DRAFT Study protocol

Real-life effectiveness evaluation of asthma treatment in Korea

Evaluating inhaler device 'switch success' and the real-life effectiveness in the Ajou University Hospital Database in Korea

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TITLE	Real-life effectiveness evaluation of asthma treatment in Korea
Subtitle	Evaluating inhaler device 'switch success' and the real-life effectiveness in a Korean population
Protocol version number	1.1
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, treatment options for asthma management
Country of study	Korea

Contents

1.0 Background....4
2.0 Study aims and objectives....5
3.0 Study specification....6
3.1 Study design 6
3.2 Study population 6
3.2.1 Inclusion and exclusion criteria 6
3.3 Data source 7
3.4 Study variables 7
3.5 Study endpoints 9
3.6 Statistical analysis 10
3.6.1 Software used 10
4.0 Regulatory and ethical compliance....11
5.0 Data dissemination....12
6.0 Pending Executive Decisions....12
7.0 Advisory group....13
8.0 Research team....13
9.0 Timelines (Tentative)....13
10.0 References....14
11.0 APPENDIX (to be confirmed by Prof. Park)....15
Appendix 1: Summary of inclusion / exclusion criteria for study. 15
Appendix 2: Definitions: variables and categories. 15
Appendix 3: Baseline results table 16
Appendix 4: Ajou data dictionary 18

1.0 **Background**

The international Global Initiative for Asthma (GINA) and national Korean asthma guidelines are based on evidence from studies performed in highly selective patient The The international Global Initiative for Asthma (GINA) and national Korean asthma guidelines are based on evidence from studies performed in highly selective patient populations under strictly controlled conditions.[1] These studies provide a good measure of efficacy, with high internal validity, however their external validity may be questioned for a number of reasons.

Firstly, the majority of asthma patients treated in daily clinical practice differ substantially from the trial populations. These patients are often non-smoking, between 18-40 years of age and are often without relevant comorbidities).[2] Secondly, in trial settings, asthma patients are under a strict ecology of care and are usually well trained on inhaler technique and closely monitored. . In contrast, in real-life poor inhalation and suboptimal treatment adherence are common, and associated with reduced asthma control, higher number of hospitalisations and higher economic expenses.

To date, few studies have been performed to assess the effect of common asthma treatments in real-life Korean practice. The current availability of detailed data sets with extensive longitudinal data and the development of quality standard for observational research (REG/EACCI taskforce) provide the opportunity to fill this important evidence gap.

Despite the recommendation of many national guidelines to use one type of inhaler device, it remains unknown whether this is observed in the real life setting. Currently, two main types of inhalers are available: Dry Powder Inhalers (DPIs) and presurrized Metered Dose Inhalers (pMDIs). Currently, DPIs occupy 90% of the fixed dose combination (FDC) prescription market share in Korea, despite the fact that pMDIs are usually cheaper. Furthermore, classical short-term randomised controlled trials suggest that pMDIs are non-inferior to DPIs. There is a need to carry out large oberservation database studies to compare to differences in terms of asthma outcomes between different inhaler devices, as asthma control may potentially be improved thorugh device change (‘switch”).

This is an important and timely question, as this switch is happening in many nations, especially with the development of more advanced pMDIs, which appear to have better overall lung delivery and more tolerance of poor inhaler technique. Moreover, it has been shown that the use of multiple mixed devices is associated with more inhaler technique errors and worse asthma control. As many patients use a pMDI reliever, switching to a pMDI preventer might improve health and economic outcomes.

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

The study will aim to characterise longutudinal treatment and asthma outcomes, in Korea and the differences in outcoms between DPI and pMDI inhalers for ICS/LABA treatment. The aim of the current study is stated below.

2.1 Aim

To assess differences in asthma outcomes between DPI and pMDI users in Korea

2.1.1 Objectives

1. To evaluate the 'switch success' 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 determine if there are any differences in key clinical paramaeters (e.g. exacerbations, blood eosinophil counts, IgE levels) between patients prescribed ICS/LABA using either DPIs or pMDIs

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 that continue to collect prescriptions of new ICS/LABA pMDI after initial prescription. Switch success is considered as >70% of the population maintaining their treatment at least 6 months after the switch. The study is powered for the 'switch success' of asthma patients changing their therapy to and continuing on ICS/LABA pMDI from existing ICS/LABA DPIs. Both patients switching to ICS/LABA pMDIs and those remaining on ICS/LABA DPIs will be fully characterised during baseline period.

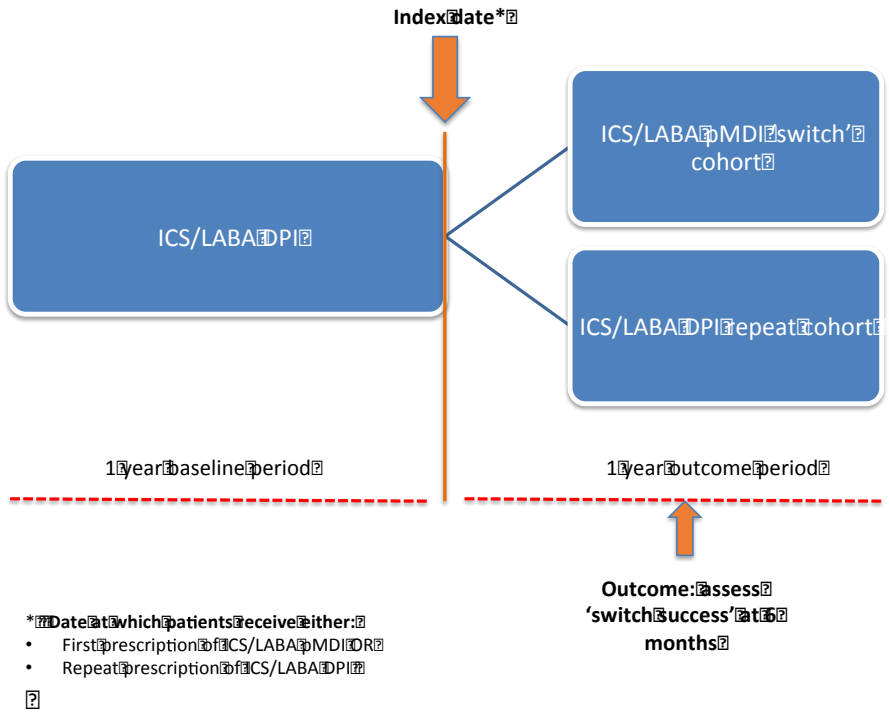

Figure 1: Study design

3.2 Study population

3.2.1 Inclusion and exclusion criteria

Inclusion criteria:

(1) Codes for asthma (ICD-10) dependent on availability

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

(3) Active asthma, defined as ≥ 2 prescriptions for LABA/ICS DPI at baseline

(4) ≥ 2 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 any chronic respiratory disease (e.g. COPD defined by ICD-9 code of J42.x-J44); except asthma, at any time; and/or

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

3.3 Data source

For this study, data collected from the Ajou University Hospital will be used. This database contains detailed and extensive longitudinal data of asthma patients with moderate/severe control. Data includes lung function tests, diagnositic values (blood eosinophil counts, IgE levels .

3.4 Study variables

3.4.1 Demographics

- Age (years)
- Gender (male, female)

3.4.2 Comorbidities (Note: this data/coding is subject to availabiliy through the Ajou University Hospital database)

Comorbidities of interest will include:

- Allergic and non-allergic rhinitis (ICD-10: J30, J31.0)
- Nasal Polyps (ICD-10: J33)
- Ezcema (ICD-10: L20-L30)
- Pneumonia (ICD-10: J09-J18)
- Gastro-oesophageal reflux disease (GERD) (ICD-10: K21)
- Other chronic lung diseases (ICD-10: J44, J47)
- Charlson comorbidity index score[1] (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]

[1]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

3.4.3 Disease severity and control

Asthma patients (Note: this data/coding is subject to availabiliy through the Ajou University Hospital database)

- Number of asthma-related hospitalisations in the year prior to switch date. Hospitalisations were considered asthma-related when the principal or secondary diagnosis was asthma (ICD-10 codes: J45.x– J46).
- Hospital outpatient attendances in the year prior to the switch date. Outpatient services were considered asthma-related when the principal or secondary diagnosis was asthma (ICD-10 codes: J45.x– J46).
- Number of other respiratory related hospitalisation and/or outpatient attendances in the year prior to switch date. These were the ones with ICD-10 codes for COPD (J42.x–J44.x, except J430) or a COPD-related disease (pneumonia: J12.x-J17.x, pulmonary thromboembolism: I26, I26.0, and I26.9, dyspnea: R06.0, or acute respiratory distress syndrome: J80). (Rhee et al, COPD 2014)
- 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).
- Reliever medication (SABA) prescriptions in the year prior to the switch date (categorized as 0, 1-200, 201-400, 401-800, 801+ μg/day).
- Number of courses of acute oral steroids in the year prior to the switch date.
- Other medications, for example:
  i. Number of paracetamol prescriptions in the year prior to switch date.
  ii. Number of non-steroidal anti-inflammatory drugs (NSAIDs) prescribed in the year prior to the switch date.
  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 dosing instructions at the time of therapy switch / continuation (for specification, see 5.4.5).
- Subject to availablity in the Ajou University database, lung function tests, patient reported outcomes (questionnaires) and laboratory diagnositic tests (blood eosinophil counts, IgE levels etc.) will be assessed

3.4.4 Prescriptions

- Respiratory-related drug therapies, in the year prior to the switch date:

- Short-acting β_2 agonist (SABA) and/or short-acting muscarinic antagonist (SAMA)
- Long-acting β_2 agonist (LABA), including patches
- Long-acting muscarinic antagonist (LAMA)
- Inhaled corticosteroids (ICS)
- Fixed combinations of LABA and ICS
- LTRA
- Theophylline

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

3.5 Study endpoints

3.5.1 Primary endpoint

Switch success, defined as:

Percentage of ICS/LABA pMDI patients who received ≥ 2 prescriptions of ICS/LABA pMDI (i.e. ≥ 1 prescription in addition to that issued at their prescription date) at 6 months and continued on ICS/LABA pMDI, i.e. did not fall back to ICS/LABA DPI. Some patients will 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.

3.5.2 Secondary effectiveness endpoints

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).

(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[2] (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[3]

(d) **Overall Asthma Control**

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

(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

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

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

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

- diagnostic code for oral candidiasis or prescription of antifungal therapy.

(i) **Mean daily ICS dose**

- μg mean daily ICS (beclomethasone equivalent) dosage

3.6 Statistical analysis

3.6.1 Software used

Statistical analysis will be performed using STATA version 14 software (StataCorp, Texas, USA) and SAS version 9.3 software (SAS Institute, Marlow, Buckinghamshire, United Kingdom).

[2] 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

[3] 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

3.6.2 Primary outcome: switch success

Proportion of patients achieving 'switch success' to ICS/LABA pMDI from ICS/LABA DPI, using a one-sided 95%CI approach as specified in "sample size rationale".

3.6.3 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)

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 relevant committees. Then, final version of this protocol will be registered with www.encepp.eu.

Any ethical approval required by Ajou University Hospital to be determined by the final protocol stage.

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 **Pending Executive Decisions**

The following are a list of queries that need to be addressed before a final protocol draft can be formalised:

- Final list of steering committee members needs to be established
- Ajou Univeristy database queries (for Prof Park)
    - Which coding system for diagnosis and medication prescription are used in the database?
        - All diagnosis and drug codes will be added to the appendix once the codying system has been confirmed
    - What ethical approval needs to be completed prior to study commencement?
    - Can the data be taken/analysed outside of Korea?

7.0 **Advisory group**

Communication with the SC will be held at key milestones: protocol approval, data reviews and, publication planning. Experts to be included to the steering committee of this study will be determined at the final protocol stage.

8.0 **Research team**

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9.0 **Timelines (Tentative)**

Table 1: Study Timelines

Action	Timeline
Protocol writing/approval	4 weeks
Ethics approval	4-6 weeks
Database review	4-6 weeks
Data analysis and stats	3 months
Report writing	4 weeks
Steering committee review	4 weeks
First draft of manuscript	12 weeks

10.0 References

1. GINA guidelines
2. Herland Respir Med 2005,

11.0 APPENDIX (to be confirmed by Prof. Park)

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-9 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
- 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) and/or 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
  - LTRA
  - Omaluzimab
  - Theophylline

Appendix 3: Baseline results table

		ICS/LABA Repeat DPI	ICS/LABA Switch pMDI	p-value
Age (years)	mean (SD)			
Age (categorised)	40 - 60, n (%)			
	61 - 80, n (%)			
	> 80, n (%)			
Sex, male	n (%)			
Socio-economic status	non-missing, n (%)			
	High status, n (%)			
	Moderate, n (%)			

	Low, n (%)			
Risk Domain Asthma Control, uncontrolled				
Overall asthma control, uncontrolled				
Severe asthma exacerbations	0, n (%)			
	1, n (%)			
	2-3, n (%)			
	≥ 4, n (%)			
Severe respiratory events	0, n (%)			
	1, n (%)			
	2-3, n (%)			
	≥ 4, n (%)			
Acute oral corticosteroid courses (during baseline period)	0, n (%)			
	1, n (%)			
	≥2, n (%)			
Antibiotic prescriptions for LRTI (during baseline period)	0, n (%)			
	1, n (%)			
	≥2, n (%)			
Asthma therapy (during baseline period)	None, n (%)			
	SABA (+/- SAMA), n (%)			
	LABA (+/- LAMA), n (%)			
	LTRA+/-LABA+/-LAMA			
	ICS			
	ICS+/-LABA+/-LAMA			
	ICS+LTRA+/-LABA+/-LAMA			
	Theophylline/methylxanthine			
	Oral beta-agonist			
	OCS			
	Other (omaluzimab)			
Daily dose of ICS (ug/day)				
SABA inhaler usage (µg per day, during baseline period)	0, n (%)			
	≤ 200, n (%)			
	201-400, n (%)			
	401-800, n (%)			
	>800, n (%)			
Comorbidities				
Allergic rhinitis				
Non-allergic rhintis				
Nasal polyps				
Eczema				

Diabetes				
GERD				
CCI score (for baseline period)	0, n (%)			
	1 - 4, n (%)			
	>4, n (%)			
ED visits				
Hospital Primary				
Hospital Secondary				
Hospital Tertiary				
ICU				
Chest X-rays				
Chest CTs				
PFT				

Appendix 4: Ajou data dictionary

Patient

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

Field Name	*Content*

Clinical

The **Clinical** file contains medical history events. This file contains all the medical history data entered on the hospital 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.

Field Name	*Content*

Therapy

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*

Medication codes specification

- Respiratory drugs
    - Short-acting β_2 agonist (SABA) and/or short-acting muscarinic antagonist (SAMA)
    - Long-acting β_2 agonist (LABA), and LABA patches
    - Long-acting muscarinic antagonist (LAMA)
    - Inhaled corticosteroids (ICS)
    - Fixed combinations of LABA and ICS
    - LTRA
    - Omaluzimab
    - Theophylline
- Exacerbations
    - Oral corticosteroids
    - Antibiotics

- Oral candida drugs
- Paracetamol
- NSAIDS