Observational Study Protocol

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Patient characteristics, treatment patterns, clinical outcomes, and health care resource utilization in severe asthma subgroups: A retrospective analysis of the International Severe Asthma Registry (EVEREST)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
ADEPT	Anonymous Data Ethics Protocols and Transparency
BEC	Blood Eosinophil Count
CD	Cluster of Differentiation
ERS/ATS	European Respiratory Society/American Thoracic Society
FeNO	Fraction of exhaled Nitric Oxide
ICS	Inhaled Corticosteroid
IgE	Immunoglobulin E
IL	Interleukin
ISAR	International Severe Asthma Registry
ISC	ISAR Steering Committee
LABA	Long-Acting Beta Agonists
LAMA	Long-Acting Muscarinic Antagonists
LTRA	Leukotriene Receptor Antagonists
OSC	Oral Corticosteroid
REG	Respiratory Effectiveness Group

RESPONSIBLE PARTIES

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PROTOCOL SYNOPSIS

Patient characteristics, treatment patterns, clinical outcomes, and health care resource utilization in severe asthma subgroups: A retrospective analysis of the International Severe Asthma Registry

Background/Rationale:

Asthma is a heterogeneous disease with a complex pathophysiology that presents with a wide range of clinical manifestations and treatment responses. Global estimates show that 358 million people worldwide are diagnosed with asthma[1], of whom approximately 10% have a severe form of the disease[2]. Despite its low overall prevalence, severe asthma contributes disproportionately to morbidity, mortality, and healthcare costs, and accounts for approximately 50% of total asthma healthcare expenditures[3]. Recent advances in treatment strategies for severe asthma include the development and release of targeted biologics for treatment. Eligibility for biologic treatment is based on clinical and pathobiological markers, including biomarkers such as immunoglobulin E (IgE), fractional exhaled nitric oxide (FeNO), and blood eosinophil count (BEC). Despite these advances in treatment, the clinical burden for severe asthma remains high.

With the availability of current and emerging biologic treatment for severe asthma, this study aims to better understand patients who are most likely to respond to particular classes of biologic drugs. Specifically, the primary goal of this analysis is to use data from the International Severe Asthma Registry (ISAR) registry to describe characteristics and unmet needs for patients with subtypes of severe asthma, including patients who are ineligible for current biologic treatment (biologic-ineligible), patients who are biologic-eligible, patients who are biologic-eligible with and without biologic treatment, patients on biologic therapy with uncontrolled asthma, patients with multiple positive asthma-specific biomarkers, patients with low vs high blood eosinophils count (BEC), and patients with allergic asthma. As an exploratory objective, this study will also examine the variability of asthma-specific biomarkers over time.

Objectives and Hypotheses:

Type of Objective	Objectives	Outcome Measures	Hypotheses
Primary	To describe the demographic and clinical characteristics, treatment patterns, healthcare resource utilization, and clinical outcomes for severe asthma population overall, by region/country (where feasible) and for the following groups: • Biologic status: -Biologic-eligible vs ineligible -Biologic-eligible with vs without biologic treatment -Biologic users with uncontrolled asthma (including those who stop/switch treatment) • Multiple biomarkers (BEC, FeNO, IgE): triple positive, at least 2 positive, at least 1 positive, and triple negative values • Eosinophil status • Allergic sensitization status (splitting out patients with IgE<30 and >700) • LT-OCS use status (yes/no)	• Patient demographic characteristics • Patient clinical characteristics • Asthma-specific treatment patterns • Exacerbations and other clinical outcomes • Healthcare resource utilization For all subgroups, outcomes are described in the 12 months pre-index. Specifically for biologic user subgroups, characteristics in both 12 months pre- and post-index will be described	• Not applicable • This analysis will be descriptive comparing those fulfilling the subgroup criteria vs those that do not
Secondary	Not applicable	Not applicable	Not applicable
Safety	Not applicable	Not applicable	Not applicable
Exploratory	• To describe the real-world fluctuation of biomarkers (IgE, FeNO, BEC) over time among patients with severe asthma with and without biologic therapy. Both numerical and category changes will be assessed.	Change in serum totals for: • IgE • FeNO • BEC (pre-biologic)	• Not applicable • This analysis will be descriptive.

Abbreviations: BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin

Methods:

Study design:

A historical cohort study employing ISAR data will be used to address the primary objectives of this analysis. Baseline patient characteristics will be examined among subgroups of patients i) meeting eligibility for biologic therapy (biologic-eligible vs ineligible, biologic-eligible without vs without biologic treatment, biologic user with vs without uncontrolled asthma); ii)

with multiple biomarker status; iii) eosinophil status; and iv) allergic status. Baseline will encompass the 12 months preceding an index date defined by the first availability of relevant biomarker measurement(s). Additionally, for biologic users, biologic users with and without uncontrolled asthma, the disease burden in the 12 months post-index will be described. The subgroup analysis examining asthma control will include patients who received at least three doses of a biologic treatment at any point during the study period; this group will also include patients on biologic therapy who switch/stop their treatment. The exploratory analysis will examine biomarker variability over the study follow-up period.

Data Source(s):

Data for this study will be sourced from ISAR, a multi-country, multicenter, observational epidemiologic data repository, with retrospective and prospective data of severe asthma patients. The key feature of the registry is that it has standardized data fields irrespective of data source. ISAR includes a combination of existing and new severe asthma registries, where primary data are collected via electronic Case Report Forms (eCRF) on a multiple web-based platforms (Openclinica, REDCap, or individual country developed) or through data derived from specialized electronic medical record systems. Anonymized person-level data from all participating countries at the time of study initiation will be included in the analysis. For the primary analyses, endpoints and subgroup definitions will be implemented using prospective ISAR data (ISAR visits starting 01Dec2017). For exploratory analyses, all available biomarker data, including data before 01Dec2017, will be used.

Study Population:

The study population for the primary analysis will include all patients with severe asthma who meet all of the study inclusion criteria and none of the study exclusion criteria.

Inclusion Criteria:

- Patients 18 years or older at registry enrolment
- Global Initiative for Asthma (GINA) (2018) Step 5 Treatment at enrolment OR GINA (2018) Step 4 Treatment
- To be included in the exploratory analysis, patients must have at least two valid measurements of the same biomarker at different times

Exclusion Criteria:

Patients who received bronchial thermoplasty.

Subgroups:

To address the study's primary objective, the following subgroups will be analysed among the full study population of patients with severe asthma. The subgroups are not intended to be mutually exclusive, i.e., patients can contribute data to more than one subgroup analysis. Criteria for each subgroup analysis are described below. The population for the primary

analysis will be restricted to patients that have non-missing baseline data for the criteria, described below, needed to characterize the subgroups.

- Subgroup 1: Eligibility for biologics for asthma, including these subgroups:
  - Biologic-eligible vs biologic-ineligible subgroup
  - Biologic-eligible with vs without biologic treatment
  - Biologic users with uncontrolled asthma (including those who switch/stop their treatment)
- Subgroup 2: Patients subgroups by biomarkers, including patients triple positive biomarker values, patients with triple negative biomarker values, patients with at least two positive biomarker values, and patients with at least one biomarker values.
- Subgroup 3: Patients with baseline BEC values (high vs low BEC)
- Subgroup 4: Patients with allergic sensitization

Outcome(s):
Outcome variables will include the following measurements:

- Demographic characteristics
- Medical history
- Comorbidities
- Asthma medication
- Spirometry
- Blood and sputum tests
- Allergy tests
- Health care resource utilization (HCRU)

Sample Size Estimations:

This study will rely on previously collected data and is descriptive with no hypothesis testing; therefore, no formal power calculations were conducted. This study is mainly descriptive and will present point estimates (means, proportions, rates) derived from unadjusted and stratified tabulations of the data. The preliminary count from the ISAR identified over 8,647 patients with severe asthma. The sample size will decrease after applying further inclusion and exclusion criteria.

Statistical Analysis:

The analysis for the primary objective will be descriptive in nature. Descriptive statistics, overall, by region/country (when feasible), and subgroups, will be generated for continuous and categorical variables. The full cohort of patients with severe asthma will serve as a benchmark for all subgroups, comparisons between subgroups will not be made. Point estimates and confidence intervals will be reported for all variables.

AMENDMENT HISTORY

Date	Section of study protocol	Amendment or update	Reason
26 August 2022	Responsible parties, Synopsis, Rationale, Methodology, Objectives, Variable measurement	-Add biologic-eligible with and without treatment, Bx users with controlled asthma subgroups. -Update study design. -Extend the list of comorbidities	Extend analyses to key subgroup of interest
26 November 2022	Ad-hoc analyses	Add a second approach to define biologic eligibility by specific biologic and by country	To take into account the variation by country for biologic eligibility

MILESTONES

Milestones	Planned Dates
Study design concept approved	Feb 2021
External service provider/contract research organization selected (if relevant)	N/A
Study protocol approved	May 2021
First subject/patient in (or database start date)	N/A
Last subject/patient in (or database end date)	N/A
Last subject/patient last visit	N/A
Final database lock	N/A
Clinical study report approved	Dec 2022
Operational Information	**Details**
Approximate study budget	$70,000
Budget holder(s), including cost-sharing	David Ginkel
Delivery model (internal – Global Medical Affairs, Marketing Company, Site Management and Monitoring – or external)	Internal
Planned data re-use	N/A
Approach towards patient centricity (e.g., engagement with patient groups related to study)	N/A
International coordinating investigator or executive steering committee	N/A

1. BACKGROUND AND RATIONALE

1.1 Background

Asthma is a heterogeneous disease with a complex pathophysiology of chronic inflammation that presents with a wide range of clinical manifestations and treatment responses. Global estimates show that 358 million people worldwide are diagnosed with asthma[1], of whom approximately 10% have a severe form of the disease[2]. According to the Global Initiative for Asthma (GINA), mild asthma is defined as being well-controlled with as needed reliever treatment alone, or in combination with a low-intensity controller treatment. Moderate asthma is defined as well controlled but also includes a step 3 treatment (e.g. low-dose inhaled corticosteroids and long-acting beta2-agonists [ICS-LABA]). Severe asthma requires a 4 or 5 step treatment i.e. high dose ICS/LABA to prevent it from becoming uncontrolled and may also remain uncontrolled despite this treatment[2]. Many patients with severe asthma experience a lack of asthma control, which is associated with subsequent acute asthma exacerbations[4]. Despite its low overall prevalence, severe asthma contributes disproportionately to morbidity, mortality, and healthcare costs[5], and accounts for approximately 50% of total asthma healthcare expenditures[3].

Traditionally asthma has been treated with quick-relief inhalers in combination with inhaled or oral corticosteroid (ICS/OSC) therapy. Short- and long-term OCS therapy is still widely used to treat patients with asthma, particularly those with severe disease[6]. Recent advances in treatment strategies for severe asthma include the development and release of targeted biologics, rather than OCS that generally suppresses inflammation[7]. One common asthma phenotype is a systemic type 2 inflammatory reaction initiated in response to allergens. A type 2 inflammatory reaction refers to a specialized immune response that is characterized by T helper 2 (TH2) differentiation and stimulation of B cell production of the immunoglobulin E (IgE) antibody subclass and eosinophilia[8]. This pathologic process is common to many diseases with a presence of barrier dysfunction such as asthma, atopic dermatitis (AD), and chronic rhinosinusitis with nasal polyps[9]. Interleukin (IL)-4 and IL-13 are potent mediators of type 2 immunity driving a TH2-type response. IL-4 initiates T cell differentiation towards the TH2 subtype and induces production of type 2-associated cytokines and chemokines, such as IL-5. Omalizumab was the first IgE-specific humanized monoclonal antibody (mAb) to get regulatory approval for asthma therapy. Biologic treatments targeting IL-4 and IL-13 (Dupilumab) and anti-IL-5 (Nucala [mepolizumab], Cinqair [reslizumab], Fasenra [benralizumab]) have since been developed[8].

There has been a recent rapid progress in the identification of biomarkers of asthma such as blood eosinophil count (BEC), fraction of exhaled nitric oxide (FeNO), and immunoglobulin

(IgE) that are easy to measure[10]. These biomarkers have been found to stratify risk of adverse outcomes effectively and have the potential to result in more effective and economical use of existing and new treatments. Since asthma is a heterogeneous disease it is now recommended that it is deconstructed into component parts before treatment is planned, using a precision medicine approach that is applicable in non-specialist care[10].

In 2019 the ERS/ATS (European Respiratory Society/American Thoracic Society) published new guidelines[11] for the management of severe asthma, in which they compiled evidence and made recommendations on the use of novel biologic treatments:

- Using anti- IL-5 and anti-IL-5 receptor α (Nucala [mepolizumab], Cinqair [reslizumab], Fasenra [benralizumab]) for severe uncontrolled adult eosinophilic asthma phenotypes, using a BEC cut-point $\geqslant 150\ \mu L^{-1}$ to guide anti-IL-5 initiation.

- For anti-IgE therapy (Xolair [Omalizumab]) ERS/ATS recommended considering specific eosinophil ($\geqslant 260\ \mu L^{-1}$) and FeNO ($\geqslant$19.5 ppb) cut-offs to identify adolescents or adults with the greatest likelihood of response to the treatment.

- Using anti-IL-4/13 ([Dupixent] Dupilumab) for adult patients with severe eosinophilic asthma and for those with severe corticosteroid-dependent asthma regardless of blood eosinophil levels.

Since the recommendations were based on few studies the quality of evidence was considered to be low and these recommendations should be reconsidered as new evidence becomes available.

1.2 Rationale

Asthma is a heterogeneous disease with a complex pathophysiology that presents with a wide range of clinical manifestations and treatment responses. Global estimates show that 358 million people worldwide are diagnosed with asthma,[12] of whom 1% to 3% have a severe form of the disease.[13] Despite its low overall prevalence, severe asthma contributes disproportionately to morbidity, mortality, and healthcare costs,[14] and accounts for approximately 50% of total asthma healthcare expenditures.[3] Recent advances in treatment strategies for severe asthma include the development and release of targeted biologics for treatment. Eligibility for biologic treatment is based on clinical and pathobiological markers, including biomarkers such as immunoglobulin E (IgE), fractional exhaled nitric oxide (FeNO), and blood eosinophil count (BEC). Despite these advances in treatment, the clinical burden for severe asthma remains high.

With the availability of current and emerging biologic treatment for severe asthma, this study aims to better understand patients who are most likely to respond to particular classes of biologic drugs. Specifically, the primary goal of this analysis is to use data from the International Severe Asthma Registry (ISAR) registry to describe characteristics and unmet needs for patients with subtypes of severe asthma, including patients who are ineligible for current biologic treatment (biologic-ineligible), patients who are biologic-eligible, patients who are biologic-eligible with and without biologic treatment, patients on biologic therapy with and without uncontrolled asthma, patients with multiple positive asthma-specific biomarkers, and patients with eosinophils (low vs high BEC). As an exploratory objective, this study will also examine the variability of asthma-specific biomarkers over time.

2. METHODOLOGY

2.1 Study Design – General Aspects

A retrospective cohort study employing ISAR data will be used to address the objectives of this analysis. Baseline data collected for the 12 months prior to index date (see Table 1) will be used to define patient subgroups according to their eligibility for biologic therapy, multiple biomarker status, eosinophilic status, and allergic status Figure 1. Study timeline and outcome measures for patients with severe asthma. Patients who initiated a biologic for asthma during the study period will additionally be followed for asthma control status (by GINA 2019 definition) if they received ≥3 doses and to evaluate any treatment switch/stop. Index date for the comparison group, i.e. group meeting none of the subgroup criteria, will be the date of registry enrolment. We will describe demographic, clinical characteristics, comorbidities, asthma treatment, HCRU of the patient subgroups during the baseline period. (Figure 1). Additionally, for biologic users, biologic users with and without uncontrolled asthma, the disease burden in the 12 months post-index will be described.

We will also examine biomarker variability over the study period among patients with repeated measures only. All data available over time will be utilized to analyze variability of biomarkers (Figure 1).

Figure 1. Study timeline and outcome measures for patients with severe asthma patients

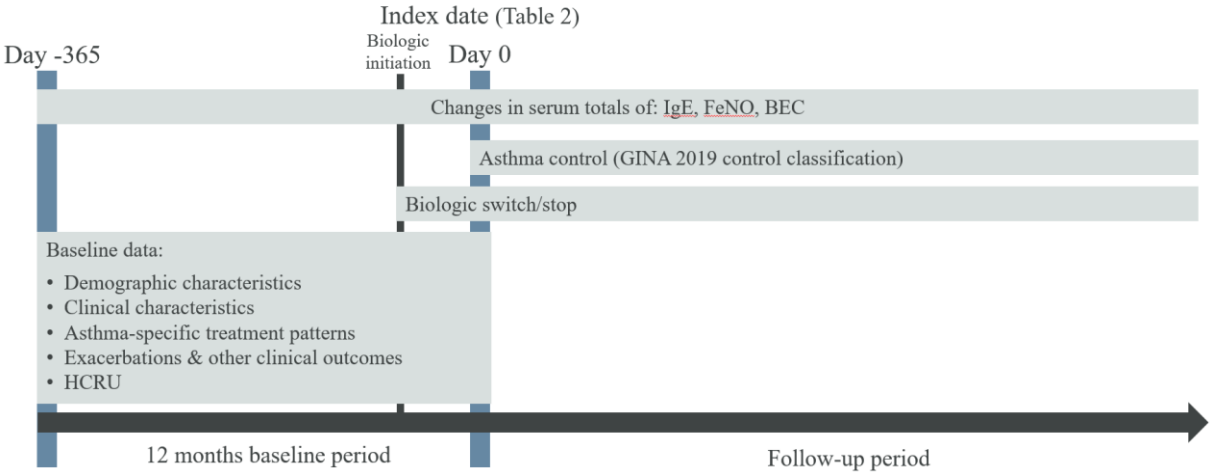

Table 1. Definition of index date and description of follow-up data collected for all subgroups

Subgroup	Index date	Follow-up data
1. Eligibility for biologics	First visit with measurement(s) meeting the eligibility criteria. For biologic users, use the ISAR visit (starting 01Dec2017) that is closest to date on first biologic	None
2. On biologics, uncontrolled asthma	Date of 3rd treatment Among those that switch/stop, use ISAR visit (starting 01Dec2017) closest to date on first biologic	For GINA 2019 definition of control & termination/switch of treatment at any time following initiation of biologic
3. Multiple biomarkers	Date of first visit with at least one of IgE, FeNo, or BEC measurement(s) available.*	None
4. BEC values	Date of visit with the highest available BEC measurement	None
5. Allergic sensitization	Date of first visit with positive SPT/allergen-specific IgE	None

For index visits occurring during the registry follow-up, date of birth, gender, ethnicity, and date of asthma symptom onset will be taken from the questionnaire administered at registry enrolment. If >1 visit occurred during baseline, data at nearest visit or collated across visits will be used (see 4.2).
*Requirement for a proximity cut-off in biomarker measurements will be considered once the biomarker distributions across time have been evaluated.

2.1.1 Data Source(s)

Data for this study will be sourced from the ISAR[15]. The ISAR is a multi-country, multicenter, observational epidemiologic data repository, with retrospective and prospective data of severe asthma patients treated within secondary and tertiary care centers. The key feature of the registry is that it has standardized data fields irrespective of data source. ISAR includes a combination of existing and new severe asthma registries, where primary data are collected via electronic Case Report Forms (eCRF) on a web-based platform. Data on patient demographics, medical history, diagnostics, asthma treatment, patient-reported outcomes, spirometry, and biomarkers are captured at enrolment and follow-up visits, with an expected minimum of one annual follow-up. Anonymized person-level data from all participating countries at the time of study initiation will be included in the analysis.

ISAR has governance provided by the Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG). Informed consent has been obtained where required in sharing of anonymized data.

For the primary analyses, endpoints and subgroup definitions will be implemented using prospective ISAR data (ISAR visits starting 01Dec2017). For exploratory analyses, all available biomarker data, including data before 01Dec2017, will be used.

3. OBJECTIVES AND HYPOTHESES

The specific objectives and outcomes measures for this study are described in Table 2.

Table 2. Study Objectives and Outcomes

Type of Objective	Objectives	Outcome Measures	Hypotheses

Type of Objective	Objectives	Outcome Measures	Hypotheses
Primary	To describe the demographic and clinical characteristics, treatment patterns, healthcare resource utilization, and clinical outcomes for severe asthma population overall, by region/country (where feasible), and by: • Biologic status: -Biologic-eligible vs ineligible -Biologic-eligible with vs without biologic treatment -Biologic users with uncontrolled asthma (including switch/stop treatment) • Multiple biomarkers (BEC, FeNO, IgE): triple positive, at least 2 positive, at least 1 positive, and triple negative values • Eosinophil status • Allergic sensitization status (splitting out patients with IgE<30 and >700) • LT-OCS use status (yes/no)	• Patient demographic characteristics • Patient clinical characteristics • Asthma-specific treatment patterns • Exacerbations and other clinical outcomes • Healthcare resource utilization **Using ISAR prospective visits starting 01Dec2017*	• Not applicable • This analysis will be descriptive comparing those fulfilling the subgroup criteria vs those that do not
Secondary	Not applicable	Not applicable	Not applicable
Safety	Not applicable	Not applicable	Not applicable
Exploratory	• To describe the real-world fluctuation of biomarkers (IgE, FeNO, BEC) over time among patients with severe asthma with and without biologic therapy. Both numerical and categorical changes will be assessed.	Change in serum totals for: • IgE • FeNO • BEC (pre-biologic) **Using all ISAR visits (prospective and retrospective visits)*	• Not applicable • This analysis will be descriptive

Abbreviations: BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin

3.1 Study Population

The study population for the primary analysis will include all patients in ISAR with severe asthma who meet all of the study inclusion criteria (Section 3.3) and none of the study exclusion criteria (Section 3.4).

Person-level data from all participating countries from the time of patient enrolment until the most recent data extraction will be included in this analysis.

We will use ISAR prospective data (ISAR visits starting 01Dec2017) to identify and describe characteristics of patient subgroups for answering the primary objectives. For the objective limited to patients being treated with a biologic at any time during the study period and who have data on asthma control following treatment with an asthma biologic or a treatment switch/stop, the whole follow-up will be considered for control status (by GINA questionnaire). Baseline data (in this case, 12 months prior to biologic initiation) will be used to describe patient characteristics.

For the exploratory objective, all data across study period (both prospective and retrospective visits) for patients with at least two measurements will be utilized to analyse variability of biomarkers.

3.2 Inclusion Criteria

For inclusion in the main analysis the following inclusion criteria will be applied:

- Patients 18 years or older at registry enrolment
- Global Initiative for Asthma (GINA) (2018) Step 5 Treatment at enrolment OR GINA (2018) Step 4 Treatment and uncontrolled at enrolment
- To be included in the exploratory analysis, patients must have at least two valid measurements of the same biomarker at different times

3.3 Exclusion Criteria

Patients lacking informed consent and who received bronchial thermoplasty will be excluded.

3.4 Participant Follow-up

Follow-up will be observed as per clinical practice. One follow-up visit per year is the minimum number of visits to a severe asthma specialist centre expected, but not required, per patient; other patients will have more than one visit per year. All available visit data will be included in the current study, with the index visit (Table 1) being considered the baseline, followed by visit 1, 2 etc (Figure 1). Visits following the index will be used to quantify asthma control and treatment switch/stop for patients initiated on biologic treatment. All visits will be used to evaluate fluctuations of biomarkers for the exploratory analysis.

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

All variables will be extracted from existing registries or electronic medical records using a standardized eCRF.

4.1 Subgroups

To address the study's primary objective, outcome measures (Table 2) among the following subgroups will be analyzed among the full study population of patients with severe asthma. The subgroups are not intended to be mutually exclusive, i.e., patients can contribute data to more than one subgroup analysis. Criteria for inclusion into each subgroup are described below. The population for the primary analysis will be restricted to patients that have non-missing data for the criteria at index, as described below and in Table 1, needed to characterise the subgroups. The comparison group for all subgroups will need to meet *none* of the listed criteria.

- **Subgroup 1**: Eligibility for biologics for asthma
  - This category includes the following subgroups:
    - Biologic eligible and ineligible
    - Biologic-eligible patients treated vs untreated with biologics
    - Patients on asthma biologics with uncontrolled asthma

  - Eligibility for biologics will be defined based on baseline values; patients need to meet any one of the following set of criteria:
    - A positive skin prick test or allergen-positive test (having a comorbidity of allergic rhinitis or eczema would be used in lieu of missing information on allergen tests), and pre-biologic therapy total serum IgE level above or equal to 30 IU/mL, OR
    - Pre-biologic therapy BEC ≥150 cells/μL if patient is on maintenance oral corticosteroids (OCS), OR
    - BEC ≥300 cells/μL and having two or more yearly severe exacerbations pre-biologic therapy, OR
    - FeNO ≥25 parts per billion (ppb) and having two or more yearly severe exacerbations pre-biologic therapy, OR
    - FeNO ≥25 ppb and OCS dependent asthma (defined as patients on any maintenance OCS or ≥4 OCS bursts [subject to data evaluation]), OR
    - Eligibility will be assumed for patients being actively treated with a biologic at baseline.
  - Patients who did not meet any of the criteria listed above based on non-missing data will be considered to be ineligible for biologics. Patients with any missing data will be excluded from the biologic ineligible subgroup, but if one of the criteria is met then they can be included in the biologic eligible subgroup with missing data.

- Long-term OCS users will also be examined separately and defined as i) any maintenance OCS and ii) ≥4 OCS bursts in the past 12 months. The comparison group will be patients not meeting these criteria.
- Patients on asthma biologics with and without uncontrolled asthma

  This analysis will be limited to patients being initiated with a biologic at any time during the study period. Uncontrolled asthma will be defined as:
  - Having taken at least 3 doses of the biologic therapy and classified as having uncontrolled asthma, defined by GINA 2019 asthma control classification[1], following initiation OR
  - Having taken at least 3 doses of the biologic therapy and having a severe exacerbation following initiation, OR
  - Having taken at least 3 doses of the biologic therapy and on maintenance OCS, OR
  - Switched or stop due to ineffectiveness their biologic therapy (defined as reported lack of clinical efficacy) at any time following initiation

- **Subgroup 2**: Patients subgroups by biomarkers, including patients triple positive biomarker values, patients with triple negative biomarker values, patients with at least two positive biomarker values, and patients with at least one biomarker values.
  - This analysis will be limited to patients with IgE, FeNO, or BEC values available at index. If more than one biomarker measurement is available, then the highest one will be used. Requirement for a proximity cut-off in biomarker measurements will be considered once the biomarker distributions across time has been evaluated.
  - Patients with triple positive biomarker values will include patients who meet *all* of the criteria listed below. Patients with triple negative biomarker values include patients who meet *none* of the criteria. Patients with at least two positive biomarker values include patients who meet at least two of the following criteria. Patients with only one positive biomarker values include patients who meet only one of the following criteria.
    - IgE ≥75kU/L
    - FeNO ≥25 ppb
    - BEC ≥300 cells/μL[2]
  - Where possible, biomarkers will be measured prior to biologic therapy initiation.
- **Subgroup 3**: Patients with BEC values (high vs low BEC)
  - This analysis will include patients with BEC values available at index. For patients without anti-IL5 or maintenance OCS in the prior 4 weeks of the blood measures, a BEC threshold of

[1] Defined as including one or both of: 1) Poor symptom control (frequent symptom or reliever use, activity limited by asthma, night waking due to asthma); 2) Frequent exacerbations (≥2/year) requiring OCS, or serious exacerbations (≥1/year) requiring hospitalizations

[2] Results will be presented for the overall subgroup (triple positive, 2+ possible) along with each combination of positive biomarkers.

<300 cells/μL will be used. For patients on maintenance OCS a lower cut-off of 150 cells/μL will be used.

- **Subgroup 4**: Allergic sensitization
  - Allergic patient will be defined as patients with positive skin prick test or positive specific serum IgE test to a perennial allergen. Perennial allergens will include house dust mite (HDM), moulds, cockroach, and pets.

Biomarker stability

Biomarker stability will be evaluated among patients with ≥2 available biomarker measures both by numerical change and categorical change overtime. The following biomarker thresholds will be used to measure categorical change over time:

- IgE ≥75kU/L, AND
- FeNO ≥25 parts per billion (ppb), AND
- BEC ≥300 cells/μL[3]

4.2 Outcomes

The following list of demographic and clinical variables from ISAR will be used to describe characteristics of the overall patient population and the subgroups. Missing data will be included in a missing data category. All variables will be measured during the baseline period, which refers to the 12 months preceding the index date (Table 1, Figure 1). Where baseline data from more than one visit is available, measurement closest to index, highest or lowest measurement, or collated data will be used as outlined in Table 3 and Table 4. Demographic variables and date of asthma symptom onset will be taken from the questionnaire administered at registry enrolment.

4.2.1 Demographic variables

Demographic variables are described in Table 3.

Table 3. Demographic Variables

Variable Name	Description	If >1 visit available
Age	Patient age in years (index date minus date of birth).	Data from the registry enrolment visit (date of birth)

[3] Results will be presented for the overall subgroup (triple positive, 2+ possible) along with each combination of positive biomarkers.

	Categories: <18, 18-65, >65 years	
Sex	Patient sex	Data from the registry enrolment visit
Height	Patient height measurement in meters (m)	Measurement closest to index
Weight	Patient weight measurement in kilograms (kg)	Measurement closest to index
Body Mass Index (BMI)	• Defined as the ratio of weight (kg) to squared height (m^2). • Categories: Underweight (< 18.5 kg/m^2) Normal weight (≥ 18.5 kg/m^2 and < 25 kg/m^2) Overweight (≥ 25 kg/m^2 and < 30 kg/m^2) Obese (≥ 30 kg/m^2)	Measurement closest to index
Ethnicity	Categories: White Asian African Mixed Other Unknown	Data from the registry enrolment visit
Smoking status	• Categories: Non-smoker Current smoker Ex-smoker	Measurement closest to index
Pack years	Defined as the number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked	Measurement closest to index
Region of residence	Europe, Middle East, Russia, Asia, Australia/New Zealand, North America, South America	Measurement closest to index

4.2.2 Clinical variables

Clinical variables of interest are listed and defined in Table 4.

Table 4. Clinical Variables

Variable Name	Description	If >1 visit available
ISAR Severe Asthma Criteria		
ISAR inclusion (GINA[4] guidelines)	Patient on GINA (2018) Step 5 treatment **OR** Patient on GINA (2018) Step 4 treatment with: • Severe asthma symptoms or • Severe asthma exacerbations requiring systemic corticosteroids	Data from index visit used
Medical History		
Asthma duration	Number of whole years (or months if less than 1 year) from date of first asthma symptom onset to the date of entry into the study	Data from the registry enrolment visit
Number of exacerbations	• Count of exacerbations requiring rescue OCS during the period of interest (continuous and categorical values [1, 2, 3, 4 or more]) • Binary categories: yes/no exacerbation	Data collated across visits
Adherence	• Yes: clinical impression • Yes: prescription records • No	Affirmative if any 'yes' responses have been given. Negative if all responses are 'no'
Healthcare Resource Utilization		
Number of invasive ventilations for severe asthma	- Count of episodes of invasive ventilation ever - Categorize: yes/no	Data collated across visits
Number of hospital admissions	-Count of hospital admissions for asthma during the period of interest - Categorize; yes/no, patients with 0, 1, 2, >2 events	Data collated across visits
Number of emergency department admissions	-Count of emergency department admissions for asthma during the period of interest -Categorize; yes/no; patients with 0, 1, 2, 3, 4… events	Data collated across visits
Asthma control	Categorized according to the GINA Asthma Control Criteria/Asthma Control Questionnaire (ACQ)/Asthma Control Test (ACT) as: • Controlled (GINA: none of the following: daytime symptoms >twice/week, night waking due to asthma, reliever needed >twice/week, activity limitation due to asthma; 0≤ACQ≤0.75; ACT≥20) • Partly controlled (GINA: 1-2 of the following: daytime symptoms >twice/week, night waking due to asthma, reliever needed >twice/week, activity limitation due to asthma; 0.75<ACQ≤1.5) • Uncontrolled (GINA: ≥3 of the following: daytime symptoms >twice/week, night waking due to asthma, reliever needed >twice/week, activity limitation due to asthma; ACQ>1.5; ACT<20)	If data discordant, the worst outcome will be used (i.e. uncontrolled if partly uncontrolled and uncontrolled; partly controlled if controlled and partly controlled)

[4] Global Initiative for Asthma 2017: GINA Stepwise approach for asthma control

Variable Name	Description	If >1 visit available
Blood and Sputum Tests		
IgE level	- Counts of IgE, measured in kilounits per liter (kU/L) or international units per liter (IU/mL) -Categories: IgE ≥75, < 75 kU/L	Highest measurement will be used
BEC	-Counts of blood eosinophils, measured in cells per microliter. -Categories: <150, 150-<300, ≥300 For long-term OCS users, a cut-off of 150 cells/μL will also be examined	Highest measurement will be used
Sputum eosinophil level	-Counts of sputum eosinophils, expressed as percentage (%) of the total cell count. Categories:	Highest measurement will be used
Allergy Testing		
Skin prick test	• House dust mite (HDM), animal dander (cat, dog), pollen (tree, grass), molds (Aspergillus), other • Categorized as positive reaction if wheal diameter is >3 mm.	Highest measurement will be used
Serum IgE Test	Positive OR Negative OR No data	If data discordant, the worst outcome will be used (i.e. if negative and positive then positive)
Spirometry		
Pre-bronchodilator FEV_1 (percentage of predicted)	Measured pre-bronchodilator forced expiratory volume in one second (FEV_1) as a percentage (%) of predicted FEV1	Lowest measurement will be used
Pre-bronchodilator FVC (percentage of predicted)	Measured pre-bronchodilator forced vital capacity (FVC) as a percentage (%) of predicted FVC	Lowest measurement will be used
Pre-bronchodilator FEV_1	FEV_1 measured in liters (L), before administering bronchodilator	Lowest measurement will be used
Pre-bronchodilator FVC	FVC measured in liters (L) before administering bronchodilator	Lowest measurement will be used
FeNO test	Measurements of FeNO concentration in exhaled breath, measured in parts per billion (ppb) at a flow rate of 50mL/s	Highest measurement will be used
PC20 methacholine/histamine challenge test	Methacholine challenge test (also known as bronchoprovocation test) measured in mg/ml.	Lowest measurement will be used
Comorbidity[5]		
Potentially T-2 related comorbidities		
Allergic rhinitis	Self-reported or diagnosis for allergic rhinitis	Data closest to index
Chronic rhinosinusitis	Self-reported or diagnosis for chronic rhinosinusitis	Data closest to index
Eczema	Self-reported or diagnosis for eczema	Data closest to index
Nasal polyps	Self-reported or diagnosis for nasal polyps	Data closest to index
Atopic disease	Self-reported or diagnosis for eczema or allergic rhinitis	Data closest to index

[5] The time frame to collect comorbidities data is relatively short. Comorbidities with only substantial data will be analyzed for this study.

Variable Name	Description	If >1 visit available
Urticaria	Self-reported or diagnosis for urticaria	
Food allergy	Self-reported or diagnosis for food allergy	Data closest to index
Aspirin sensitivity	Self-reported or diagnosis for aspirin sensitivity	Data closest to index
Eosinophilic esophagitis	Self-reported or diagnosis for eosinophilic esophagitis	Data closest to index
Potentially OCS-related comorbidities		
Obesity	Self-reported or diagnosis for obesity	Data closest to index
Hypertension	Self-reported or diagnosis for hypertension	Data closest to index
Obstructive sleep apnea	Self-reported or diagnosis for obstructive sleep apnea	Data closest to index
Anxiety/depression	Self-reported or diagnosis for anxiety/depression	Data closest to index
Dyslipidemia	Self-reported or diagnosis for dyslipidemia	Data closest to index
Osteoporosis	Self-reported or diagnosis for osteoporosis	Data closest to index
Diabetes	Self-reported or diagnosis for diabetes	Data closest to index
Pneumonia	Self-reported or diagnosis for pneumonia	Data closest to index
Coronary heart disease	Self-reported or diagnosis for coronary heart disease	Data closest to index
Pulmonary embolism/VTE	Self-reported or diagnosis for pulmonary embolism/VTE	Data closest to index
Cataract	Self-reported or diagnosis for cataract	Data closest to index
Peptic ulcer	Self-reported or diagnosis for peptic ulcer	Data closest to index
Chronic kidney disease	Self-reported or diagnosis for chronic kidney disease	Data closest to index
Heart failure	Self-reported or diagnosis for indicated history of heart failure	Data closest to index
Adrenal insufficiency	Self-reported or diagnosis for adrenal insufficiency	Data closest to index
Cerebrovascular accident	Self-reported or diagnosis for cerebrovascular accident	Data closest to index
Comorbidities mimicking/exacerbating asthma		
Gastroesophageal reflux disease (GERD)	Self-reported or diagnosis for GERD	Data closest to index
COPD	Self-reported or diagnosis for COPD	Data closest to index
Bronchiectasis	Self-reported or diagnosis for bronchiectasis	Data closest to index
VCD/laryngeal spasms	Self-reported or diagnosis for VCD/laryngeal spasms	Data closest to index
Dysfunctional breathing	Self-reported or diagnosis for dysfunctional breathing	Data closest to index
Medication in addition to ICS/LABA		
Maintenance OCS	Prescription of OCS for maintenance[6] Daily dose, duration of treatment, and start date	Data collated across visits
ICS+LABA	Prescription for inhaled corticosteroids and long-acting β-adrenoreceptor agonist (ICS+LABA) as separate or combination inhalers	Data collated across visits

[6] May require sensitivity analyses to ascertain long-term OCS use

Variable Name	Description	If >1 visit available
	Daily dose, duration of treatment, and start date	
ICS + LABA + Theophylline	Prescription for ICS+ LABA plus Theophylline Daily dose, duration of treatment, and start date	Data collated across visits
ICS + LABA + LTRA	Prescription for inhaled corticosteroids, long-acting β-adrenoreceptor agonist and leukotriene receptor antagonist Daily dose, duration of treatment, and start date	Data collated across visits
ICS + LABA + LAMA	Prescription for ICS+ LABA plus long-acting muscarinic receptor antagonists (LAMA) Daily dose, duration of treatment, and start date	Data collated across visits
ICS + LABA + LAMA + LTRA	Prescription for ICS+LABA+LAMA + LTRA Daily dose, duration of treatment, and start date	Data collated across visits
Anti-IgE	Prescription for Anti-IgE: omalizumab Daily dose, duration of treatment, and start/end dates	Data collated across visits
Anti-IL5/IL5R	Prescription for anti-interleukin 5 (Anti-IL5): mepolizumab, reslizumab, benralizumab Daily dose, duration of treatment, and start/end dates	Data collated across visits
Anti-IL4/IL13	Prescription for anti-interleukin 4/13 Daily dose, duration of treatment, and start/end dates	Data collated across visits
Macrolide antibiotic	Prescription for macrolide antibiotics: azithromycin, clarithromycin, erythromycin, roxithromycin, fidaxomicin, telithromycin Daily dose, duration of treatment, and start date	Data collated across visits
Steroid-sparing agent	Prescription for steroid-sparing agent Daily dose, duration of treatment, and start date	Data collated across visits

Abbreviations: FeNO, fractional exhaled nitric oxide; FEV1, Forced expiratory volume in one second; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting β-adrenoreceptor agonist; LAMA, long-acting muscarinic receptor antagonists; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; PEF, peak expiratory flow

4.2.3 Biomarker stability (Exploratory objective)

Biomarker stability will be measured both by numerical change, categorical change, and rate of change overtime between: 1-the first and the last measure, 2-the highest and lowest measure.

Among patients on OCS or anti-IL5 treatment, changes in BEC before and after treatment will be calculated as well.

The following biomarker thresholds will be used to measure categorical change over time

- IgE ≥75kU/L, AND
- FeNO ≥25 parts per billion (ppb), AND
- BEC ≥300 cells/μL

Specific positive biomarker combination (Exploratory objective)

Patients with specific positive biomarker combinations (e.g. high BEC and high FeNo; high IgE and high BEC) will be defined using the following criteria:

- IgE ≥75kU/L
- FeNO ≥25 parts per billion (ppb)
- BEC ≥300 cells/μL^7

5. STATISTICAL ANALYSIS PLAN

5.1 Statistical Methods – General Aspects

The analysis for the primary objective will be descriptive in nature. Descriptive statistics will be calculated for continuous and categorical variables accordingly.
For variables measured on the interval or ratio scale, summary statistics produced will include:

- Sample size (n)
- Frequency and percentage of missing data
- Mean
- Standard deviation (SD)
- 95% confidence intervals (CI)
- Range (minimum–maximum)
- Median
- Interquartile range (25th and 75th percentile)

For categorical variables, the summary statistics will include:

- Sample size (n)
- Count for each category, including a missing data category
- Percentage of the total number of observations for each category, including a missing data category

5.2 Subgroup Analyses

Patients who received biologic treatments (i.e. biologics user in subgroup 1 and subgroup 2, section 4.1) will be further stratified by classes of biologics they received; in an exploratory analysis, those treated with benralizumab will be examined separately. For subgroup 2, we will also separately examine patients that remained uncontrolled or switched from 2 or more biologic treatments.

In the exploratory analysis, patients will be further stratified on treatment (biologic/no biologic, OCS, and anti-IL5). Analysis on FeNO will be stratified by smoking status.

5.3 Ad-hoc analyses

Ad-hoc analyses that used a different approach to identify biologic eligibility by country-specific and biologic-specific criteria was added from the approved protocol. In this analyses, biologic eligible patients were defined as those who either had been prescribed a biologic available during the study period (either omalizumab, benralizumab, dupilumab, mepolizumab, or reslizumab) or those meeting the prescribing criteria from the Biologic Accessibility Score (BACS), developed by the ISAR group collaborating with 28 participating countries (Appendix 1).

BACS biologic prescription criteria comprised a list of 18 initial criteria (age, weight, asthma phenotype, blood eosinophil count, total serum IgE, FeNO, allergic asthma diagnostic requirements [e.g., skin prick test], background therapy, biologic history, adherence, OCS use, exacerbation history, asthma control, lung function, symptoms, asthma diagnosis, care manager [e.g., severe asthma specialist], and correct inhaler technique). Details of the biologic-eligible criteria specific to biologic and per country are published previously (16).

6. SENSITIVITY ANALYSIS

Sensitivity analysis for subgroup 2 analysis will be performed using ACQ for asthma control definition.

Also, sensitivity analysis for subgroup stratified by biomarkers will be conducted, in which the impact of following thresholds will be assessed:

- FeNO ≥50 parts per billion (ppb)
- BEC ≥150, ≥400, ≥450 cells/μL
- IgE ≥30, ≥100, 30-700, ≥700 IU/ml

6.1.1 Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest

Descriptive statistics will be generated for the overall population of severe asthma patients, by region/country, and for the individual subgroups.

6.1.2 Exploratory Objective(s): Calculation of Epidemiological Measure(s) of Interest

The outcomes that will be studied for this exploratory analysis include:

- For each patient who has at least two measurements of a certain biomarker, the change in biomarker value from the first to the last measurement and from highest to lowest measures will be calculated. The percentage of patients that experience a change in value, for each biomarker, will be quantified and plotted. Numeric changes (absolute and percent change from first measurement) between the two visits for each biomarker as well as the rate (biomarker change divided by time between measurements) will be summarized across patients by the mean, median, standard deviation, range, and interquartile range.

- For patients with more than 2 biomarker measurements, the average rate of change will be calculated along with the change between each follow-up measurement. Numeric changes between visits for each biomarker will be summarized by the mean, median, standard deviation, range, and interquartile range. The frequency of biomarker testing (e.g., IgE, FeNO, and BEC) will be summarized by each subgroup of patients. This analysis will be done among patients who are and who are not treated with a biologic. Among patients on a biologic treatment, changes in biomarker values before and after treatment will be calculated and presented. Among patients on OCS or anti-IL5 treatment, changes in BEC before and after treatment will be calculated as well.

Using the categories outlined in Table 5, the proportion of patients who experience change in biomarker category will also be calculated.

Table 5. Biomarker Stability Outcomes

Biomarker	Measure	Outcome
IgE level	Continuous and categorical: • ≥75 IU/ml • <75 IU/ml	Change from prior value to most recent value
BEC	Continuous and categorical: Without Maintenance OCS • ≥300 cells/µL • <300 cells/µL With Maintenance OCS • ≥150 cells/µL • <150 cells/µL	Change from prior value to most recent value
FeNO test	Continuous and categorical: • ≥25ppb • <25ppb	Change from prior value to most recent value

Abbreviations: BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E

6.2 Bias

6.2.1 Methods to Minimize Bias

Potential measurement error that may lead to information bias could be present both at the original point of data entry (e.g. original registry, electronic medical record system) or at the point of data entry into ISAR. The former would be under the governance of the country-level systems and their respective data quality checks. For the latter, ISAR has a standard operating procedure (SOP) for data collection, a dedicated data management plan, and pre-programmed data quality checks (see sec. 0) to ensure correct data entry into the eCRF. Therefore, while errors may occur at data entry, they are likely to be minimal and non-differential.

6.2.2 Adjustment for Multiple Comparisons

This is a descriptive analysis and will not evaluate any comparisons.

6.2.3 Strengths and Limitations

This analysis is based on data collected from the ISAR, a global severe asthma registry collecting patient-level data. As with all registry data, it is subject to certain limitations. While data collection is standardized across countries, a significant strength of the registry, initial case assessment and treatment patterns may vary across contribution locations due to reasons such as different healthcare delivery systems across countries. This may make it difficult to detect certain patterns or associations in a combined analysis, but has the strength of demonstrating the impact of healthcare access and delivery systems on clinical outcomes. The availability of follow-up data may also vary by country. There is some potential for misclassification in some data elements (e.g., diagnosis, exacerbations), which may or may not be differential depending on data quality at the source of entry.

For new registries entering into ISAR, there may be an element of selection when it comes to sites contributing data to the registry. The data coming from these sites may therefore not be representative of care delivered to severe asthma patients across the individual countries.

6.3 Sample Size and Power Calculations

This study will rely on previously collected data and is descriptive with no hypothesis testing; therefore no formal power calculations were conducted. This study is mainly descriptive and will present point estimates (means, proportions, rates) derived from unadjusted and stratified tabulations of the data. The preliminary count from the ISAR identified over 8,647 patients with severe asthma. The sample size will decrease after applying further inclusion and exclusion criteria.

7. STUDY CONDUCT AND REGULATORY DETAILS

7.1 Study Conduct

7.1.1 Study Flow Chart and Plan

Key study events are outlined below.

Study event	Date
AZ SDC approval	February 2021
AZ protocol approval	May 2021
Protocol and data request submission to ISAR	June 2021
Anonymised Data Ethics & Protocol Transparency Committee approval; data cut sent to AZ	June 2021-May 2022
Data analysis	Dec 2021- Oct 2022
Study report	Dec 2022
Study publication	Q1 2023

7.1.2 Quality Control

Data entry into the eCRF is completed by designated personnel trained on data entry via either an on-site or remote training session[15]. Furthermore, a SOP on data collection with instructions on how to complete the eCRF with detailed explanation of the data fields, is provided to all participating registries. An ISAR data management plan is in place that outlines the functions, processes and specifications for data collection, extraction, delivery and cleaning. Many of the eCRF fields are numeric or categorical to minimize risk of data entry errors. There are also pre-programmed data quality checks that automatically spot out-of-range or anomalous entries into the eCRF during data entry. All data queries generated by either the electronic data capture system or the database holder is reviewed and resolved by country data managers and or study coordinator; all data modifications are documented in an audit log.

7.2 Protection of Human Subjects

The Anonymised Data Ethics & Protocol Transparency (ADEPT) Committee, an independent body of experts commissioned by the Respiratory Effectiveness Group (REG) to govern the standard of research conducted on ISAR, evaluates all submitted research proposals according to pre-specified criteria[16] to ensure scientific integrity, robustness, and compliance with all ethical considerations and that the proposed research is clinically appropriate and valuable to patients, public health and health care[15].

All data collectors have been trained in human subject research with relevant experience in Good Clinical Practice or country-specific equivalent guidelines. Only anonymised data is collected from ISAR collaborating registries and partners with strict security measures in place for data sharing and hosting. A SOP for data transfer is provided to each registry to ensure the anonymous and safe transfer of data. Transferred data receives unique ISAR patient identification numbers with the linkage key to the relevant patients held solely by the patient's healthcare provider. In countries with stricter data privacy laws, data will be held within the country and anonymized country-level data shared only on a project-by-project basis.

7.2.1 Subject Informed Consent

Informed consent from patients has been acquired where needed to allow for sharing of anonymized data.

8. PUBLICATIONS

We intends to publish description of the burden of the target populations for anti-TSLP biologic therapy, including clinical and HRU outcomes, which is the primary objective of the study. Sub-population(s) for which sample sizes are small and where results may therefore be difficult to interpret will be published as exploratory analyses. We will publish on biomarker trends as exploratory given the current understanding of the limitation of that data (i.e. high proportion of missing data).

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10. APPENDICES

Appendix 1.

Appendix 1. BACS scores by biologic anc

11. ATTACHMENTS

12. SIGNATURES

ASTRAZENECA SIGNATURE(S)

Patient characteristics, treatment patterns, clinical outcomes, and health care resource utilization in severe asthma subgroups: A retrospective analysis of the International Severe Asthma Registry

This Observational Study Protocol has been subjected to an internal AstraZeneca review
I agree to the terms of this Study protocol.

AstraZeneca representative

Ekaterina Maslova, Associate Director, Epidemiology	Date (Day Month Year)

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This Observational Study Protocol has been subjected to an internal AstraZeneca review
I agree to the terms of this Study protocol.

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