Study protocol

Real-life effectiveness evaluation of asthma treatment in Korea

A historical, observational study to evaluate the real-life effectiveness and cost-effectiveness of asthma treatment in the HIRA Database of Korea

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TITLE	Real-life effectiveness evaluation of asthma treatment in Korea
Subtitle	A historical, observational study to evaluate the real-life effectiveness and cost-effectiveness of asthma treatment in the HIRA Database of Korea
Protocol version number	1.0
Medicinal product	- All asthma pharmacological treatments containing ICS/LABA fixed-dose combinations
Study aims and objectives	- To assess differences in inhaler outcomes (DPI versus pMDI) - To provide recommendations for optimal, cost-effective, treatment options for asthma management
Country of study	Korea

Contents

1.0 Background

Asthma is a chronic airways inflammatory disease that features symptoms such as shortness of breath, wheezing, night-time or early morning variability and chest tightness [1]. The underlying pathology is a heterogeneous, with different underlying disease processes including allergic, late-onset, chronic and other phenotypes featuring different patterns of inflammation, structural changes and airflow obstruction. Asthma is a major cause of disability and mortality [2] with an increasingly recognised economic burden in Korea [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 [1], while national Korean guidelines have also been introduced in order to improve adherence to guidelines [5]. Use of inhaled corticosteroids is recognised as a key component of management, both in disease control and reduction in oral corticosteroid side effects. In the United States, the current overall rate of anti-inflammatory medication use for asthma is 20.1%, and ICS represents a major portion of that at 72.5%. In Europe, about 43% of the asthma population has used ICS. The ICS prescription rate in Korea is much lower. In a survey conducted in 2000, which evaluated asthma control in the Asia-Pacific region, the reported ICS use was assessed as 1.2% in Korea [6].

In the International Asthma Insights and Reality (AIR) survey, among 29 participating countries, 8 of them in Asia Pacific, Korean asthmatics rated poorly, and percentages of children with lost schooldays and adults with lost workdays caused by asthma were 16% and 8%, respectively [1].

In order to increase ICS use and reduce hospitalization, emergency department visits, and ultimately the economic burden of asthma costs, the Korean Academy of Asthma, Allergy and Clinical Immunology; the Korean Academy of Tuberculosis and Respiratory Diseases; and the Korean Academy of Medical Science cooperated to develop a clinical guideline for asthma, which was funded by the Korea Centers for Disease Control and Prevention (KCDC). This guideline was published in November 2007 and revised in March 2011[1].

Despite the introduction of guidelines, the trend towards ideal practice has not been followed, with many physicians not following recommendations leading to inappropriate management. Identified issues included the low proportion of inhaled corticosteroid use compared to European and American studies as well as high oral corticosteroid use. The reimbursement criteria of the Health Insurance Review and Assessment (HIRA) Service and patient's

[1] K.A Society “Korean Asthma guidelines’ 2011

preference for oral drug were cited as barriers for ICS prescription. Notably the domestic asthma clinical guideline has no significant effect on ICS prescription, especially in primary clinics where 85% of asthma patients are managed [2].

Changing to more effective ICS delivery methods is clearly important if guideline practice is to be followed. The use of multiple mixed devices is associated with more inhaler technique errors and worse asthma control. As many patients use a pMDI SABA reliever, switching to a pMDI preventer might improve health and economic outcomes by simplifying the process of learning inhaler technique [3].

Two main types of inhalers are available in Korea: Dry Powder Inhalers (DPIs) and pressurized Metered Dose Inhalers (pMDIs) [7].

Feature	Pressurised Metered Dose Inhaler	Dry powder Inhaler
Syncing of breath	Yes	No
Inspiratory flow required	30L/min	30-120L/min
Spacer	Yes	No
Propellant	Yes	No
Dose counter	In some models	Clear when medication is required
Cost	Lower	Higher ([4], [5, 6])
Critical errors	Fewer errors[6]	More errors[6]

Table 1: Differences between pMDI and DPI inhalers

GINA guidance [7] recommends that the inhaler type should be an individual decision to optimise care for the patient. Currently, DPIs occupy over a 90% of the fixed dose combination (FDC) prescription market share in Korea which is notably higher than other countries such as the United Kingdom where only 40% of inhalers are dry powder based [8].

DPIs have been available since 1967, but have their own challenges such as requiring higher inspiratory pressure. It has been suggested by the UK national health technology assessment inhaler review group that switching inhaler types does not result in inferior asthma control [9].

In Korea, about 85% of patients with asthma are being managed in the community by primary care physicians [10], making this population of key value for assessing real-life effectiveness. At the same time, healthcare costs are increasing worldwide, including Korea [9] tempting cost considerations to factor into inhaler device choice. Therefore, it is not only important to look at the impact of optimizing asthma treatment from a clinical point of view, but also from a health economic perspective. Caution has been advised around the possibility of negative consequences regarding switches of inhaled medications and devices [11].

Few studies have been performed to assess the health-economic effect of changing asthma treatment in real-life Korean practice. The current availability of large data sets from claims databases (e.g. HIRA) and the development of quality standards for observational research provide the opportunity to fill this important evidence gap.

The primary objective of this project will be to assess differences in asthma outcomes between DPI and pMDI users in Korea.

The study will be embedded in a Korean asthma optimization framework that is looking at the state-of-the-art of asthma treatment currently and over the last 5 years.

The study objectives are specified in section 2.0. Eventually, the outcomes of this project are expected to lead to hands-on recommendations for optimal, cost-effective, treatment options for asthma management.

2.0 Study aims and objectives

2.1 Aim

To assess asthma outcomes in patients who switch from DPI to pMDI devices and who continue with DPI devices in Korea.

2.1.1 Objectives

1. To evaluate the 'switch persistence' of changing asthma patients from ICS/LABA DPIs to ICS/LABA pMDI inhalers in a real-world population in Korea after 6 months.
2. To compare multiple clinical and health economic outcomes within the DPI -> pMDI switch cohort 1 year before and 1 year after the switch.
3. To compare multiple clinical and health economic outcomes between the DPI -> pMDI switch cohort and the repeat DPI cohort 1 year before and 1 year after the (matched) switch date.

3.0 Study specification

3.1 Study design

This is a historical cohort database study with a baseline and outcome period designed to evaluate the proportion of asthma patients who persist with collecting prescriptions of new ICS/LABA pMDI after their initial prescription. Switch persistence is considered as >70% of the population collecting 3 or more prescriptions of their 'new treatment' (or maintaining their old treatment) 6 months after the switch [12].

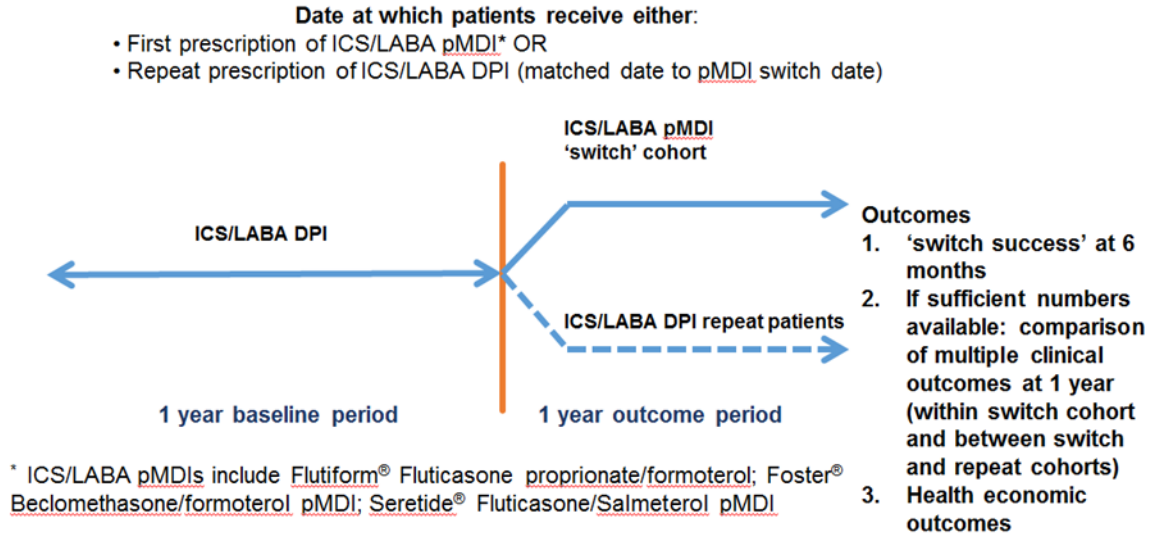

Figure 1: Study design

5.2 Study population

5.2.1 Inclusion and exclusion criteria

Inclusion criteria:

(1) ICD-10 code for asthma (J45.x-J46)

(2) Aged 12-80 years at date of first prescription for LABA/ICS pMDI or a repeat prescription for LABA/ICS DPI

(3) Actively treated GINA stage 3 asthma, defined as ≥ 2 prescriptions for LABA/ICS DPI at baseline

(4) ≥ 3 prescriptions for LABA/ICS during outcome period

(5) Same ICS dose at last prescription for LABA/ICS DPI at baseline and first prescription of LABA/ICS after switch date

Exclusion criteria:

Patients who have had:

(1) A diagnosis for COPD defined by ICD-10 code of J43.x-J44, (excluding chronic bronchitis); interstitial lung disease J80-J84, tuberculosis A15, A16, bronchiectasis J47, diffuse panbronchiolitis J21.9, and lung cancer C34.9

(2) Received maintenance oral corticosteroids[2] during the baseline year, and/or received multiple FDC ICS/LABA or separate ICS or LABA prescriptions at switch date

5.3 Data source

For this study, data from the Korean Health Insurance Review and Assessment (HIRA) service database will be used. In South Korea, all patients have a compulsory and universal health plan. The HIRA database covers the complete medical healthcare utilization data of the entire population of South Korea of over 50 million people over the period 2009-2014. It provides a unique and unbiased overview of healthcare utilization (including almost all primary care, pharmacy and hospital data) on a national level. The HIRA database has been extensively described[13] and has been used in several previous studies including specific studies in the respiratory field[14].

5.4 Study variables

5.4.1 Demographics (calculated at index date)

- Age (years)
- Gender (male, female)
- Socio-economic status (by reimbursement type: health insurance or medical aid)

5.4.2 Comorbidities

Comorbidities of interest (calculated as baseline co-morbidity prior and including index date, and outcome co-morbidity in the outcome year, or preceding the end of the outcome year as appropriate) will include:

[2] "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

- Code for actively treated allergic and non-allergic rhinitis (ICD-10: J30, J31.0) diagnosed prior to the end of the relevant year AND in receipt of antihistamine in the relevant year prior to index date and at the end of the outcome period
- Nasal Polyps (ICD-10: J33) diagnosed prior to the index date
- Actively treated eczema (ICD-10: L20-L30) diagnosed prior to the end of the relevant year in receipt of emoillient or topical corticosteroid in the relevant year both prior to the index date and at the end of the outcome period
- Pneumonia (ICD-10: J09-J18) coded in the baseline period or in the outcome period
- Gastro-oesophageal reflux disease (GERD) (ICD-10: K21) diagnosed prior to the index date for the baseline year, or prior to the end of the outcome year
- Other chronic lung diseases (ICD-10: J44, J47)Charlson comorbidity index score[3] (CCI) score - a weighted index that takes into account the number and seriousness of comorbid diseases to estimate the risk of death from comorbid diseases[52]– calculated at the index date and prior

5.4.3 Disease severity and control

Asthma patients

- Number of asthma-related primary care consultations in the year prior to the switch date. For primary care services, visits were considered asthma-related when the patient has a recorded principal or secondary diagnosis as asthma (ICD-10 codes: J45.x– J46) AND the principal or secondary diagnosis for consultation is J09-J18 (influenza and pneumonia), J20-22 (lower respiratory tract infection) or asthma (J45/46), J96 (respiratory failure) and J82 (eosinophilic asthma), OR disorders of breathing R6
- Number of asthma-related hospitalisations and/or hospital outpatient attendances in the year prior to the switch date). Hospitalizations and out-patient services were considered asthma-related when the principal or secondary diagnosis was asthma (ICD-10 codes: J45.x– J46) AND the principal or secondary diagnosis for consultation is J09-J18 (influenza and pneumonia), J20-22(lower respiratory tract

[3]Based on the International Classification of Diseases, 9th revision (ICD-9) predicts the ten-year mortality for patients with comorbidities, where each comorbidity is assigned a score.

* with a diagnostic code recorded at any time prior to or at the last extraction date

** with a diagnostic code recorded + treatment course at any time prior to or at the last extraction date

infection) or asthma (J45/46), J96 (respiratory failure) and J82 (eosinophilic asthma), OR disorders of breathing R6

- Number of other respiratory related hospitalizations and/or outpatient attendances in the year prior to switch date coded as events with ICD-10 codes for chronic lower respiratory diseases (J45) or dyspnea: R06.0).
- Number of prescriptions for any antibiotic where the reason for the prescription is a lower respiratory tract infections (LRTI; in the year prior to the switch date which is coded as J09-J18 (influenza and pneumonia), J20-22 (lower respiratory tract infection). Codes for antibiotics are specified in the appendix
- Reliever medication (SABA) prescriptions in the year prior to the switch date (categorized as 0, 1-200, 201-400, 401-800, 801+ µg/day). SABA codes are specified in the appendix
- Number of courses of acute oral steroids in the year prior to the switch date. Codes for oral corticosteroid courses are specified in the appendix
- Other medications, for example:
    i. Number of paracetamol prescriptions in the year prior to switch date. Codes are provide in the appendix
    ii. Number of non-steroidal anti-inflammatory drugs (NSAIDs) prescribed in the year prior to the switch date. Codes are provided in the appendix
    iii. Number of prescriptions for any respiratory therapy (split by number of prescriptions for each) in year prior to switch
- Number of severe exacerbations (as defined under “secondary effectiveness endpoints, section 5.5.2”) in year prior to switch date
- Asthma control (as defined under “secondary effectiveness endpoints, section 5.5.2”) in the year prior to switch date
- Respiratory drugs prescribed and prescribed dose at the time of therapy switch / continuation (for specification, see 5.4.5)

5.4.4 Prescriptions

- Respiratory-related drug therapies, in the year prior to the switch date:
    - Short-acting β_2 agonist (SABA)
    - Short acting muscarinic antagonist (SAMA)
    - Long-acting β_2 agonist (LABA)
    - Long-acting muscarinic antagonist (LAMA)

- Inhaled corticosteroids (ICS)
- Fixed combinations of LABA and ICS
- SABA/SAMA combination therapy
- LTRA
- Omaluzimab
- Theophylline or other methylxanthines
- Oral β_2 agonist

SABA reliever usage, in the year prior to the index date: average daily dose in µg/day calculated as

([Count of inhalers x doses in pack] / 365) x µg strength

And categorized in 0, 1-200, 201-400, 401-800, 801+ µg/day

All drugs codes are specified in the appendix

5.5 Study endpoints

5.5.1 Primary endpoint

Switch persistance, defined as:

Percentage of ICS/LABA pMDI patients who received ≥ 3 prescriptions of ICS/LABA pMDI in addition to that issued at their prescription date at 6 months.

Some patients are expected to switch back to their previous ICS/LABA DPIs because of a resistance to change rather than as a reflection of dissatisfaction with their new therapy.

A switch-back rate of >30% has been evaluated as potentially indicative of dissatisfaction with the change. A sub-analysis will be performed to assess the number of patients remaining on the same device, whether that being a sub-type of DPI or pMDI.

5.5.2 Secondary effectiveness endpoints

(a) % non-exacerbating patients of 'switch' cohort at 1 year, compared to baseline

- % of 'switch' cohort who have no severe exacerbations within 1 year of switching at 1 year, compared to year before switching

(b) **Severe asthma exacerbation rate** (American Thoracic Society/European Respiratory Society statement definition) within the 1 year period, defined as:

- Asthma-related hospitalisations or AE attendance[4] (7-day window for hospitalization date and date of asthma diagnosis registration) or
- Acute courses of oral corticosteroid prescriptions for asthma

(c) **Risk Domain Asthma Control (RDAC)** defined as absence of:

- Asthma-related hospitalisation or AE attendance with primary diagnosis (7-day window for hospitalization date and date of asthma diagnosis registration)
- Acute courses of oral corticosteroids or antibiotics with consultation for LRTI[5]

(d) **Overall Asthma Control**

- RDAC as defined above PLUS ≤200 µg salbutamol/≤500mcg terbutaline average daily dose. Codes are provided in the appendix

(e) **Treatment success**, defined as**:**

- Risk domain asthma control and
- No additional or change in therapy, as denoted by an increase in ICS dose of ≥50% or the addition of theophylline or a leukotriene antagonist or LABA

(f) **Asthma – related hospitalisation rate**, defined as:

- Number of admissions, with each admission defined as an admission within 7 days either side of lower respiratory code to avoid double counting

(g) **Average daily SABA usage**:

- 0, 1-200, 201-400, 401-800, 801+ µg daily SABA dosage. SABA codes are provided in the appendix

(h) **Incidence of oral thrush**:

- diagnostic code for oral candidiasis or prescription of antifungal therapy. Codes are provided in the appendix

(i) **Mean daily ICS dose**

- µg mean daily ICS (fluticasone equivalent) dosage

If sufficient numbers are available (sample size required: 163 per cohort, as specified in the sample size summary), for all of the following additional outcomes, the outcome year will be compared to the baseline year within the switch cohort. These analyses are powered on the "non-exacerbation" endpoint (a).

5.5.3 Secondary cost-related endpoints

[4] Availability of hospitalisation data may be dependent on the data source used, therefore exact definitions may have to be discussed with the steering committee at protocol stage

[5] Price D, Small I, Haughney J, *et al.* Clinical and cost effectiveness of switching asthma patients from fluticasone-salmeterol to extra-fine particle beclometasone-formoterol: a retrospective matched observational study of real-world patients. Prim Care Respir J 2013;22(4): 439-448

- Change in asthma-related costs (per patient per year) for each of the categories below individually and in total, including:
    - Respiratory drug prescriptions, including ICS, SABA, LABA, LAMA, LTRA, theophylline, acute oral corticosteroids and antibiotics for LRTIs;
    - Primary care consultations;
    - Respiratory-related hospital costs

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

5.5.4 Tertiary effectiveness endpoints

If sufficient numbers available (sample size required: as specified in the sample size summary), for all of the following additional outcomes, outcomes will be compared in a matched analysis with patients continuing on ICS/LABA DPI. These analyses are powered on the proportion of patients with "no-exacerbations" endpoint (j).

(j) % non-exacerbating patients of 'switch' cohort at 1 year, compared to control (DPI continuation)

- % of 'switch' cohort who have no severe exacerbations within 1 year of switching at 1 year, compared to year before switching

(k) **Severe asthma exacerbation rate** (American Thoracic Society/European Respiratory Society statement definition) within the 1 year period, defined as:

- Asthma-related hospitalisations or AE attendance[6] (7-day window for hospitalization date and date of asthma diagnosis registration) or
- Acute courses of oral corticosteroid prescriptions for asthma

(l) **Risk Domain Asthma Control (RDAC)** defined as absence of:

- Asthma-related hospitalisation or AE attendance with primary diagnosis (7-day window for hospitalization date and date of asthma diagnosis registration)
- Acute courses of oral corticosteroids or antibiotics with consultation for LRTI[7]

(m) **Overall Asthma Control**

[6] Availability of hospitalisation data may be dependent on the data source used, therefore exact definitions may have to be discussed with the steering committee at protocol stage

[7] Price D, Small I, Haughney J, *et al.* Clinical and cost effectiveness of switching asthma patients from fluticasone-salmeterol to extra-fine particle beclometasone-formoterol: a retrospective matched observational study of real-world patients. Prim Care Respir J 2013;22(4): 439-448

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

(n) **Treatment success**, defined as**:**

- Risk domain asthma control and
- No additional or change in therapy, as denoted by an increase in ICS dose of ≥50% or the addition of theophylline or a leukotriene antagonist or LABA

(o) **Asthma – related hospitalisation rate**, defined as:

- Number of admissions, with each admission defined as an admission within 7 days either side of lower respiratory code

(p) **Average daily SABA usage**:

- 0, 1-200, 201-400, 401-800, 801+ µg daily SABA dosage

(q) **Incidence of oral thrush**:

- diagnostic code for oral candidiasis or prescription of antifungal therapy

(r) **Mean daily ICS dose**

- µg mean daily ICS (beclomethasone equivalent) dosage

5.5.5 Tertiary cost-related endpoints

- Change in asthma-related costs (per patient per year) for each of the categories below individually and in total, including:
  - Respiratory drug prescriptions, including ICS, SABA, LABA, LAMA, LTRA, theophylline, acute oral corticosteroids and antibiotics for LRTIs;
  - Primary care consultations;
  - Respiratory-related hospital costs.

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

5.6 Statistical analysis

5.6.1 Software used

Statistical analysis will be performed using SPSS Statistics version 23 software (IBM SPSS Statistics, Feltham, Middlesex, United Kingdom) and SAS version 9.3 software (SAS Institute, Marlow, Buckinghamshire, United Kingdom).

5.6.3 Comparative statistics

Summary statistics

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

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

Results will be reported as:

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

- Categorical variables:
  - Sample size (n)
  - Count and percentage by category (distribution)

Planned additonal statistical analyses

Additional analyses (within switch cohort):

- Continuous variables (such as mean ICS dose) will be compared using student's t-tests. Proportions (such as exacerbation free asthma patients) will be compared using Chi-square tests

Additional analyses (between groups):

- Adjusted odds and rates of events will be compared between matched treatment groups using conditional binary/ordinal logistic regression or conditional Poisson regression models, respectively

5.7 Sample size and power calculation

Sample Size Rationale:

Primary analysis 'Switch Success': A previous study conducted by RiRL UK (Mundipharma R03212b-Effectiveness of ***flutiform***® Stage 2 [15]) on the switch success of ICS/LABA DPI to ICS/LABA pMDI has been used to inform the following power calculations for the 6-month outcome period. Based on an expected "switch-back" probability of approximately 0.20 (20%) among patients switching from existing ICS/LABA DPI to ICS/LABA pMDI at their prescription

date, a sample size of 100 patients per switch cohort would be 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 "switch success".

Additional analyses (within switch cohort) Additional analyses within the switch cohort, are based on the proportion of patients with "no exacerbations" (OCS prescription + hospitalisation +AE attendance, or OCS dispensing + AE attendance + hospitalisation depending on available data, as exacerbation proxy). Non-inferiority will be tested between the outcome and the baseline periods within the switch cohort. As such,163 patients will be 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 will have 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 0.000, assuming that the proportion of discordant pairs is 0.242 (based on previous RiRL UK research Mundipharma R03212b-Effectiveness of ***flutiform***® Stage 2).

Additional analyses (between switch and repeat cohort) Additional analyses between the switch cohort, are based on the proportion of patients with "no exacerbations" (OCS prescription + hospitalisation +AE attendance, or OCS dispensing + AE attendance + hospitalisation depending on available data, as exacerbation proxy).

Non-inferiority. 1:1 matching

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 will have 90% power to reject the null hypothesis that the proportions 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 1:1 matching

A two group continuity corrected χ^2 test with a 0.050 one-sided significance level will have 90% power to detect the difference between a ICS/LABA pMDI proportion, π_1, of 0.791 and a ICS/LABA DPI proportion, π_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 [15]).

Non-inferiority versus superiority

The plan for the exploratory stage is to test for non-inferiority in the first instance to show that switching from a DPI to a pMDI shows no reduction in efficacy. If we are able to show this and the results are positive, ie. we see an improvement in efficacy, the intention is to demonstrate superiority. We have therefore calculated the numbers required for both aims to ensure that we have enough numbers included to allow for both results.

With regards to multiplicity, we considered that more than one sample size calculation implies multiple testing. However, the primary endpoint is 'Switch Persistance' and this will be the primary focus of the study.

As a secondary analysis we aim to look at non-inferiority in terms of effectiveness. The second sample size is provided as 100 patients would not be sufficient to demonstrate non-inferiority in efficacy, so we have planned to include enough patients in the study to achieve this. i.e. the primary endpoint will have more patients than required to show switch success.

A solution would be to use a hierarchical approach which is implied within the study design. As if we would not achieve Switch success, we could not make any claims on efficacy of the two devices.

Sample Size Summary

Primary endpoint (switch persistence):

Total: 100 Per group: 100

Additional analyses ("within switch cohort [between baseline and outcome period with same patients"):

Total: 163 Per group: 163

Additional analyses ("between switch [pMDI] and repeat cohort [repeat DPI]"):

Non-inferiority:

Total: 416 Per group: 208

Superiority:

Total: 2123 Per group: 1062

4.0 Regulatory and ethical compliance

The study protocol and design were developed, shall be implemented and reported in accordance with the criteria of the European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and follows the ENCePP Code of Conduct (EMA 2014). Once a final version of the protocol is reviewed and agreed by the advisory group, formal ethics and research management approval of this study will be obtained from the ADEPT Committee and equivalent Korean ethics committee, which verifies the scientific and ethical soundness of all research using real-life data. Then the final version of this protocol will be registered with www.encepp.eu and local registries.

5.0 Data dissemination

Initial results will be presented to the Steering Committee of this study. Several manuscripts containing the methodology (protocol paper) and main results of the three studies will be submitted for publications to journals specialising in respiratory medicine as soon as the analyses are completed and the results are verified. In addition, abstracts will be submitted to respiratory congresses (e.g. REG, APSR and ATS) to communicate preliminary findings.

6.0 Advisory group

Communication with the SC will be held at key milestones: protocol approval, data reviews and validation for phase 1-3, publication planning. Following experts will be included to the steering committee of this study:

- Ass prof. Hye Yun Park
- Prof. Hae Sim Park
- Prof. Kwang Ha Yoo
- Ass. prof. Chin Kook Rhee
- Prof. DK Kim

7.0 Research team

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Research in Real Life

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Research in Real Life/Mundipharma

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8.0 Timelines

Table 1: Timelines

Action	**Timeline**
Contract execution	4 weeks
Ethical Approvals	3 months
Database review and stats	6 months
Final report writing	4 weeks
Steering committee feedback	4 weeks
First draft of paper (details: see below)	6 weeks after steering committee feedback

9.0 APPENDIX

Appendix 1: Summary of inclusion / exclusion criteria for study.

Inclusion criteria		Study
Asthma patients	Aged 12-80 years at first prescription	✓
	Evidence of asthma diagnosis (a diagnostic code)	✓
Evidence of at least 2 prescriptions for ICS/LABA FDC DPI therapy during the baseline period		✓
Continuous study period comprising of a minimum of 1-year baseline and 6-month outcome period		✓
Evidence of at least 1 prescription for ICS/LABA pMDI or repeat DPI during outcome period excluding the first ICS/LABA pMDI prescription		✓
Evidence of same ICS dose after switch date/repeat date as that prescribed in baseline		✓
Exclusion criteria		
A diagnosis for any chronic respiratory disease (e.g. COPD defined by ICD-10 code of J42.x-J44); except asthma, at any time; and/or Received maintenance oral corticosteroids during the baseline year, and/or received multiple FDC ICS/LABA or separate ICS or LABA prescriptions at switch date		V

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Appendix 2: Definitions: variables and categories

- Age (at the time of the switch)
- Gender
- Socio-economic status (by reimbursement status: reimbursed or medical aid)
- Severe asthma exacerbations, defined as the occurrence of any of the following:
    - Acute course of oral corticosteroids
    - Antibiotics prescribed with a lower respiratory consultation
    - Respiratory-related, unscheduled hospital admission / emergency department attendance (i.e. severe exacerbation)
- SABA reliever usage, in the year prior to the index date: average daily dose in µg/day calculated as

  ([Count of inhalers x doses in pack] / 365) x µg strength
- CCI score, calculated for the baseline period: a weighted index that takes into account the number and seriousness of comorbid diseases to estimate the risk of death from comorbid diseases[15]
- Respiratory-related therapies, in the year prior to the index date:
    - Short-acting β_2 agonist (SABA)
    - Long-acting β_2 agonist (LABA)
    - Long-acting muscarinic antagonist (LAMA)
    - Inhaled corticosteroids (ICS)
    - Fixed combinations of LABA and ICS
    - LTRA
    - Omaluzimab
    - Theophylline or other methylxanthines
    - Oral β_2 agonist

Appendix 3: Baseline results table (sample)

		ICS/LABA Repeat DPI	ICS/LABA Switch pMDI	p-value
Age (years)	mean (SD)	45 (10)	46 (10)	0.67
	Under 40 n(%)	32%	35%	0.67
Age (categorised)	40 - 60, n (%)	33%	36%	0.67
	61 - 80, n (%)	27%	22%	0.67
	> 80, n (%)	8%	7%	0.67
Sex, male	n (%)	45%	43%	0.67
Socio-economic status	non-missing, n (%)	13%	15%	0.67
	High status, n (%)	25%	25%	0.67
	Moderate, n (%)	25%	23%	0.67
	Low, n (%)	37%	35%	0.67
Risk Domain Asthma Control, uncontrolled		35%	34%	0.67
Overall asthma control, uncontrolled		28%	29%	0.67
Severe asthma exacerbations	0, n (%)	72%	72%	0.67
	1, n (%)	8%	9%	0.67
	2-3, n (%)	8%	9%	0.67
	≥ 4, n (%)	12%	10%	0.67
Severe respiratory events	0, n (%)	65%	64%	0.67
	1, n (%)	12%	13%	0.67
	2-3, n (%)	13%	13%	0.67
	≥ 4, n (%)	15%	15%	0.67
Acute oral corticosteroid courses (during baseline period)	0, n (%)	64%	64%	0.67
	1, n (%)	14%	14%	0.67
	≥2, n (%)	22%	22%	0.67
Antibiotic prescriptions for LRTI (during baseline period)	0, n (%)	68%	69%	0.67
	1, n (%)	21%	20%	0.67
	≥2, n (%)	11%	11%	0.67
Asthma therapy (during baseline period)	None, n (%)	0%	0%	0.67
	SABA (+/- SAMA), n (%)	2%	2%	0.67
	LABA (+/- LAMA), n (%)	4%	4%	0.67
	LTRA+/-LABA+/-LAMA	5%	5%	0.67
	ICS	23%	23%	0.67
	ICS+/-LABA+/-LAMA	18%	17%	0.67
	ICS+LTRA+/-LABA+/-LAMA	12%	12%	0.67

	Theophylline/methylxanthine	23%	23%	0.67
	Oral beta-agonist	14%	13%	0.67
	OCS	10%	9%	0.67
	Other (omaluzimab)	5%	5%	0.67
Daily dose of ICS (ug/day)		320	330	0.67
SABA inhaler usage (µg per day, during baseline period)	0, n (%)	15%	14%	
	≤ 200, n (%)	17%	18%	
	201-400, n (%)	19%	19%	
	401-800, n (%)	25%	25%	
	>800, n (%)	24%	24%	0.67
Comorbidities				
Allergic rhinitis		20%	20%	0.67
Non-allergic rhintis		20%	20%	0.67
Nasal polyps		20%	20%	0.67
Eczema		20%	20%	0.67
Diabetes		20%	20%	0.67
GERD		20%	20%	0.67
CCI score (for baseline period)	0, n (%)	26%	26%	
	1 - 4, n (%)	64%	64%	
	>4, n (%)	10%	10%	0.67
Healthcare utilization (mean/sd)				
Primary care visits		4 (1.2)	4 (1.3)	0.67
ED visits		0.1 (0.1)	0.1 (0.1)	0.99
Hospital Primary		0.1 (0.1)	0.1 (0.1)	0.99
Hospital Secondary		0.1 (0.1)	0.1 (0.1)	0.99
Hospital Tertiary		0.1 (0.1)	0.1 (0.1)	0.99
ICU		0.01 (0.1)	0.01 (0.1)	0.99
Chest X-rays		0.1 (0.1)	0.1 (0.1)	0.99
Chest CTs		0.01 (0.1)	0.01 (0.1)	0.99
PFT		0.1 (0.1)	0.1 (0.1)	0.99
Medical costs				
Outpatient care		500	500	0.99
Inpatient care		400	400	0.99
Medication		300	300	0.99

Phase 1 switch persistence (sample):

	N	%
Total patients prescribed with pMDI	16456	100
Patients successfully switched* to pMDI	**14556**	**88.4**

Phase 2 non-inferiority of proportion of no exacerbations (sample):

	Patients changing from DPI to MDI (n = 153 000)	
	Lower limit of 95% CI	**Non-inferiority met?**
"No exacerbations" in outcome period from baseline (%) - Asthma-related emergency department attendance; OR - Asthma related inpatients admissions; OR - Prescription for an acute course of oral corticosteroids from a lower respiratory event	-0.045 (-4.5)	YES

Phase 3 health economic outcomes (sample)

	Treatment Group		p-value*
	DPI	**pMDI**	

Total Asthma and Asthma related healthcare costs including ICS/LABA	N (% non-missing)	1146 (100)	382 (100)	0.201
	Mean (SD)	471.09 (292.81)	372.59 (237.52)	
	Median (IQR)	413 (265, 585)	338 (233, 441)	
Total Asthma and Asthma healthcare costs excluding ICS/LABA	N (% non-missing)	1146 (100)	382 (100)	0.162
	Mean (SD)	101.35 (145.34)	89.76 (164.64)	
	Median (IQR)	53.28 (31.24, 107.88)	47.5 (24.24, 86.56)	

Appendix 4: HIRA data dictionary

Patient

The Patient file contains basic patient demographics, patient registration and practice registration details.

Field Name	*Content*
	ID - Anonymised patient identifier
	Age of patients
	Sex of patients
	Social economical status (health insurance vs. medical aid)

Clinical

The **Clinical** file contains medical history events. This file contains all the medical history data entered on the GP system, including symptoms, signs and diagnoses. This can be used to identify any clinical diagnoses, and deaths. Patients may have more than one row of data. The data is coded using Read codes, which allows linkage of codes to the medical terms provided.

Field Name	*Content*
Medical exam	
	Chest X-ray – performed or not
	Chest CT - performed or not
	PFT - performed or not
Comorbidity - Almost all comorbidity is also to be identified by using ICD-10 code	
	Allergic rhinitis
	non-allergc rhinitis
	Nasal polyp
	Eczema
	Pneumonia
	GERD
	Other chornic lung disease
	Oral thrush
Medical use	
	OPD visit
	Date of OPD visit (yyyy/mm/dd)
	Primary ICD-10 code
	Secondary ICD-10 code (1st to 10th)
	Cost of OPD visit

	ER visit
	Date of ER visit (yyyy/mm/dd)
	Date of ER discarge (yyyy/mm/dd)
	Primary ICD-10 code
	Secondary ICD-10 code (1st to 10th)
	Cost of ER visit
	Admission to hospital
	Date of admission (yyyy/mm/dd)
	Date of discharge (yyyy/mm/dd)
	Primary ICD-10 code
	Secondary ICD-10 code (1st to 10th)
	Cost of admission
	ICU admission
	Date of ICU admission (yyyy/mm/dd)
	Date of ICU discarge (yyyy/mm/dd)
	Primary ICD-10 code
	Secondary ICD-10 code (1st to 10th)

Referral

The **Referral** file provides details of all referrals for the defined patient cohort identified by a medical code indicating the reason for referral. This table contains information involving patient referrals to external care centres (normally to secondary care locations such as hospitals for inpatient or outpatient care).

Field Name	Content
	Type of hospital – primary, sedoncdary, tertiary
	Referral – Yes, No
	Referral type 1 – primary to secondary, primary to tertiary, secondary to tertiary
	Referral type 2 – OPD to OPD, OPD to ER, OPD to admission
	Primary ICD-10 code
	Secondary ICD-10 code (1st to 10th)

Therapy1

The **Therapy** file contains details of all prescriptions on the GP system. This file contains data relating to all prescriptions (for drugs and appliances) issued by the GP. Patients may have more

than one row of data. Drug products and appliances are recorded by the GP using the Multilex product code system.

Field Name	*Content*
	Date of prescription (yyyy-mm-dd)
	Type of drug prescription
	Number of drug
	Dosage of drug
	Primary ICD-10 code
	Secondary ICD-10 code (1^{st} to 10^{th})
	Cost for medication

Practice

The **Practice** file contains details for practices, including region and collection information.

Field Name	*Content*
	Type of hospital – primary, sedoncdary, tertiary
	Region of hospital

Medication codes specification

- Respiratory drugs
  - Short-acting β_2 agonist (SABA)

Name	Dose	Unit
fenoterol HBr	500	µg
fenoterol HBr	60	mg
procaterol HCl	2	mg
salbutamol sulfate	120	µg
salbutamol	20	mg
salbutamol sulfate	3	mg
salbutamol sulfate	6	mg
salbutamol sulfate	40	mg
terbutaline sulfate	100	mg
terbutaline sulfate	5	mg

  - Short-acting muscarinic antagonist (SAMA)

ipratropium bromide	250	µg
ipratropium bromide	500	µg
ipratropium bromide	6	mg

  - SABA+SAMA

fenoterol HBr	10	mg
ipratropium bromide	4	mg
ipratropium bromide	4.2	mg
salbutamol sulfate	24	mg
ipratropium bromide	20.8	mg
salbutamol sulfate	120.4	mg

  - Long-acting β_2 agonist (LABA)

formoterol furmarate dihydrate	0.8	mg
formoterol furmarate	1.53	mg
salmeterol xinafoate	25	µg
indacaterol	150	µg
indacaterol	300	µg

- Long-acting muscarinic antagonist (LAMA)

micronized tiotropium bromide monohydrate	22.5	µg
micronized tiotropium bromide monohydrate	28.27	mg

- Inhaled corticosteroids (ICS)

beclomethasone dipropionate	100	µg
beclomethasone dipropionate	200	µg
beclomethasone dipropionate	40	mg
beclomethasone dipropionate	12	mg
beclomethasone dipropionate	20	mg
beclomethasone dipropionate	6	mg
budesonide	20	mg
budesonide (micronized)	24	mg
budesonide	500	µg
budesonide	0.36	g
budesonide (micronized)	20	mg
budesonide (micronized)	60	mg
budesonide (micronized)	40	mg
budesonide (micronized)	80	mg
fluticasone propionate	250	µg
fluticasone propionate	2	mg
fluticasone propionate	30	mg
fluticasone propionate	6	mg
fluticasone propionate	0.5	mg
ciclesonide	0.17	g
ciclesonide	0.34	g
triamcinolone acetonide	24	mg

- Fixed combinations of LABA and ICS

fluticasone propionate	6	mg
salmeterol xinafoate	3	mg
fluticasone propionate	15	mg
salmeterol xinafoate	3	mg
fluticasone propionate	30	mg
salmeterol xinafoate	3	mg
formoterol fumarate dihydrate	4.5	µg
budesonide (micronized)	160	µg
fluticasone propionate	20	mg
salmeterol xinafoate	5.8	mg
fluticasone propionate	40	mg
salmeterol xinafoate	5.8	mg
fluticasone propionate	8	mg
salmeterol xinafoate	5.8	mg

formoterol fumarate dihydrate budesonide (micronized)	4.5 80	μg μg
formoterol fumarate dihydrate budesonide (micronized)	9 320	μg μg
beclomethasone dipropionate formoterol fumarate dihydrate	172.41 10.34	mg mg
fluticasone propionate salmeterol xinafoate	2.8 1.4	mg mg
fluticasone propionate salmeterol xinafoate	7 1.4	mg mg
fluticasone propionate salmeterol xinafoate	14 1.4	mg mg
formoterol fumarate dihydrate fluticasone propionate	5 125	μg μg
formoterol fumarate dihydrate fluticasone propionate	5 50	μg μg
formoterol fumarate dihydrate fluticasone propionate	1.2 30	μg μg

- LTRA

pranlukast hydrate	112.5	mg
pranlukast hydrate	100	mg/g
pranlukast hydrate	100	mg
pranlukast hydrate	50	mg
pranlukast hydrate	70	mg
pranlukast hydrate	75	mg
zafirlukast	20	mg
montelukast sodium	10	mg
montelukast sodium	5	mg
montelukast sodium	4	mg

- Omaluzimab

Omalizumab	202.5	mg

- Theophylline or other methylxanthines

acepifylline	250	mg
aminophylline	100	mg
aminophylline	250	mg
aminophylline	225	mg
bamiphylline HCl	300	mg
bamiphylline HCl	600	mg
diethylamino ethyl theophylline	100	mg
diprophylline	200	mg

diprophylline	300	mg
oxtriphylline	100	mg
oxtriphylline	20	mg
oxtriphylline	400	mg
theophylline anhydrous	5.333	mg
theophylline	100	mg
theophylline	130	mg
theophylline	200	mg
theophylline	20	g
theophylline	200	mg
theophylline	400	mg
aminophylline	50	mg
chlorpheniramine maleate	1.5	mg
methylephedrine HCl	8.75	mg
phenobarbital	4	mg
aminophylline chlorpheniramine maleate methylephedrine HCl phenobarbital	50 4 12.5 8	mg mg mg mg
aminophylline diphenhydramine HCl ephedrine hydrochloride papaverine HCl phenobarbital	100 10 10 10 8	mg mg mg mg mg
diprophylline redistilled turpentine oil oxidation products	150 20	mg mg
doxofylline	400	mg

- Oral β_2 agonist

bambuterol HCl	10	mg
bambuterol HCl	1	mg
clenbuterol HCl	1	µg
fenoterol HBr	2.5	mg
formoterol fumarate	20	µg
formoterol fumarate	40	µg
formoterol fumarate	20	µg
formoterol fumarate	40	µg
hexoprenaline sulfate	500	µg
hexoprenaline sulfate	5	µg
orciprenaline sulfate	20	mg
orciprenaline sulfate	500	µg
procaterol HCl	25	µg
procaterol HCl	50	µg
procaterol HCl	5	µg
salbutamol sulfate	2.4	mg
salbutamol sulfate	4	mg

salbutamol sulfate	480	µg
salbutamol sulfate	8	mg
salbutamol sulfate	9.64	mg
salbutamol sulfate	4	mg
terbutaline sulfate	2	mg
terbutaline sulfate	500	µg
terbutaline sulfate	300	µg
terbutaline sulfate	5	mg
tulobuterol	0.5	mg
tulobuterol	1	mg
tulobuterol	2	mg

- Exacerbations
  - Oral corticosteroids

betamethasone	500	µg
betamethasone sodium phosphate	500	µg
deflazacort	6	mg
deflazacort	30	mg
dexamethasone	500	µg
dexamethasone	750	µg
dexamethasone	4	mg
hydrocortisone	10	mg
hydrocortisone	20	mg
hydrocortisone	5	mg
methylprednisolone	16	mg
methylprednisolone	4	mg
methylprednisolone	8	mg
methylprednisolone	2	mg
prednisolone	5	mg
prednisolone	1	mg
prednisolone	3	mg
triamcinolone	1	mg
triamcinolone	2	mg
triamcinolone	4	mg
prednisolone stearylglycolate	6.65	mg

  - Antibiotics

- Oral candida drugs

Nystatin	100	KU

MX_PRODUCT_NAME	MX_STRENGTH
DAKTARIN oral gel	0
DAKTARIN oral tab 250mg	250
FUNGILIN loz 10mg	10
FUNGILIN sf susp 100mg/ml	100
NYSTAN tabs 500,000 units	500000
NYSTAN past 100,000 units	100000
FUNGILIN tabs 100mg	100
NYSTAN oral susp 100,000 units/ml	100000
FLUCONAZOLE oral susp 50mg/5ml	50
FLUCONAZOLE oral susp 200mg/5ml	200
DIFLUCAN susp 50mg/5ml	50
DIFLUCAN susp 200mg/5ml	200
NYSTATIN tabs 500,000 units	500000
NYSTATIN oral susp 100,000 units/ml	100000
NYSTATIN grans for sf susp 100,000 units/ml	100000
AMPHOTERICIN loz 10mg	10
AMPHOTERICIN susp 100mg/ml	100
AMPHOTERICIN tabs 100mg	100
MICONAZOLE oromucosal gel 24mg/ml	24
MICONAZOLE tabs 250mg	250
NYSTATIN-DOME oral susp 100,000 units/ml	100000
NYSTAMONT sf susp 100,000 units/ml	100000
ITRACONAZOLE oral soln 10mg/ml	10
SPORANOX liq 10mg/ml	10
DAKTARIN oral gel 24mg/ml	24
POSACONAZOLE oral susp 40mg/ml	40
nystatin sugar-free suspension 100,000 units/ml	100
nystatin pastilles 100,000 units	100
miconazole denture lacquer 5%	5
NYSTAN granules for sugar-free suspension 100,000 units/ml [SQUIBB]	100
DUMICOAT denture lacquer 5% [ACTAVIS]	5
INFESTAT oral suspension 100,000 units/ml [OPUS]	100
NYSTATIN oral suspension 100,000 units/ml [SANDOZ]	100

NYSTATIN sugar free oral suspension 100,000 units/ml [LAGAP]	100
NYSTATIN sugar-free suspension 100,000 units/ml [HILLCROSS]	100
miconazole buccal tablets 50mg	50
NYSTATIN oral suspension 100,000 units/ml [LAGAP]	100
LORAMYC MUCO-ADHESIVE buccal tablets 50mg [SPE PHARM]	50
DAKTARIN sugar free oral gel 2% [MCNEIL]	2

- Paracetamol

Acetaminophen Tab	500	mg
Acetaminophen Tab	300	mg
Acetaminophen Tab	172	mg
Acetaminophen Tab	650	mg
Acetaminophen Tab	400	mg
Acetaminophen Tab	350	mg
Acetaminophen Tab	86	mg
Acetaminophen Tab	125	mg
Acetaminophen Tab	325	mg
Acetaminophen Tab	32	mg

- NSAIDS

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