165823.8)	123768.4 (140794.9)	
	Min, Max	(0, 1895860)	(0, 1462520)	
	N (% not missing)	1926 (100.0)	642 (100.0)	0.534
	Mean (SD)	415502.1 (1710146.6)	521797.9 (4389845.4)	

	Measure	DPI Repeat Cohort	pMDI Change Cohort	p-value*
All emergency attendances cost (KRW)	Min, Max	(0, 24869720)	(0, 98929310)	
LRTI-related emergency attendances cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.534
	Mean (SD)	415502.1 (1710146.6)	521797.9 (4389845.4)	
	Min, Max	(0, 24869720)	(0, 98929310)	
Asthma-related emergency attendances cost (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.488
	Mean (SD)	70830.5 (447297.0)	57512.6 (405670.8)	
	Min, Max	(0, 9497400)	(0, 5925780)	
All hospitalisation costs (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.436
	Mean (SD)	2522084.8 (5370517.0	2828381.5 (10117765.	
	Min, Max	(15530, 56124940)	(28000, 206665300)	
All asthma-related hospitalisation costs (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.367
	Mean (SD)	1321445.8 (2558673.6	1493076.0 (4878361.2	
	Min, Max	(15530, 30106520)	(15680, 102603970)	
Drug costs (without ICS) (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.676
	Mean (SD)	281533.1 (345278.1)	275180.4 (390747.4)	
	Min, Max	(0, 3411261)	(0, 6529331)	
Drug costs (with ICS) (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.187
	Mean (SD)	606012.4 (448589.0)	580228.6 (508725.1)	
	Min, Max	(52191, 3903227)	(59673, 7053205)	
Total costs (without ICS) (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.390
	Mean (SD)	1602978.9 (2706296.4	1768256.4 (4962105.6	
	Min, Max	(29124, 30696112)	(17792, 103387801)	
Total costs (with ICS) (KRW)	N (% not missing)	1926 (100.0)	642 (100.0)	0.450
	Mean (SD)	1927458.3 (2746379.4	2073304.6 (4998129.4	
	Min, Max	(99334, 31328002)	(111144, 104238353)	

* Wilcoxon signed rank test with continuity correction; N/A, not applicable

11.13 Phase 3: Exploratory cost-effectiveness outcomes

Bootstrapped mean costs and the proportion of patients with no exacerbations are not reported due to oversight in copying analysis results. Limitations on time and budget do not allow for a re-extraction of uncompiled analysis results and thus all available results are reported below.

11.13.1 Exploratory cost-effectiveness of treatment: no exacerbations

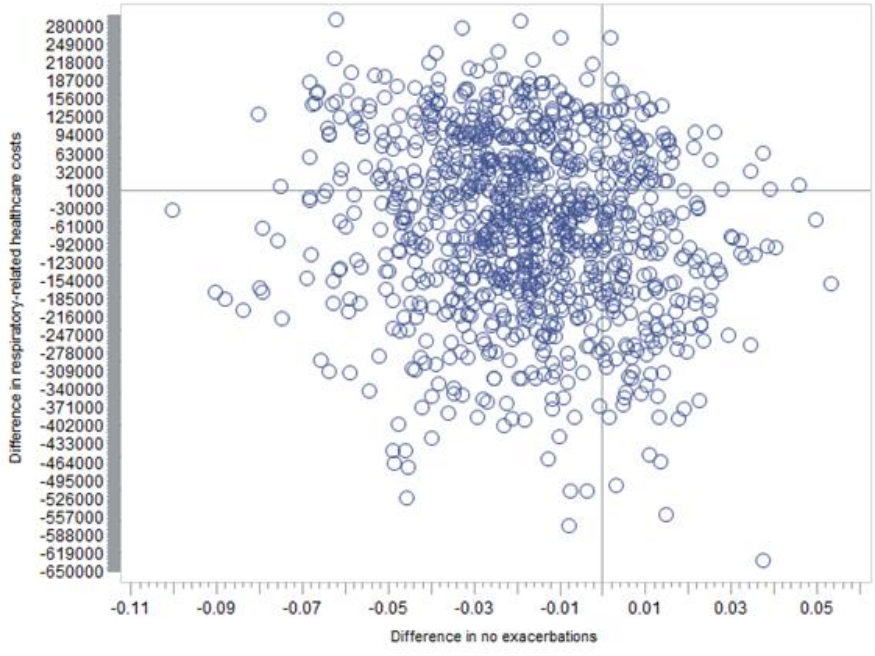

Figure 9: Phase 3 – cost-effectiveness plane for ‘no exacerbations’ outcome

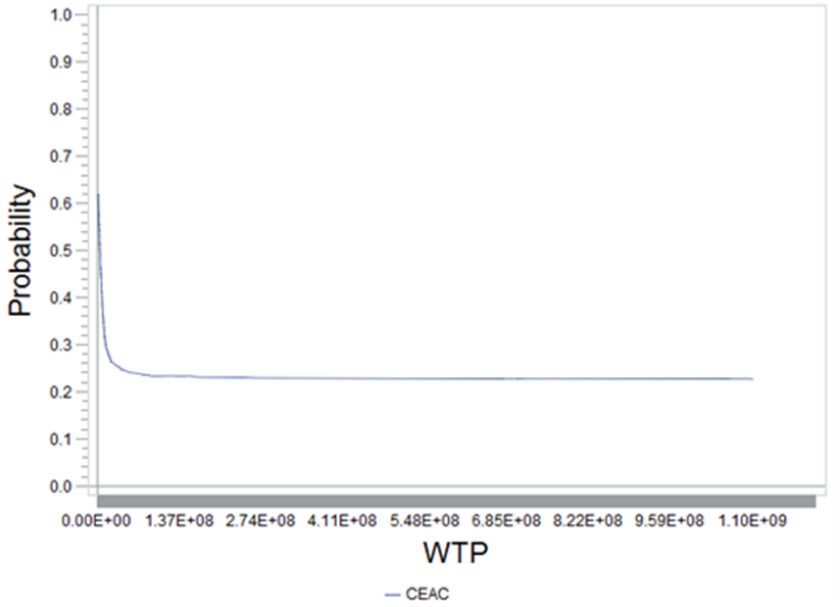

Figure 10: Phase 3 – cost-effectiveness acceptability curve (CEAC) diagram for ‘no exacerbations’ outcome

WTP, willingness to pay

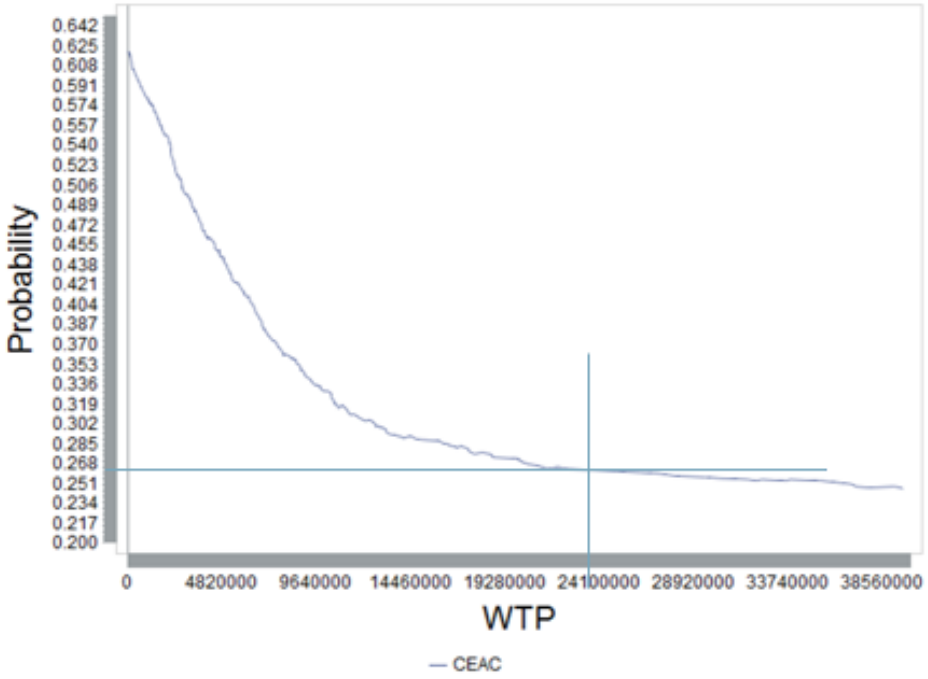

Figure 11: Phase 3 – enlarged CEAC diagram for 'no exacerbations' outcome

WTP, willingness to pay

11.13.2 Exploratory cost effectiveness of treatment: risk domain asthma control

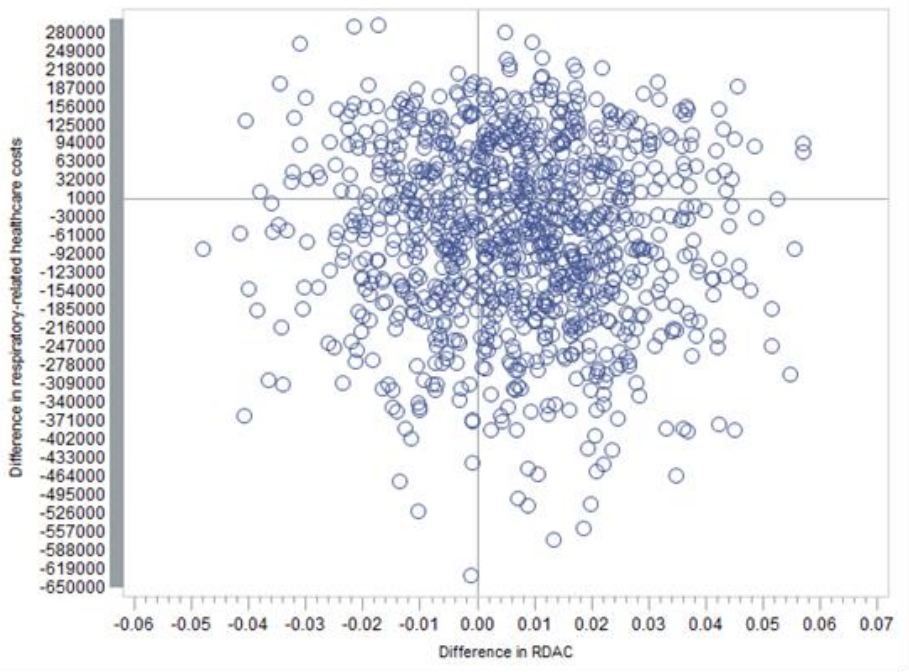

Figure 12: Phase 3 – cost-effectiveness plane for risk domain asthma control

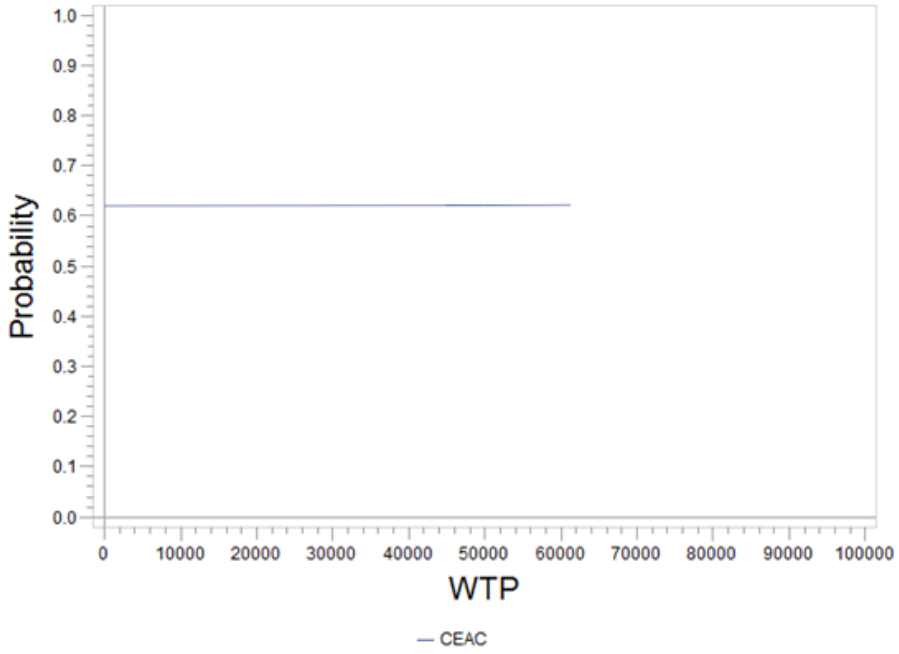

Figure 13: Phase 3 – CEAC diagram for risk domain asthma control

WTP, willingness to pay.

12 References

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