Study protocol

Precision Medicine Intervention in Severe Asthma (PRISM) study: molecular phenotyping of patients with severe asthma and response to biologics

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Title: Precision Medicine Intervention in Severe Asthma (PRISM) study: molecular phenotyping of patients with severe asthma and response to biologics

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Abstract

Severe asthma represents an important clinical unmet need despite the introduction of biologic agents. Although advanced omics technologies have aided researchers in identifying clinically relevant molecular pathways, there is lack of integrated omics approach in severe asthma particularly in terms of its evolution over time.

The collaborative Korea-UK research project, Precision Medicine Intervention in Severe Asthma (PRISM), was launched in 2020 with the aim of identifying molecular phenotypes of severe asthma by analyzing multi-omics data encompassing genomics, epigenomics, transcriptomics, proteomics, metagenomics, and metabolomics. PRISM is a prospective, observational, and multicenter study involving patients with severe asthma attending severe asthma clinics in Korea and the UK.

Data including patient demographics, inflammatory phenotype, medication, lung function, and control status of asthma will be collected along with biological samples (blood, sputum, urine, nasal epithelial cells, and exhaled breath condensate) for omics analyses. Follow-up evaluations will be performed at baseline, 1 month, 4–6 months, and 10–12 months to assess the stability of phenotype and treatment responses for those patients who have newly begun biologic therapy. Standalone and integrated omics data will be generated from the patient samples at each visit, paired with clinical information. By analyzing these data, we will identify the molecular pathways that drive lung function, asthma control status, acute exacerbations, and the requirement for daily oral corticosteroids and that are involved in the therapeutic response to biological therapy.

PRISM will establish a large multi-omics dataset of severe asthma to identify potential key pathophysiological pathways of severe asthma.
Keywords: severe asthma, biologics, multi-omics data, protocol
Introduction

Severe asthma is a major clinical unmet need causing deterioration in quality of life and socioeconomic burden.[1] Although a deeper understanding of the pathophysiology of asthma has led to the development of biologic agents targeting Type 2 (T2) inflammation, therapeutic responses vary between patients.[2-4] Given the similar eligibility criteria for T2-targeting biologics, the different clinical courses imply that there are various factors involved in the clinical manifestations of severe asthma. Furthermore, there are pathways that need to be discovered in those who are unsuitable or do not respond to T2-targeted biologics. The introduction of omics technologies, including transcriptomics, epigenomics, metagenomics, metabolomics, and proteomics, has provided a research approach for physicians to identify molecular markers that are not readily detected with usual diagnostic tests in the clinic.[5, 6] As a consequence, analyses of omics data are expected to unravel the complex pathophysiologic cascade of severe asthma.[7, 8]

Previous work from the Cohort for Reality and Evolution of Adult Asthma in Korea (COREA) and Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) has initiated this omics approach. Using the pre-existing data from COREA, distinct microbiota of patients with asthma compared with healthy controls by metagenomic analysis of extracellular vesicles in exhaled breath condensate (EBC) have been reported.[9] We have identified significant single nucleotide polymorphisms in Korean patients with asthma in genome-wide association studies.[10] The European U-BIOPRED consortium has also reported novel molecular phenotypes and markers in severe asthma based on proteomic, transcriptomic, and metabolomic data generated from blood, sputum, airway epithelial cells, and exhaled breath.[11-15] Specifically, cluster analysis of sputum transcriptomics has identified three clusters of severe asthma, which were characterized by eosinophilic
phenotype, inflammasome, and metabolic/mitochondrial pathway, respectively.[16] These data collectively emphasize the presence of molecular pathways underlying the varied expression of asthma, which may also serve as predictors of therapeutic responses or potential therapeutic targets. Nevertheless, there is still a scarcity of integrated omics data in patients with severe asthma, especially with respect to longitudinal stability or changes. As demonstrated in chronic obstructive pulmonary disease (COPD), the integration of multi-omics data has led to the identification of molecular phenotypes or endotypes with greater resolution and requiring far fewer patients for stratification, which is a key goal of precision medicine.[17] Analysis of up to four multi-omics platforms in sputum cells has also led to great granularity of various molecular phenotypes particularly the low-T2 phenotypes in U-BIOPRED.[8]

With the support of the Bio & Medical Technology Development Program of the National Research Foundation by the Korean government and of the UK government’s Medical Research Council, a multi-omics study of severe asthma was initiated in both countries as a collaborative project. The Korea-UK Precision Medicine Intervention in Severe Asthma (PRISM) study aims to identify molecular phenotypes of severe asthma by analyzing multi-omics data including genomics, epigenomics, transcriptomics, proteomics, metagenomics, and metabolomics. Moreover, the study will seek improved biomarkers of the optimal therapeutic response for these molecular phenotypes beyond the conventional markers used presently such as blood eosinophil counts, sputum eosinophils, and fractional exhaled nitric oxide (FeNO) in patients with severe asthma undergoing treatment with the currently available T2-directed biologic therapies. We will also identify the molecular phenotypes of severe T2-low asthma and their potential therapeutic markers. PRISM will examine these participants over several visits for 12–24 months; therefore, we will determine the stability or changes in the molecular phenotypes of the participants, whether they are
undergoing treatment with a T2 biologic or not.

Materials and Methods

Study population and recruitment

The study will be conducted in 38 centers in Korea and 3 severe asthma centers in the UK (list provided in the Supplementary Material) from May 2020 to December 2022. Due to the deleterious effects of COVID-19, the recruitment period has been extended by 18 months in the UK centers. The goal is to recruit 200 patients with severe asthma in each country and obtain multi-omics data as well as clinical parameters reflecting the status of asthma. The sample size was decided based on the duration of the study and number of participating centers as there was no a priori hypothesis to be tested. At present, there are no standardized criteria for sample size determination in omics studies. The diagnosis of severe asthma is based on the European Respiratory Society/American Thoracic Society (ERS/ATS) criteria published in 2014.[1] When a patient meets the eligibility criteria for use of a biologic agent, physicians determine the proper medication according to the guidelines in effect in Korea and the UK, as appropriate (Table 1). The study protocol is registered at ClinicalTrials.gov (NCT05164939). The Institutional Review Board of participating centers approved the study and all patients provided written informed consent (IRB No. 2019-1676).

Inclusion and exclusion criteria

Patients who meet all of the following criteria are included in the study: 1) male or female subjects aged between 18 years and 80 years, 2) individuals who comply with the study protocol requirements, 3) individuals who are able to read, comprehend, and write at a
sufficient level to complete the study-related materials, 4) patients who have been through a severe asthma protocol that has confirmed the diagnosis of severe asthma, maximized treatments and ensured adherence to therapy, and 5) patients who have been on stable asthma therapy for at least a month before screening. Patients with uncontrolled asthma despite using medications for Global Initiative for Asthma (GINA) guideline steps 4–5 or those required these medications to suboptimally control their asthma are classified as having severe asthma.[1]

Patients are not eligible for the study if they meet any of the following criteria: 1) medical interview, physical examination, or screening investigation findings that lead the investigators to consider the subject unfit either because of risk to the subject due to the study or due to the influence these factors may have on the study results; 2) history of recreational drug use or allergy that in the opinion of the investigators makes their participation contraindicated; 3) participation within 3 months in any a trial testing a new molecular entity or drug; 4) unstable asthma requiring hospitalization or high-dose oral corticosteroids (>30 mg of prednisolone per day) within 4 weeks of screening; 5) prior treatment with bronchial thermoplasty, which is defined as completion of all thermoplasty treatment sessions within 6 months of screening; 6) history of significant pulmonary disease other than severe asthma; 7) history of pulmonary eosinophilic syndrome or hypereosinophilic syndrome; or 8) history of bronchopulmonary aspergillosis.

**Study design (Figure 1)**

This is a prospective and observational cohort study. During the four-month screening period, the eligibility of participants is assessed. In addition, phenotyping is conducted based on the results of a skin prick test, blood testing, induced sputum analysis, and FeNO levels. T2-high
asthma is defined when the participant has one of the following conditions; 1) blood eosinophils $\geq 150/\mu L$ in Korea or $\geq 300/\mu L$ in the UK considering eligibility for biologics, 2) FeNO $\geq 20$ ppb, 3) sputum eosinophils $\geq 2\%$, or 4) clinically allergen-driven asthma.[18] Once classified as having T2-high asthma, the patient may be treated with a biologic agent including omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab or continue with conventional treatment after discussion between the physician and patient. Table 1 describes the differing inclusion criteria for the prescription of biologics in Korea and the UK. The first administration of a biologic agent occurs at the enrollment visit (visit 1). The dose and treatment interval of each medication follows the recommended protocols for each pharmaceutical agent. Patients with T2-high asthma who do not use biologics and those with T2-low asthma continue their conventional treatment, and these patients with severe asthma are also included in the study.

The participants are evaluated at baseline (enrollment visit), one month (visit 2), 4–6 months (visit 3), and 10–12 months (visit 4) (Table 2). At the enrollment visit, detailed information regarding demographic factors, past medical history, and comorbidities is collected. The results of imaging studies including chest X-rays, sinus X-rays, rhinoscopy, and computed tomography of the chest are also collected. At every visit, patients undergo blood testing, induced sputum analysis, and lung function tests. In addition, samples (blood, sputum, urine, nasal epithelial cells, and EBC) for multi-omics analysis are obtained (Table 3). The types of samples and matched omics analyses were selected according to priority based on clinical relevance and practical issues such as the amount of sample that could be obtained and the cost of the analysis. An experienced physician performs nasal brushing to collect epithelial cells from the nostrils of the participants. The EBC is collected using R-tube device (Respiratory Research, Austin, Texas, USA) during 10 minutes of normal breathing. In selected patients, bronchoscopy is additionally performed. Along with objective diagnostic
tests, all participants are required to complete the Asthma Control Test (ACT), Severe Asthma Questionnaire (SAQ), European Quality of Life Five Dimension (EQ-5D), Cough Questionnaire for Asthma (CQA), and Sino-Nasal Outcome Test-22 (SNOT-22). The Asthma Quality of Life Questionnaire (AQLQ) and Quality of Life Questionnaire for Adult Korean Asthmatics (QLQAKA) are used only in UK and Korea, respectively. The newly developed CQA was incorporated which aimed to characterize the cough in asthmatics. Regarding exacerbation, we will collect not only the number of reported exacerbations during a year but also the management, including the total dose of systemic corticosteroids and additional medications, and type of hospital utilization (outpatient clinic, general ward, intensive care unit) based on medical records. In Korea, detailed clinical assessment and collection of biological samples are conducted when the participants visit outpatient clinics or emergency rooms due to acute exacerbations.

The overall treatment response is assessed after 1, 6, and 12 months. Based on the clinical course during the first 6 months of treatment, the physician may decide either initiation, cessation, or switching of the biologic agent if the patient shows an insufficient treatment response. Data from Global Evaluation of Treatment Effectiveness (GETE) scale, as well as reasons for discontinuation or switching would be collected. According to the change in treatment, the participant is recategorized; thus, baseline clinical data and samples are collected. In cases in which the biologic agent needs to be changed, a four-month wash-out period is ideally required, but this may not be possible as the switch may occur as quickly as within one month.

**Data analysis**

*Outcomes and data interpretation*
The study aims to assess the stability of inflammatory markers in patients with severe asthma over the course of their treatment, which may involve biologic therapies. For those treated with biologic therapies, treatment response will be assessed based on improvement in lung function (increase of forced expiratory volume in 1 second ≥ 100ml and 10%), asthma control status (improvement of ACT ≥3 points), and reduction of acute exacerbations (100% reduction) as well as cessation of oral corticosteroids.[19, 20] The demographic and clinical variables associated with treatment response will be identified using appropriate statistical methods. One of the aims of this study is to determine the best parameters to determine the true clinical response to biologic treatment, which is improvement in all the following key domains of asthma: acute exacerbation, lung function, symptoms, and oral corticosteroid use. For those not on biologic treatment, we will determine the stability of the phenotype over a one-year period.

In parallel with the analysis of clinical data, single omics data, including genomics, metagenomics, metabolomics, transcriptomics, and proteomics, will be generated from the patient samples and integrated as a whole for each participant. The dataset will be uploaded in a web-based platform after removing personally identifiable information to allow participating researchers to access the data. These omics data will be merged with the clinical dataset and analyzed in both a cross-sectional and longitudinal manner. The analysis will be performed in collaboration with experts from each omics platform using specialized data analysis programmes. The analyses would be primarily conducted in each country to minimize confounders derived from regional differences that may affect the response interpretation, such as inherent ethnicity, practice patterns, and criteria for selecting biologics. Additionally, when combining the data from two countries, comparison of baseline characteristics would be initiated to identify potential confounders requiring adjustment in further analyses.
Analytical approaches of omics platforms

1. **Molecular clustering of the UK and Korean cohorts.** We will use various approaches such as similarity network fusion (SNF) and topological data analysis (TDA) for integration of the various multi-omics data collected as used previously in U-BIOPRED for severe asthma and by collaborators for COPD.[21, 22] These packages will be accessed through R Bioconductor (SNF) and using the Ayasdi visualization package for TDA. Other approaches including gene set variation analysis (GSVA), weighted gene co-expression network analysis (WGCNA) along with pathway analysis will also be used.

2. **Molecular phenotyping of patients with severe asthma.** Patients will be phenotyped according to the gene expression of the top six genes and proteins using real-time quantitative polymerase chain reaction and multiplex analysis with the highest expression scores from omics analysis in sputum cells as detailed for transcriptome-associated cluster (TAC) status. For those with no sputum sample available or a poor-quality sputum sample for RNA extraction, we will use signatures in blood RNA and serum protein levels that match the TAC classification.[23]

3. **Biomarkers of response to anti-T2 therapies.** We will determine which molecular phenotype or signature or biomarker best identifies patients who respond to anti-T2 biologic therapies compared with the use of the molecular phenotype signatures. In a more exploratory context, we will use clustering approaches (e.g., model-based mixture models or hierarchical/k-means clustering) to define phenotypic clusters grouping patients with similar clinical traits at each given timepoint. Over-representation analyses will identify clusters that are enriched in responding patients to anti-T2-biologics.

4. **Defining potential therapeutic targets.** These pathways or targets will be interrogated using techniques such as GSVA25 or other gene set enrichment analyses in Bioconductor to
identify expression of key targets either at the transcriptomic or protein or metabolite levels in various tissue compartments. Linking these analyses in different compartments with genetic features may provide a distinct genetic fingerprint linked to distinct phenotypes and/or therapeutic super-response/non-response that may be useful in larger screening studies.

**Currently available data**

As of May 2022, a total of 186 patients have been enrolled the study. Among them, 163 patients and 23 patients were classified as T2-high and T2-low asthma, respectively. For those with T2-high asthma, reslizumab (46/163, 28.22%) was prescribed most frequently, followed by mepolizumab (36/163, 22.09%), dupilumab (42/163, 25.77%), omalizumab (10/164, 6.13%), and benralizumab (3/164, 1.84%). The majority of patients (159/186, 85.48%) had partly controlled or uncontrolled asthma during treatment with high intensity anti-inflammatory medication. Approximately one-fourth of participants (46/186, 24.73%) were using systemic corticosteroids regularly.

**Discussion**

The PRISM study is composed of a severe asthma registry with an organized multi-omics dataset and has an ultimate goal of identifying novel molecular phenotypes of severe asthma. Therefore, the study includes patients with severe asthma irrespective of their inflammatory phenotype and their use of biologic agents to enable further comparisons between groups. The integrated clinical and omics data will be analyzed according to clinical markers of asthma severity and of treatment response. Since there is no consensus on the definition of ‘responders’ to biologic agents, we plan to identify responders according to multiple aspects, namely, improved lung function, improved control status, reduced number of exacerbations, and decreased dose of required systemic corticosteroids.[19] The full impact of the COVID-
The impact of the COVID-19 pandemic on the PRISM study is uncertain; it may have both deleterious and beneficial effects on the health of the severe asthma population studied.

Our study will have several strengths. First, we will obtain multiple samples from both readily accessible airway compartments as well as systemic compartments at different timepoints during the treatment of each participant. This will help us to evaluate the stability of the omics data, which may vary between the types of omics and specimens.[24] Second, omics data from various samples will be generated simultaneously in line with the clinical assessment of asthma. This could provide insights regarding how single omics interact with each other and affect the manifestations of asthma. Third, the participation of two countries will provide independent cohorts for external validation. Moreover, comparisons between the participants from different counties may reveal markers related to ethnicity. Fourth, integrated datasets of multiple omics will enable the application of a multi-omics approach to severe asthma and the identification of treatable molecular phenotypes. Finally, the inclusion of both T2-high and T2-low severe asthma may help to elucidate the distinct pathophysiology of subtypes within these two overarching phenotypes and to identify potential biomarkers for T2-low asthma for which specific therapies are lacking.

However, there are inherent limitations that cannot be fully controlled in a multicenter observational study involving the collection of human samples. These include disproportionately prescribed medication, center effects, batch effects, and differences in indications and treatment regimens between countries. To overcome these issues, the researchers share standard operating procedures, and the obtained samples are processed and stored centrally. Moreover, potential confounders will be thoroughly assessed and adjusted during analyses. The identified molecular pathways in the present study will also be validated in a subsequent clinical trial as a next step.
Nevertheless, to our knowledge, the PRISM study will establish the largest omics dataset in patients with severe asthma. The results of the study may provide clues for upcoming omics researchers as well as identify molecular pathways that are essential for precision medicine for asthma.[25]
Table 1. Indications and doses of biologic agents in Korea and the UK

<table>
<thead>
<tr>
<th>Biologics</th>
<th>Country</th>
<th>Indication</th>
<th>Dose</th>
<th>Interval (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>Korea</td>
<td>• add-on therapy for patients with allergic asthma</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>• 1) positive skin test or in vitro test for perennial aeroallergens and</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>2) frequent night and daytime symptoms combined with decreased lung function (FEV1 &lt; 80%) and 3) severe persistent allergic asthma with a documented history of several acute exacerbations of asthma despite use of high dose ICS and LABA</td>
<td>Adjustment by serum total IgE level and body weight</td>
<td>2 or 4</td>
</tr>
<tr>
<td></td>
<td>UK</td>
<td>• add-on therapy to improve control of asthma in adults and adolescents with severe persistent allergic asthma who have: 1) a positive skin test or in vitro reactivity to a perennial aeroallergen 2) reduced lung function (FEV1 &lt; 80%) 3) four or more asthma exacerbations requiring systemic corticosteroids in the previous 12 months or has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months</td>
<td>100mg</td>
<td>4</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>Korea</td>
<td>• add-on therapy for patients with uncontrolled severe eosinophilic asthma</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• blood eosinophil count ≥ 150/μL at initiation of treatment or ≥ 300/μL within previous 12 months</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>UK</td>
<td>• add-on therapy for patients with severe refractory eosinophilic asthma, only if: 1) blood eosinophil count ≥ 300/μL and at least 4 exacerbations requiring systemic corticosteroids in the previous 12 months or continuous OCS of at least the equivalent of prednisolone 5 mg per day over the previous 6 months or 2) blood eosinophil count ≥ 400/μL and at least 3 exacerbations requiring systemic corticosteroids in the previous 12 months</td>
<td>3mg/kg</td>
<td>4</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>Korea</td>
<td>• add-on therapy for patients with uncontrolled severe eosinophilic asthma</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• blood eosinophil count ≥ 400/μL at initiation of treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UK</td>
<td>• add-on therapy for patients with uncontrolled severe eosinophilic asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• blood eosinophil count ≥ 400/μL and at least 3 exacerbations requiring systemic corticosteroids in the previous 12 months</td>
<td></td>
<td></td>
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<tr>
<td>Benralizumab</td>
<td>Korea</td>
<td>• add-on therapy for patients with uncontrolled severe eosinophilic asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UK</td>
<td>• 1) Uncontrolled severe eosinophilic asthma and 2) blood eosinophil count ≥ 300/μL and four or more asthma attacks in the last 12 months requiring steroid treatments or reliance on OCS for the last 6 months or 3) blood eosinophil count ≥ 400/μL and at least 3 exacerbations requiring systemic corticosteroids in the previous 12 months</td>
<td>30mg</td>
<td>every 4 weeks for the first 3 doses, then every 8 weeks thereafter</td>
</tr>
<tr>
<td>Dupilumab</td>
<td><strong>Korea</strong></td>
<td><strong>UK</strong></td>
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</tbody>
</table>
| • add-on therapy for patients with uncontrolled severe asthma  
• Type 2 high asthma with either  
  1) severe eosinophilic asthma  
  (blood eosinophil count ≥ 150/μL or FeNO ≥ 25 ppb)  
  or  
  2) OCS-dependent severe asthma | 600 mg loading dose followed by 300 mg | 2 |
| • add-on maintenance therapy for severe asthma with type 2 inflammation that is inadequately controlled in people ≥12 years despite maintenance high-dose inhaled corticosteroids and another treatment only if:  
  1) blood eosinophil count ≥ 150/μL and FeNO ≥ 25 ppb and at least 4 or more exacerbations in the previous 12 months  
  2) ineligibility for other biologicals or asthma that has not responded to other biologic therapy | 400 mg loading dose followed by 200 mg |

FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; OCS, oral corticosteroids; FeNO, fractional exhaled nitric oxide
Table 2. Summary of data collected during the study

<table>
<thead>
<tr>
<th>Collected data</th>
<th>Visit 1 (baseline)</th>
<th>Visit 2 (1 month)</th>
<th>Visit 3 (4–6 months)</th>
<th>Visit 4 (10–12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent and demographic information</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical characteristics (e.g., asthma medication, exacerbation history)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung function tests</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bronchodilator response</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial provocation test (O)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinoscopy (O)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchoscopy (O)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Skin prick test</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FeNO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging tests</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sinus X-ray (O)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest CT (O)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questionnaires</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACT, ACQ, AQLQ (UK only), QLQAKA (Korea only)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Severe Asthma Questionnaire</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cough Questionnaire for Asthma</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>SNOT-22</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Biologic samples</td>
<td></td>
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<td></td>
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<tr>
<td>Blood</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Sputum</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Exhaled breath condensate (O)</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>Urine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nasal epithelial cells (O)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>BECs and BALF (O)</td>
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</table>

(O) indicates that the test is optional.

FeNO; fractional exhaled nitric oxide; CT, computed tomography; ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; QLQAKA, Quality of Life Questionnaire for Adult Korean Asthmatics; EQ-5D, European Quality of Life Five Dimension; SNOT-22, Sino-Nasal Outcome Test-22; BECs, bronchial epithelial cells; BALF, bronchoalveolar lavage fluid
Table 3. Summary of samples and related omics analysis

<table>
<thead>
<tr>
<th>Items</th>
<th>Genomics/Epigenetics</th>
<th>Transcriptomics (bulk and single cell)</th>
<th>Proteomics</th>
<th>Metabolomics</th>
<th>Metagenomics</th>
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<tr>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Exhaled breath condensate</td>
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<td>X</td>
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<td>X</td>
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<tr>
<td>Sputum cells and supernatant</td>
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<td></td>
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<tr>
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<td></td>
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<tr>
<td>Bronchial epithelial cells/ Bronchoalveolar lavage</td>
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</table>
Figure Legend

Figure 1. Schematic of PRISM study

CBC, complete blood count; FeNO, fractional exhaled nitric oxide; ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CQA, Cough Questionnaire for Asthma; SAQ, Severe Asthma Questionnaire; SNOT-22 Sino-Nasal Outcome Test-22
REFERENCES


Acknowledgments

The authors would like to thank the members of the study centers for participating in the PRISM study.
Figure 1.

Enrollment (visit 1)
1 month (visit 2)
4-6 month (visit 3)
10-12 month (visit 4)

Biologics or conventional treatment

Baseline assessment
- Demographic information
- History of asthma
- Comorbidities
- Phenotype of asthma

Baseline and follow-up assessment
- Lung function test, bronchodilator response
- CBC, Induced sputum analysis, FeNO
- Questionnaires:
  - ACT, ACQ, AQLQ, CQA, SAQ, EQ-5D, SNOT-22
- Asthma medication
- History of acute exacerbation
- Treatment response
- Biologic samples for omics analysis