**Research Protocol**

**Title:** Comparative effectiveness and safety of omalizumab and dupilumab in children with asthma

# Study Lead:

Chang Hoon Han, MD

Hamin Kim, MD

Seng Chan You, MD, PhD

Kyung Won Kim, MD, PhD

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# List of abbreviations

* IgE: Immunoglobulin E
* IL: Interleukin
* GINA: Global Initiative for Asthma
* EHR: Electrical health record
* OMOP-CDM: Observational Medical Outcomes Partnership Common Data Model

# Abstract

This study aims to compare omalizumab and dupilumab, two of the most used biologic agents in the treatment of asthma. In cases of moderate-to-severe asthma where these drugs are indicated, this study will provide valuable evidence for guiding clinical decision-making, by conducting head-to-head comparison of these drugs on their effectiveness and safety.

# Amendments and Updates

None

# Rationale and Background

Biologic agents now account for more than 20% of the drugs annually approved by the US Food and Drug Administration (FDA), representing a rapidly expanding field. [1] Their efficacy has been demonstrated in diverse areas of medicine, including allergic diseases, where they are actively used to manage conditions such as moderate to severe-persistent asthma and chronic spontaneous urticaria. [2] Most of these agents are monoclonal antibodies that specifically target pathways involved in type 2 immune responses. [3] Biologic agents currently approved for treatment of asthma include omalizumab, which directly binds to free immunoglobulin E (IgE), mepolizumab, reslizumab, and benralizumab that targets interleukin-5 (IL-5) mediated signal, and dupilumab that binds to IL-4 receptor, blocking IL-4 and IL-13 mediated signals. [2, 3]

In Global Initiative for Asthma (GINA), biologics are considered as add-on therapy when step 5 treatment with other conventional agents including high-dose inhaled corticosteroids (ICS) and long-acting β2-agonist (LABA) fail to adequately control severe asthma, and are recommended only when there is evidence of elevated type 2 immune response markers. [4] Currently there is no clear distinction in the indications for different biologic agents, and a significant portion of patients who require biologics add-on therapy may fall under the indications of multiple biologic agents. [4, 5] While there have been attempts to provide guidance for treatment decisions based on phenotypic characterizations based on factors like blood eosinophil, lung function, and comorbid allergic diseases, there is limited evidence on comparative effectiveness and safety between biologics, limiting precise recommendations. [5]

Relatively recent studies on multiple biologics in asthma, marks steady advancement of our understanding on this area. However, many studies assess effectiveness and safety of each agent individually, and only few studies provide direct head-to-head comparisons. [6, 7] Akenroye et al. compared effectiveness of dupilumab, omalizumab and mepolizumab in adult asthma patients, and discovered superior reduction in exacerbations in dupilumab compared to the other agents. [8] Bleeker et al. compared effectiveness of dupilumab and omalizumab in asthma patients 12 years old and showed fewer exacerbations and systemic steroid prescriptions in dupilumab.[9] Further validation of these promising results using different databases with more subjects is warranted. Main goal of this study is to compare omalizumab and dupilumab, providing additional evidence to support the clinical decision-making process in asthma indicated with biologics treatment.

# Aims and Objectives

This study is a cohort study which aims to:

1. Compare the effectiveness of omalizumab and dupilumab in pediatric asthma patients.
2. Compare the incidence of previously known side effects of omalizumab and dupilumab in pediatric asthma patients.

## AIM 1. Comparative Effectiveness

* Determine and compare the incidence rate of asthma exacerbation in asthma patients on either omalizumab or dupilumab.
* Compare how much reduction of steroid use was achieved in asthma patients on either omalizumab or dupilumab.

## AIM 2. Comparative Safety

* Determine and compare the incidence rate of previously known side effects of omalizumab and dupilumab, including eosinophilia, helminth infection, anaphylaxis, and conjunctivitis.

# Research Methods

## Study Design

This is a retrospective cohort study, comparing effectiveness outcomes and side effect incidence. Data sources will be electronic health record (EHR) data in Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM) format, across the OHDSI network.

## Study Population

### Study Population for Comparison of Incidence Outcomes

The primary study population includes patients under the age of 18 diagnosed with asthma, either administered with omalizumab or dupilumab. Additionally, a secondary analysis will be done to include patients of all ages diagnosed with asthma.

The target group consists of patients who were initiated with omalizumab and who meet the criteria below. The comparator group consists of patients who were initiated with dupilumab and who meet the criteria below.

As primary analysis, intention-to-treat design will be applied to derive 1-year outcomes.

As sensitivity analysis, on-treatment design will be applied. The cohort exit rule described below will be applied.

Index rule defining the index date:

* First exposure to one of the agents of interest from 2018-11-01 and after.
* Under the age of 18 at the index date.
* With continuous observation of at least 180 days before the event index date.

Inclusion rules based on the index date:

* At least 1 occurrence of asthma between 30 days before and 7 days after the index date.
* None of exposure to the drug of the other group in the observation period before the index date.

Exit rules defining the cohort end date (on-treatment):

* Event will persist until end of a continuous drug exposure of interest.
* Allowance for 60-day gaps between exposure records of the drug of interest.
* Add 30 days to the end of the last exposure record as an additional period of surveillance.
* Censored with an exposure of the drug of the other group.

Table 1 Asthma Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 317009 | Asthma | Condition | FALSE | TRUE | FALSE |
| 4308356 | Asthma finding | Condition | FALSE | TRUE | FALSE |
| 4279553 | Eosinophilic asthma | Condition | FALSE | TRUE | FALSE |
| 4077802 | Asthma monitoring | Observation | FALSE | TRUE | FALSE |
| 46287068 | At risk of severe asthma exacerbation | Condition | FALSE | FALSE | FALSE |

### Treatments of Interest

#### Target Drug: Omalizumab

Table 2 Omalizumab Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 302379 | omalizumab | Drug | FALSE | TRUE | FALSE |
| 21603362 | omalizumab; parenteral | Drug | FALSE | TRUE | FALSE |

#### Comparator Drug: Dupilumab

Table 3 Dupilumab Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 1593467 | dupilumab | Drug | FALSE | TRUE | FALSE |

### Study Population for Steroid Dose Reduction Outcome

For this section of analysis, study population includes patients under the age of 18 diagnosed with asthma, either administered with omalizumab or dupilumab, with additional criteria of exposure to steroid within a certain period (3months or 6months) before index date. Likewise, a secondary analysis will be done to include patients of all ages diagnosed with asthma.

For 3-month total steroid dose reduction outcome

* Patients meeting criteria specified in 6.2.1. Study Population for Comparison of Incidence Outcomes
* At least 1 exposure of steroids specified in Table 4, 90 days before event index date.

For 6-month total steroid dose reduction outcome

* Patients meeting criteria specified in 6.2.1. Study Population for Comparison of Incidence Outcomes
* At least 1 exposure of steroids specified in Table 4, 180 days before event index date.

Table 4 Included Steroid Concepts

|  |  |  |  |
| --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Class |
| 1550557 | prednisolone | Drug | Ingredient |
| 1551099 | prednisone | Drug | Ingredient |
| 19086888 | deflazacort | Drug | Ingredient |
| 975125 | hydrocortisone | Drug | Ingredient |
| 1507705 | cortisone | Drug | Ingredient |
| 1506270 | methylprednisolone | Drug | Ingredient |
| 903963 | triamcinolone | Drug | Ingredient |
| 1518254 | dexamethasone | Drug | Ingredient |
| 920458 | betamethasone | Drug | Ingredient |

## Outcomes

### Primary Outcomes

#### Effectiveness Outcome – Asthma Exacerbation

Asthma exacerbation outcome is operationally defined as ER or inpatient visit due to asthma. The outcome cohort definition is as below.

Index rule defining the index date:

* A condition occurrence of asthma
* At least 1 occurrence of ER or inpatient visit, where the event starts before and ends after condition occurrence.

Table 5 ER or Inpatient Visit Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 9201 | Inpatient Visit | Condition | FALSE | TRUE | FALSE |
| 9203 | Emergency Room Visit | Condition | FALSE | TRUE | FALSE |

#### Effectiveness Outcome – Steroid Dose Reduction

Steroid dose reduction outcome is defined as reduction in total steroid use, comparing certain time periods before and after index date. 3 months before and after index date for 3-month total steroid dose reduction outcome, and 6 months before and after index date for 6-month steroid dose reduction outcome.

Total cumulative dose of each steroid ingredient is calculated within the designated time periods. Total steroid use is then calculated from summation of total cumulative dose of all included agents, converted to prednisolone equivalent doses. Conversion is done with approximate equivalent dose based on relative glucocorticoid activity. [10, 11] The equation is as below.

(Total steroid use) = (Cumulative dose of prednisolone)

+ (Cumulative dose of prednisone)

+ (Cumulative dose of deflazacort 5/7.5)

+ (Cumulative dose of hydrocortisone 5/20)

+ (Cumulative dose of cortisone 5/25)

+ (Cumulative dose of methylprednisolone 5/4)

+ (Cumulative dose of triamcinolone 5/4)

+ (Cumulative dose of dexamethasone 5/0.75)

+ (Cumulative dose of betamethasone 5/0.6)

Steroid dose reduction outcome is expressed using two different methods, as steroid dose percentage and steroid dose reduction groups, defined as below.

Steroid dose percentage:

* (Total steroid use after index date) / (Total steroid use before index date) 100 (%)

Steroid dose reduction groups:

* Stop use
* Reduction of 75% or more
* Reduction of 50% or more, below 75%
* Reduction of 25% or more, below 50%
* Reduction below 25%
* No change or increased use

### Secondary Outcomes

#### Safety Outcome – Eosinophilia

Three eosinophilia outcome cohorts based on severity are defined. (Eosinophil count above 500, 1500 and 3000 per microliter of blood)

Index rule defining the index date:

* A measurement occurrence of eosinophil greater than a designated value (500, 1500, and 3000)

Table 6 Eosinophil Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 3013115 | Eosinophils [#/volume] in Blood | Measurement | FALSE | FALSE | FALSE |

#### Safety Outcome – Helminth Infection

Index rule defining the index date:

* A condition occurrence of helminth infection

Table 7 Helminth infection Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 432251 | Disease caused by parasite | Condition | FALSE | TRUE | FALSE |
| 3012744 | Ova and parasites identified in Specimen by Light microscopy | Measurement | FALSE | TRUE | FALSE |

#### Safety Outcome – Anaphylaxis

Index rule defining the index date:

* A condition occurrence of anaphylaxis

Table 8 Anaphylaxis Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 441202 | Anaphylaxis | Condition | FALSE | TRUE | FALSE |
| 4221182 | Anaphylaxis due to substance | Condition | FALSE | FALSE | FALSE |
| 4084168 | Drug-induced anaphylaxis | Condition | FALSE | FALSE | FALSE |
| 42536383 | Anaphylactic shock | Condition | FALSE | FALSE | FALSE |
| 4298385 | Anaphylaxis management | Observation | FALSE | FALSE | FALSE |

#### Safety Outcome – Conjunctivitis

Index rule defining the index date:

* A condition occurrence of conjunctivitis

Table 9 Conjunctivitis Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 379019 | Conjunctivitis | Condition | FALSE | TRUE | FALSE |

### Negative Control Outcomes

A total of 100 concepts were selected as negative controls that were not associated with both the target and comparator drugs and study outcomes.

Table 10 Negative controls outcomes

|  |  |  |  |
| --- | --- | --- | --- |
| Concept ID | Concept Name | Concept ID | Concept Name |
| 4115367 | Wrist joint pain | 438178 | Postmastectomy lymphedema syndrome |
| 4229262 | Wilson's disease | 4159151 | Posthemorrhagic hydrocephalus |
| 44813944 | Vitamin D insufficiency | 37311762 | Posterior hypospadias |
| 36684444 | Vertebral joint pain | 78830 | Post-dysenteric arthropathy |
| 140641 | Verruca vulgaris | 4091513 | Passing flatus |
| 4278836 | Ulcer on tongue | 438130 | Opioid abuse |
| 4293712 | Traumatic oral ulceration | 140648 | Onychomycosis due to dermatophyte |
| 437264 | Tobacco dependence syndrome | 136368 | Non-toxic multinodular goiter |
| 377575 | Tinnitus | 377572 | Noise effects on inner ear |
| 378427 | Tear film insufficiency | 4209423 | Nicotine dependence |
| 4051613 | Sulcus vocalis of vocal cord | 442136 | Neoplasm of uncertain behavior of trachea |
| 374053 | Sudden hearing loss | 76685 | Myasthenia gravis |
| 81151 | Sprain of ankle | 4101079 | Middle ear finding |
| 443172 | Splinter of face, without major open wound | 4128221 | Microalbuminuric diabetic nephropathy |
| 36714689 | Somatic dysfunction of pubic region | 4115107 | Mass of female genital structure |
| 36713918 | Somatic dysfunction of lumbar region | 4083487 | Macular drusen |
| 380706 | Regular astigmatism | 374912 | Leukodystrophy |
| 81634 | Ptotic breast | 37209383 | Lesion of left ovary |
| 439790 | Psychalgia | 438329 | Late effect of motor vehicle accident |
| 373478 | Presbyopia | 434203 | Late effect of contusion |
| 436676 | Posttraumatic stress disorder | 432593 | Kwashiorkor |
| 137820 | Postoperative hypothyroidism | 196168 | Irregular periods |
| 4002836 | Postoperative hemorrhage | 4335808 | Injury of posterior cruciate ligament |
| 4010333 | Postmenopausal osteoporosis | 444132 | Injury of knee |
| 4344500 | Impingement syndrome of shoulder region | 441669 | Congenital anomaly of posterior segment of eye |
| 374375 | Impacted cerumen | 432303 | Cocaine abuse |
| 436941 | Hypervitaminosis A | 4100822 | Cobalamin deficiency |
| 4182278 | Hypermethioninemia | 81378 | Chondromalacia of patella |
| 4012934 | Homocystinuria | 140842 | Changes in skin texture |
| 4012570 | High risk sexual behavior | 4213540 | Cervical somatic dysfunction |
| 4231770 | Hereditary thrombophilia | 434327 | Cannabis abuse |
| 37110444 | Harmful pattern of use of nicotine | 141055 | Cancrum oris |
| 433577 | Hammer toe | 73560 | Calcaneal spur |
| 4166231 | Genetic predisposition | 4108466 | Burn of respiratory tract |
| 40481632 | Ganglion cyst | 133655 | Burn of forearm |
| 4084433 | Fracture of posterior malleolus | 4128528 | Asymptomatic proteinuria |
| 259995 | Foreign body in orifice | 4140963 | Anorectal anomaly |
| 4110491 | Fistula of nasal sinus | 4103640 | Amputated foot |
| 4170770 | Epidermoid cyst | 45763909 | Acute disruption of ankle syndesmosis |
| 433111 | Effects of hunger | 77965 | Acquired trigger finger |
| 4237155 | Eaton-Lambert syndrome | 75911 | Acquired hallux valgus |
| 4339029 | Double depressor palsy | 44783954 | Acid reflux |
| 45757370 | Disproportion of reconstructed breast | 4092879 | Absent kidney |
| 4115402 | Difficulty sleeping | 4088290 | Absence of breast |
| 76786 | Derangement of knee | 4153106 | Abscess of breast |
| 78619 | Contusion of knee | 199192 | Abrasion and/or friction burn of trunk without infection |
| 4005447 | Congenital pyloric stenosis | 436409 | Abnormal pupil |
| 373489 | Congenital nystagmus | 434165 | Abnormal cervical smear |
| 4028847 | Congenital duplication of stomach | 375824 | Abnormal auditory perception |

# Data Analysis Plan

## Population Level Estimation

#### Covariates for Propensity scores

The types of baseline covariates used to fit the propensity score model will be:

* Demographics
  + Gender
  + Age groups (5-year bands)
  + Race
  + Ethnicity
  + Index Year/Month
* Condition Aggregation
  + In prior 30d or365d
* Drug Aggregation
  + In prior 30d or 365d
* Procedure
  + In prior 30d or 365d
* Device
  + In prior 30d or 365d
* Measurement
  + In prior 30d or 365d
  + Range Group in prior 365d
* Observation
  + In prior 30d or 365d

The concepts used in the definitions of the target and comparator cohorts are excluded from the propensity score model.

#### Data Analysis Plan

##### **Definition of Time at Risk**

Per analysis, time at risk is defined as below.

Primary analysis: Intention-to-treat (1 year)

* Time at risk start: Index date
* Time at risk end: Index date +365 day
* Minimum time at risk: 1day

Sensitivity analysis: On-treatment

* Time at risk start: Index date
* Time at risk end: Cohort end date
* Minimum time at risk: 1day

##### **Statistical Model Specification**

We compare the target cohort with the comparator cohort for the hazards of outcome during the time-at-risk by applying a Cox proportional hazards model. Incidence rates will be computed for each outcome in each exposure group.

Propensity score adjustment will be:

* PS stratification: The target cohort and comparator cohorts will be stratified into 5 stratums of the PS distribution.

Outcome model settings will be:

* Cox proportional hazards model will be used to estimate the risk of outcome between target and comparator cohorts.

##### **Analysis to Perform**

The following comparative analysis will be performed:

* One comparison:
  + New users of omalizumab with asthma (Target) vs. new users of dupilumab with asthma (Comparator)
* 2 populations:
  + Age under 18
  + All ages
* 7 outcomes:
  + Asthma exacerbation
  + Eosinophilia (Greater than 500/1500/3000)
  + Helminth infection
  + Anaphylaxis
  + Conjunctivitis
* 2 time-at-risk:
  + Intention-to-treat (1-year)
  + On-treatment
* One model: Cox-regression after PS stratification

#### Output

|  |  |
| --- | --- |
| Output | Description |
| Propensity score distribution Plot | The propensity score distribution for both cohorts will be provided. |
| Propensity model | The propensity model will show the table that reports the covariates selected from propensity score models, with associated coefficients. |
| Covariate balance scatter plot | Covariate balance scatter plot will show the absolute standardized difference of mean before and after PS adjustment. |
| Attrition diagram | Attrition diagram will show the counts to meet the inclusion and exclusion criteria. |
| Kaplan-Meier plot | Kaplan-Meier plot will display the survival over time in both cohorts. |
| Population characteristics table | A table which lists some select population characteristics before and after PS adjustment will be created. |

## Steroid Dose Reduction Outcome

#### Statistical method

The difference between the target and the comparator will be shown for both as steroid dose percentage and steroid dose reduction groups. The statistical method is as follows.

For steroid dose percentage:

* Wilcoxon rank sum test.

For steroid dose reduction groups:

* Fisher’s exact test will be used if any of the expected frequencies is <5.
* Chi-squared test will be used if all the expected frequencies are 5 or higher.

#### Output

|  |  |
| --- | --- |
| Output | Description |
| Contingency table | A table which lists the number of patients in each steroid dose reduction group and the steroid dose percentage for both target and comparator group will be created. P-value from respective tests will also be displayed. |

# Strengths and Limitations of the Research Methods

## Strength

* The new-user design can appropriately capture early events following treatment exposures while avoiding confounding from previous treatment effects.
* PS adjustment allows balancing on many potential confounders.

## Limitations

* Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured variables.
* Raw comparison will be done for steroid dose reduction outcome, and potential risk of confounding bias exists.

# Protection of Human Subjects

In this study, we will use only de-identified data from CDM. Only the results of study will be aggregated, and the data will not identify individual subjects. The study was approved by the institutional review board of Yonsei University Health System, Severance Hospital. (No.4-2024-0232)

# Plans for Disseminating and Communicating Study Results

At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal.

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