**OPC Global**

**Study Protocol**

# BIOLOGIC USAGE PATTERNS, CLINICAL OUTCOMES AND HEALTHCARE UTILIZATION (CLEAR)

## The clinical and health resources effects of continuing, switching, and stopping an initiation biologic

**Date: 03/08/2021**

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|---|---|
| **Title** | Biologic Usage Patterns, Clinical Outcomes and Healthcare Resource Utilization |
| **Subtitle** | The clinical and health resources effects of continuing, switching, and stopping an initiation biologic (**CLEAR**) |
| **Protocol version number** | V0.7 |
| **Medicinal product** | Not applicable |
| **Product code** | Not applicable |
| **Marketing authorization holder/numbers** | Not applicable |
| **Study aims and objectives** | **Aim**: To investigate the effects of distinct patterns of biologic use in a real-life cohort of patients with severe asthma.<br>**Objectives**:<br>1. To describe the demographic and clinical characteristics, including the extent of T2 phenotype, in five groups of patients with severe asthma, including those who do not initiate a biologic when eligible, and do not initiate and are not eligible, and between those who initiate: those who stop, switch, or continue the initial biologic<br>2. To assess the clinical outcomes (e.g., reduction of exacerbations, long-term OCS use, asthma control) by biologic utilization patterns<br>3. To assess healthcare resource utilization (hospitalization, emergency room visits, invasive ventilation) by biologic usage patterns (not initiating, stopping, switching or continuing) |
| **Countries of study** | Argentina, Australia, Bulgaria, Canada, Denmark, Colombia, Greece, Ireland, Italy, Japan, Kuwait, Mexico, Poland, Portugal, South Korea, Spain, Singapore, Saudi Arabia, Taiwan, UK, United States, UAE |
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# Content

## 1. BACKGROUND

The European Respiratory Society (ERS) and the American Thoracic Society (ATS) define severe asthma as "asthma which requires treatment with high-dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains uncontrolled despite this therapy". [1,2,18]. (Such definitions assume reasonable adherence, inhaler technique and treatment of comorbidities.) In the past six years, several targeted therapies have become effective treatment options for those with severe asthma [19-23]. Currently, three biologic classes target specific inflammatory pathways involved in the pathogenesis of severe asthma: 1) immunoglobulin E (IgE) with anti-IgE, 2) interleukin-5 (IL-5) with anti-IL-5 or anti-IL-5 receptor antagonist (anti-IL-5/5r), and 3) interleukin-4 (IL-4) and interleukin-13 (IL-13) with anti-interleukin-4 receptor α (anti-IL4Rα). The initiation/eligibility for biologic treatment is based on Selection of Anti therapy determined an assessment of phenotype [3,5]. In clinical practice, phenotype is commonly ascertained via biomarkers such as blood eosinophils count, serum IgE level and the fractional concentration of exhaled nitric oxide (FeNO) [10]. The stability of these biomarker measurements is unclear[12].

Currently, biologics are dispensed primarily via a 'stratified' approach' [9]. This approach caters to many patients with severe asthma with eosinophilic and/or allergic disease (high-T2). However, multiple inflammatory pathways or disease endotypes shapes are involved in the pathogenesis of asthma. Figure 1 shows the overlap ofT2 biomarkers in the ISAR cohort [24]. In addition, a significant proportion of severe asthma patients have non-T2 or mixed phenotype disease [6,7,9]. In the absence of efficacious interventions guidelines for the treatment of non/low-T2 severe asthma with targeted therapy have yet to be studied widely [10].

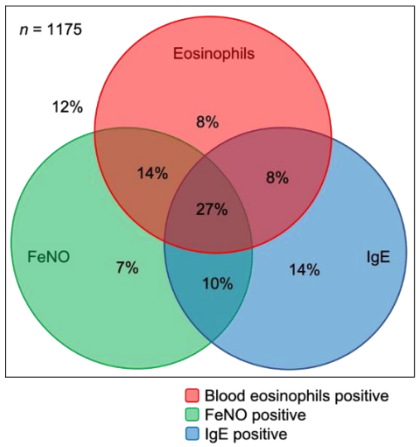



**Figure 1 Overlap of Biomarkers in ISAR [24]**

One of the promising ways of addressing all the severe asthma phenotypes may be via targeting one of the upstream inflammatory responses of the disease, such as the cytokine thymic stromal lymphopoietin (TSLP)[13]. TSLP is expressed by the airway epithelium in response to both allergic and non-allergic eosinophilic inflammation [14]. Lack of effective therapies for all patients with severe asthma, together with additional hurdles, such as accessibility or eligibility for more

than one biologic, have led to patients receiving sub-optimal or inappropriate biologics at initiation [11,12]. This can lead to various patterns of use, such as stopping or switching from the first biologic to a second, and in some cases, to a third or fourth biologic as clinicians and patients search deliberately for adequate response.

In an ISAR study on Biologic Utilization (prepublication) most patients (79%; 2791/3531) continued their first biologic, 10% (356/3531) stopped and 11% (384/3531) switched among patients who were followed up for at least a period of 6 months. This pattern was reproduced at the country level, although the ratio of 'stoppers' to 'switchers' varied. The most common reported reasons for stopping or switching a biologic was lack of efficacy benefits and/or adverse events. Disruption to the clinical management of biologics, most likely due to ineffective response and/or inappropriate initiation of the , may lead to a worsening of asthma control and an associated increase in health care utilization. This has yet to be demonstrated in a real-world setting or quantified. In addition, there may be a subgroup that is eligible yet  is not reaping the benefits of targeted therapy.

## 1.1 STUDY AIMS

This study will describe the patterns of biologic use or lack thereof and their clinical outcomes and healthcare resource uses in a real-life international cohort of patients with severe asthma.

## 1.2 STUDY OBJECTIVES

The objectives of this study are as follows:

1. To describe the demographic and clinical characteristics (including biomarker characteristics), of five severe asthma patient groups based on patterns of biologic initiation (1. Initiated and switched, 2. Initiated and continued, 3. Initiated and stopped, 4. Not initiated but eligible for biologics, 5. Not initiated and not eligible for any biologics)

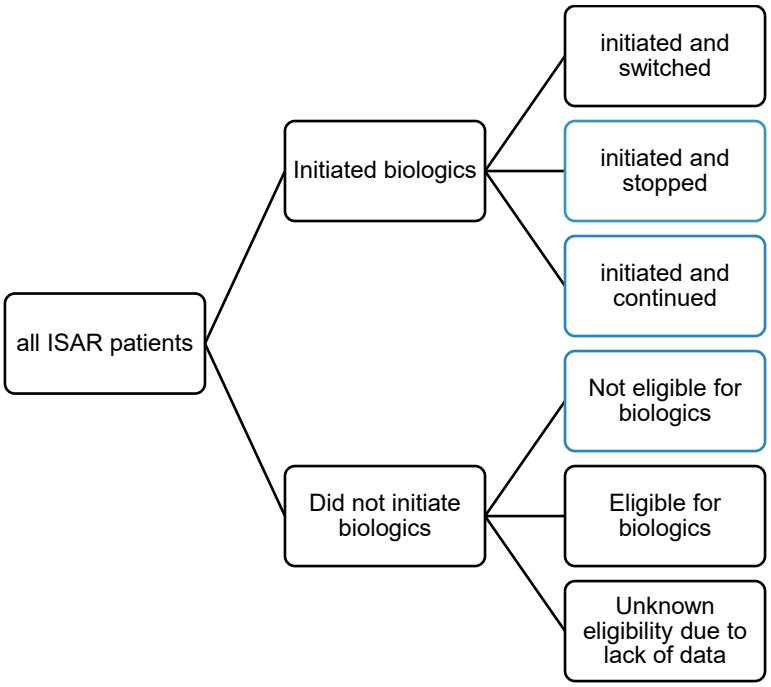



**Figure 2 Chart depicting different severe asthma patient groups in CLEAR**

**All patients who have initiated biologics are considered to have met frequent eligibility criteria (eligibility criteria mentioned below)*

2. To assess the clinical outcomes (e.g., reduction of exacerbations, long-term OCS, asthma control) across the biologic utilization patterns mentioned above
3. To assess the healthcare resource utilization (hospitalization, emergency room visits, non-invasive and invasive ventilation) depending upon which biologic is prescribed

# 2. STUDY DESIGN

## 2.1 INCLUSION AND EXCLUSION CRITERIA

**Inclusion criteria:**

- Patients' data entries from ISAR who are from countries that have at least two biologics available (defined as the presence of a license for the treatment of severe asthma),
- Patients, 18 years of age or older, with a diagnosis of severe asthma which requires treatment with guideline-suggested medications with 2018 GINA:

- Treatment Step 4 and being uncontrolled[1] OR
- Treatment Step 5.

- Registry data for a minimum of one year prior to index date (defined as the date of biologic initiation for biologic patients and date of ISAR enrolment for non-biologic patients) and 24 weeks after therapy or enrolment,
- Data received by ISAR before July 2021

**Exclusion criteria:**

- Having received bronchial thermoplasty
- Less than 18 years of age at biologic initiation or ISAR enrolment

## 2.2 STUDY DESIGN AND SAMPLE SIZE

The study sample will be drawn from the ISAR population during the time of data collection. This study will first ascertain the following patterns of biologic use:

**Initiated**

- **Continued**: use of first biologic for at least 6 months, without indication of stopping or switching
- **Switched**: stopped the initial biologic and received a (one or more) different biologic, without restriction of any time lapse between biologics
- **Stopped**: stopped the initial biologic and did not receive another biologic. Caution will be taken as stoppers maybe on the path to switchers. Therefore, data will be reviewed to add a feasible follow-up time post stopping and free of not starting another biologic to ascertain true stoppers.

**Did not initiate**:

- **Not eligible:** Did not meet the criteria for eligibility of biologic therapy and did not initiate any therapy
- **Eligible:** Eligible for biologic therapy but did not initiate any biologic therapy
- A “frequent-eligibility” criterion of each biologic class will be used to assess eligibility. This criterion will be constructed using the results from the ISAR biologic availability survey and will be subject to confirmation from the ISAR scientific steering committee (see Table 1 for possible criteria per biologic class)

**Table 1: Frequent-Eligibility Criteria per Biologic Class. Patients who did not initiate biologic therapy and are eligible will meet any of the three criteria for any of the three biologic groups.**

| | Anti-IgE | Anti-IL5/5R | Anti-IL4/13 |
|---|---|---|---|
| **Background therapy** | Met via ISAR inclusion criteria | | |
| **Positive Allergen test** | Yes, **AND** | N/A | N/A |
| **IgE levels** | ≥ 30 IU/mL, **AND** | N/A | N/A |
| **BEC** | N/A | ≥ 150 cells/μL with long-term OCS, OR<br>≥ 300 cells/μL without long-term OCS, **AND** | ≥150 cells/μL with long-term OCS, OR<br>≥300 cells/μL without long-term OCS, **OR** |
| **FeNO** | N/A | N/A | ≥25 ppb, **AND** |
| **Exacerbation OR long-term OCS** | Pre-therapy exacerbation (≥2) OR<br>On long-term OCS | Pre-therapy exacerbation (≥2) OR<br>On long-term OCS | Pre-therapy exacerbation (≥2) OR<br>On long-term OCS |

The ISAR enrolment date will mark the start of the outcome period for those who did not initiate biologics while for those who did the index date will be signified by the First Biologic Therapy Start Date. A minimum of 16-weeks of follow-up time post biologic initiation (outcome period) will be applied in alignment with the ERS recommendation for time of biologic response assessment [8]. This is also congruent with the methodology used in the ISAR research project 'Defining and Characterizing Responders to Biologic TrEAtment in Severe AsthMa Patients (BEAM).' To assess the impact of this design, the study will evaluate and report the number of patients that had three types of follow-up data: 1.) <24 weeks, 2.) > 24 weeks to 1-year 3.) >1-year.

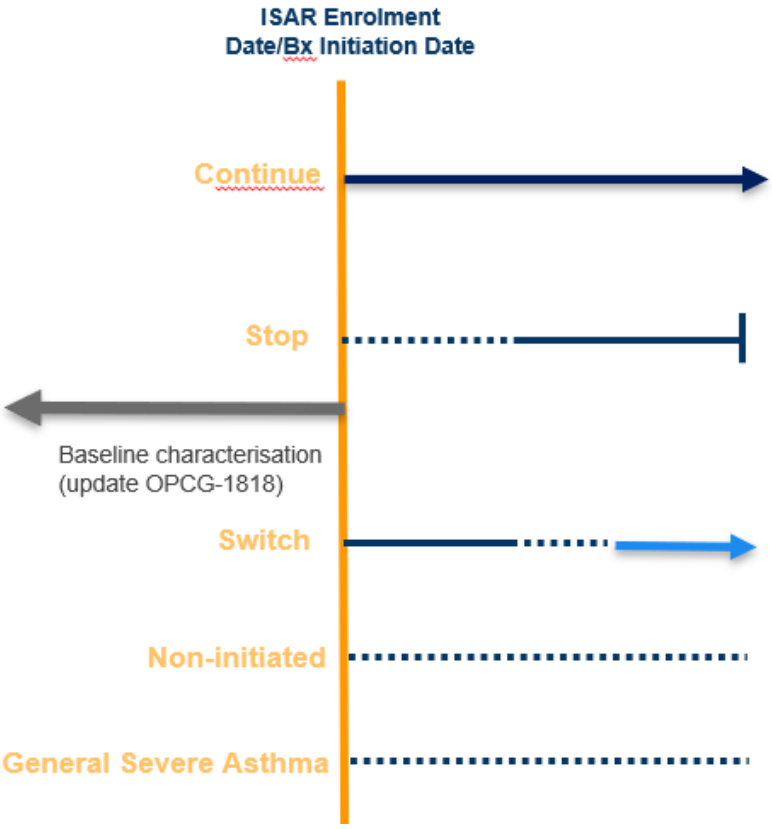



**Figure 3 Study Design**

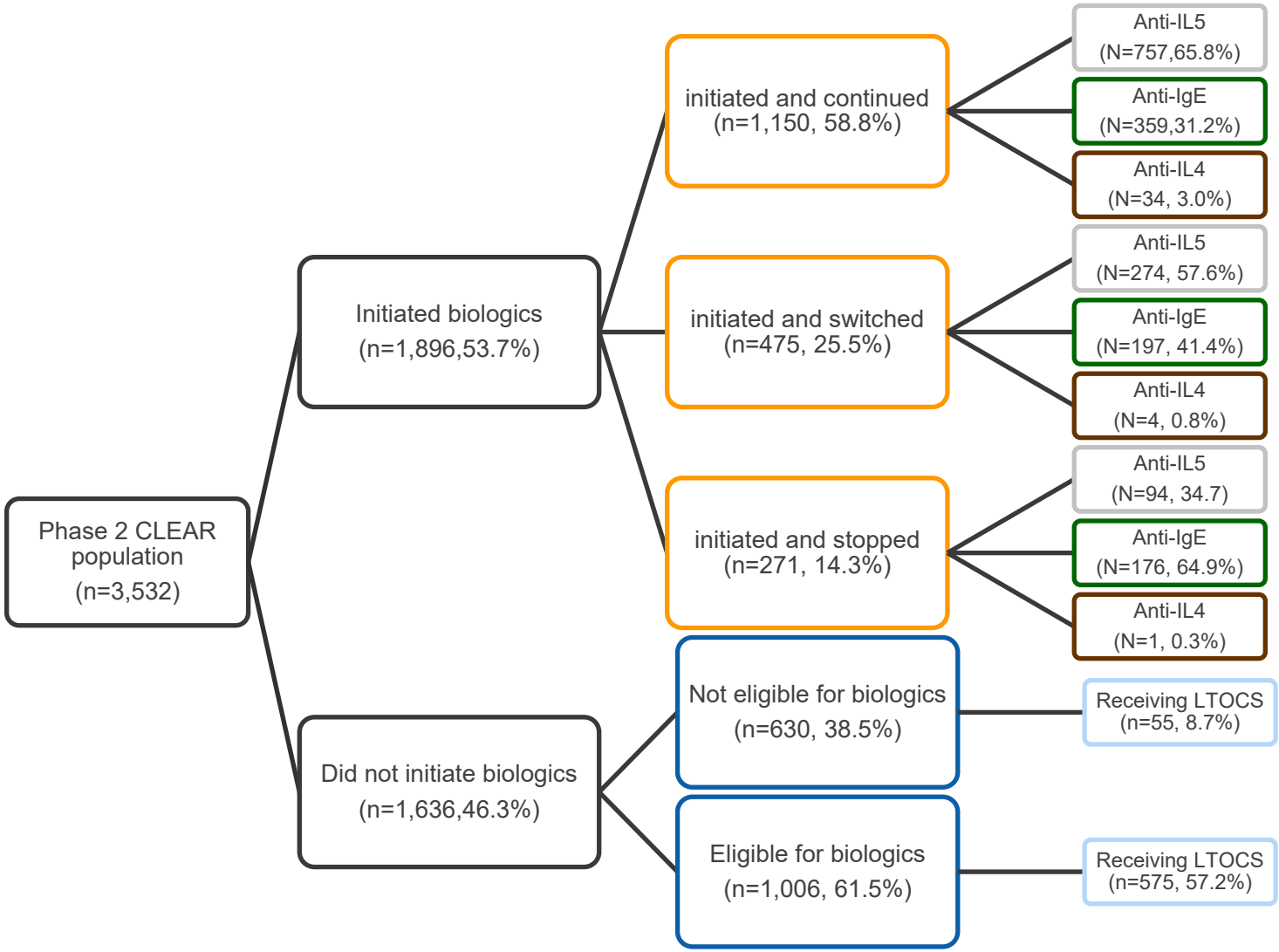
Health outcomes, such as exacerbations, asthma control status, emergency room visits, hospital visits, OCS dose (rescue and long-term), as well as health resource utilization outcomes (hospital, emergency room visits and non-invasive and invasive ventilation)) will be assessed across biologic usage groups during the outcome period. In ISAR, data on the outcomes are collected as part of routine general health assessments in accordance with respiratory care guidelines and/or recommended medical practice guidelines.

## 2.3 DATA SOURCE

The ISAR registry is a multi-country, multi-center, observational epidemiologic data repository with retrospective and prospective data of patients treated with 2018 Global Initiative for Asthma (GINA) Step 5 or uncontrolled on GINA Step 4 treatment regimens. ISAR holds standardized, patient-level, fully anonymized data for ~9,654[2] (as of November 2020) patients with severe asthma from 19 national registries (Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Saudi Arabia, South Korea, Spain, Taiwan, UAE, UK and United States). The data is collected specifically for severe asthma research. All data contributors enter data via electronic Case Report Forms (eCRF) on a web-based platform customized for real-life data collection or within specialized electronic medical records. The reason for either stopping or switching the first biologic is also collected, when applicable [4]. Patient recruitment started in December 2015 Ethical governance for ISAR is 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). The registry's scientific merit is ensured by the ISAR steering committee (ISC) that is made up of 48 severe asthma specialist or database experts from 25 countries (http://isaregistries.org/)

[2] This does not include the 671 patients from the Australian Severe Asthma Network that was received on the 1st of Dec. as it is undergoing data quality assessments at the moment.

## 2.4 FEASIBILITY



The diagram above shows the feasibility for the CLEAR study. Overall, 3,532 patients were eligible for the study. Most of them had initiated biologics and continued on them.

# 3.STUDY VARIABLES AND STUDY OUTCOMES

Values captured closest to, and at/before index date of the following variables will be used to describe the biologic utilization groups (objective 1). Again, the index date refers to the date at which the initiation biologic was started or the date of ISAR enrolment for those who did not initiate any biologics.

## 3.1 DEMOGRAPHIC AND CLINICAL VARIABLES

**Table 2 Demographic and clinical features to be described in Phase I of the study**

| | |
|---|---|
| **Patient attributes** | |
| Age | Age in completed years. |
| Sex | Female or Male. |
| Body Mass Index (BMI) | The ratio of weight (kg) to squared height ($m^2$). Categorised as 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 $kg/m^2$) and obese (⩾ 30 $kg/m^2$). |
| Age of Asthma Onset | Age in completed years or months (if less than 1 year) at which asthma symptoms began. Early onset: <18 years of age; late onset: ⩾18 years of age. |
| Smoking Status | Categorised as non-smoker, current smoker or ex-smoker; last ever. |
| **Diagnostic Measurements** | |
| Blood eosinophil count | Count of blood eosinophils (cells/uL). |
| Blood IgE level | blood level IgE (kU/L). |
| Predicted FEV1 | Predicted value of forced expiratory volume in the first second of expiration (L). |
| Pre-bronchodilator FEV1 | Measured forced expiratory volume in the first second of expiration, before the use of a bronchodilator (L). |

| | |
|---|---|
| Post-bronchodilator FEV1 | Measured forced expiratory volume in the first second of expiration, after the use of a bronchodilator (L). |
| Pre-bronchodilator FVC | Forced vital capacity, before the use of a bronchodilator (L). |
| Post-bronchodilator FVC | Forced vital capacity, after the use of a bronchodilator (L). |
| Pre-bronchodilator FEV1/FVC Ratio | Measured FEV1 as a ratio of measured FVC. |
| Post-bronchodilator FEV1/FVC Ratio | Measured FEV1 as a ratio of measured FVC. |
| Fractional exhaled nitric oxide (FENO) test | Measurements of fractional nitric oxide concentration in exhaled breath, measured in parts per billion (ppb) at a flow rate of 50mL/s. |
| Skin Prick Test | Positive skin prick test |
| **Therapy** | |
| Long-term OCS | Maintenance oral corticosteroids (OCS) |
| Anti-IgE | Prescription for Anti-Immunoglobulin E (Anti-IgE) |
| Anti-IL5 | Prescription for Anti-Interleukin 5 (Anti-IL5/5R) |
| Anti-IL4/13 | Prescription for Anti-IL4/13 |
| SCS-related comorbidities | Number of comorbidities reported from the following list: Anxiety, Depression, Osteoporosis, Diabetes, Peptic Ulcer, Pneumonia, Obstructive Sleep Apnea, Renal Failure, Heart Failure, Myocardial Infarction, Thromboembolism, Pulmonary Embolism, Serious infection (one or more). Other comorbidities based on availability of data. |
| Non-SCS-related comorbidities | Number of comorbidities reported from the following list: Allergic Rhinitis, Chronic Rhinosinusitis, Eczema, Nasal Polyps, Cancer |

## 3.2 STUDY OUTCOMES

The following outcomes measures are measured after index date (follow-up visits).

**Table 3 Clinical outcomes of interest for objective 2 of the study**

| Variable Name | Type | Description |
|---|---|---|
| Number of **annualized** asthma exacerbations[3] | Count | Annualized number of exacerbations requiring rescue steroids after index date |
| Asthma control in the past 4 weeks | Categorical | Categorized as *controlled, partly controlled, or uncontrolled* according to the GINA Asthma Control Criteria/Asthma Control Questionnaire (ACQ-6)/Asthma Control Test (ACT) |
| Total dose of oral corticosteroids[4] | Continuous | Label Dose X Frequency X Duration of Use for maintenance OCS between the index date and date of data extraction |
| Number of hospital admissions | Count | Annualized number of hospital admissions after index date |
| Number of emergency room visits | Count | Annualized number of emergency room visits after index date |

[3] Total number of exacerbations will be calculated between index date and current visit date

[4] If use of SCS started after the index date, total dose will be calculated between start- and end date of use

# 4. STATISTICAL ANALYSIS

## 4.1 OBJECTIVE 1

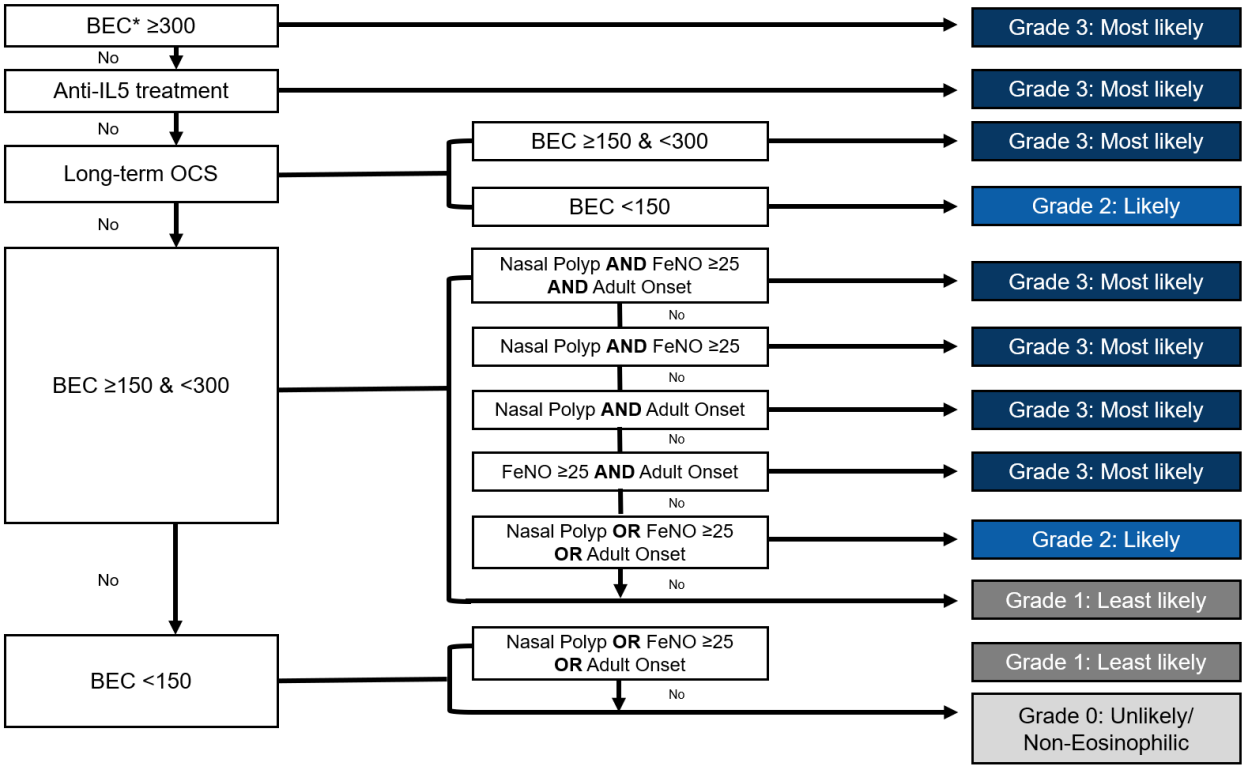
Firstly, descriptive statistics of the baseline (pre-therapy) **Demographic and Clinical Variables (section 3.1)** for the five biologic utilization groups will be conducted for continuous and categorical variables accordingly.

- For variables measured on the interval or ratio scale, summary statistics produced will include:
  - Sample size (n)
  - Percentage of the non-missing patients per variable
  - Mean
  - Standard deviation (SD)
  - Range (minimum- maximum)
  - Median
  - Inter-quartile range ($25^{th}$ and $75^{th}$ percentile)
- For categorical variables, the summary statistics will include:
  - Sample size (n)
  - Range (if applicable)
  - Count and percentage by category (distribution)

Tables will be annotated with the total population size relevant to that treatment, including any missing observations.

In addition, to describing the groups of biologic usage, the extent of T2 phenotype will be demonstrated via applying the ISAR algorithm for T2/eosinophilic grades (Figure 2). The definitions of the grades were constructed per published evidence, asthma management guidelines and have gained ISAR steering committee consensus. The highest blood eosinophilic count ever (⩾300, ⩾150-300, <150 cells/μL), naïve or non-naïve biologic treatment including anti-IgE, anti-IL-5/5R and anti-il4/13 treatment, long-term OCS ever, elevated FeNO (⩾25 ppb) ever, nasal polyps' diagnosis ever, and adult asthma onset (⩾18 years) were parameters that facilitated the construction of the eosinophilic phenotype gradient. This methodology is in the process of publication in a peer-reviewed journal. Furthermore, the population will be described

in detail using demographics and clinical characteristics mentioned in table 2. When necessary, these characteristics will be broken down based on LTOCS use. Descriptive tables will be provided on demographics of the populations, biomarkers, asthma control and comorbidities.




First the demographic and clinical characteristics as mentioned in section 3.1 will be described in detail per group. This will include describing proportions on patients from each group based on their biomarkers, long term OCS (LTOCS) use, baseline demographics such as those outlined in Section 3.1. Next, the significant difference in level of T2 phenotypes and demographic or clinical characteristics (section 3.1) across the five groups will be compared and tested for statistical significance via Chi-square tests for comparison of counts data, and t-test or one-way analysis of variance (ANOVA) for continuous variables. Where appropriate, McNemar tests, paired t-tests will be considered. Statistical significance will be defined as $p < 0.05$. Stata version 14.2 (College Station, TX, USA) will be used to conduct all statistical analyses and data manipulations.

Additionally, comparisons will be made as follows:

1. Switch vs. continue
2. Stop vs. continue
3. Patient received biologics vs. eligible but did not receive biologics
4. Biologic eligible (biologic users+ non-users but who qualify) vs. not eligible.

## 4.2 OBJECTIVE 2

As there are various factors underpinning the probability of not receiving, receiving, continuing, switching, or stopping a biologic, comparing the clinical outcomes set forth in section 3.2 will need careful consideration. One of the main confounders to consider is the availability and/or accessibility of multiple biologics in a country. Therefore, all countries included in the analysis of assessing the clinical outcomes across biological utilization groups will have at least 2 biologics available in the market (availability defined as licensed in the country) at the time of the patient's enrolment into ISAR (index date). There will be a cut-off date of 01 Jan 2014 for assessment of clinical outcomes to ensure the availability of drugs in the market.

Furthermore, according to the results of objective 1 (pre-therapy or baseline characteristics), before assessing for differences in the clinical outcomes across groups, baseline imbalance will be examined across groups and matched accordingly. Prior to this step, the clinical outcomes of each group will be described.

Standardized mean difference (SMD) will be used to quantify differences in both continuous and categorical variables between the biologic utilization groups at baseline. An SMD $\leqslant$10% indicates sufficient balance between treatment groups. It is hypothesized that data completeness will vary between treatment groups. Therefore, propensity score matching methodology is envisioned at the stage of comparing between groups to conserve the statistical power. After the matching approach, the SMD will be recalculated to verify the accuracy of the model. If residual confounders are present, they will be entered into the respective multivariate model noted below. Clinical and/or health resource outcomes may be affected by the level of eosinophilic phenotypes, thus, results may be stratified by level of ISAR Eosinophilic Grade.

**Group comparisons**

The first set of results for the primary and secondary outcomes (section 3.2) will be demonstrated for those that did not initiate a biologic versus those that did (switch, stop, continue) (initiators

versus non-initiators). The second set of results will compare the outcome results for patients that stopped or switched versus those that continued.

**Primary outcome: Exacerbation**

An asthma exacerbation will be defined as the occurrence of the following events (ERS/ATS task force definition):

- asthma-related hospital attendance/admission primary care consultation; AND/OR
- asthma-related A&E attendance; AND/OR
- an acute oral corticosteroid course of 3 days or more
- separate recordings of exacerbations within a 14 day period will be treated as the same exacerbation.

A time-to-event analysis will be performed to analyse the association between utilization pattern and time to first exacerbation with right censoring at the time of death, switching, stopping or loss to follow-up. Kaplan-Meier curves will be used to describe event-free survival over time and comparisons. Conditional Cox regression will be performed with time to the first exacerbation as the outcome variable (y) to estimate Hazard Ratios (HR) with 95% confidence intervals (CI) of the main effect. The proportional hazard assumption will be evaluated visually by means of a log-log plot of survival.

As the dispersion of the exacerbation data is expected to be high and as this outcome is conditional on the duration of follow-up, we may apply a negative binomial regression (NBR) to estimate the reduced rate of exacerbation (y=annual rate of exacerbation). We switch to a count model to take advantage of all exacerbations at follow up. Group comparisons (e.g. gender, BMI, number of biologics available etc.) will be made if interaction between a group and biologic use pattern is found. We will also run a NBR using the total post-therapy/post-ISAR enrolment exacerbations.

**Secondary outcome: Asthma control**

By applying a multinomial regression model (ordered), we will assess the probability or odds of the combined categories partially or controlled versus uncontrolled asthma for those that continue compared to those that do not initiate or switch or stop.

Secondary outcome: long term oral corticosteroid (OCS) dose

Descriptive data will summarize long term OCS (LTOCS) doses pre and post therapy and ISAR enrolment showing means, standard deviations, medians, IQR, percentage of those who stopped LTOCS altogether at follow up as well as those who decreased their doses to 5 or less miligrams. Generalized linear model (GLM) with generalized estimation equation (GEE) will be applied to estimate the reduced LTOCS dose across groups while accounting for intra-patient correlation.

**Secondary outcome: Health resource utilization**

Hospitalizations, invasive ventilations (if available) and emergency room visits will compose the outcome variable of health resource utilization (section 3.2). The difference in the number of incident hospital or emergency room visits in the outcome period across groups will be examined similarly to the primary outcome (exacerbation) discussed above. These outcomes will be considered separately for each healthcare resource and as a combined variable as well.

## 5. REGULATORY AND ETHICAL COMPLIANCE

This study was designed and will be implemented and reported in accordance with the criteria of the "European Network Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study" and follows the ENCePP Code of Conduct (EMA 2014). Once a final version of the protocol has been agreed and reviewed by the advisory group, this study will be registered with www.encepp.eu. Governance will be 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, https://www.regresearchnetwork.org/adept-committee/) to govern the standard of research conducted on internationally recognized databases.

All sites will enter into a regulatory agreement in compliance with the specific data transfer laws and legislation pertaining to each country and its relevant ethical boards and organizations.

Furthermore, all data extracted to be transferred from sites will be hashed and will enter the research database in the form of anonymized patient IDs. The data will be retrieved by OPC data analysts and utilized as an anonymized dataset to perform the analysis according to protocol. The study will be performed in compliance with all applicable local and international laws and regulations, including without limitation, ICH E6 guidelines for Good Clinical Practices.

## 6. DATA DISSEMINATION

Original results from this study will be submitted in abstract form for ATS 2022. The manuscript from this study will be submitted to a severe asthma focused peer-reviewed scientific journal in due course.

## 7. ADVISORY GROUP

| Project Steering Committee Members | Country |
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## 9. TIMELINES

Tentative timelines for delivery of this study:

| Milestones | Timeline |
|---|---|
| Study Design Concept | **Nov 2020** |
| Protocol draft | **Dec 2020** |
| Protocol finalization | Aug 2021 |
| Ethics approval | Aug 2021 |
| Data extraction & preparation | May – Aug 2021 |
| Analysis/pilot results | May – Aug 2021 |
| Study Report | Aug – Sept 2021 |
| First draft of the manuscript | August-November 2021 |

## 10. REFERENCES

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## 11. APPENDICES

***Table S1.*** *Full list of ISAR 95 core variables*

| Category | Variable field name | Recorded units |
|---|---|---|
| **Blood/Sputum** | *Highest blood eosinophil count within the past year* | *Decimal number* |
| | *Date of the highest blood eosinophil count within the past year* | *DD/MM/YYYY* |
| | *Was this the highest blood eosinophil count during an exacerbation event?* | *No/Yes* |
| | *The highest blood eosinophil count within the past year and not during exacerbation* | *Decimal number* |
| | *Date of highest blood eosinophil count within the past year and not during an exacerbation event* | *DD/MM/YYYY* |
| | *Current blood eosinophil count* | *Decimal number* |
| | *Date of current blood eosinophil count* | *DD/MM/YYYY* |
| | *The highest sputum eosinophil count within the past year (percentage)* | *Decimal number* |
| | *Date of the highest sputum eosinophil count within the past year* | *DD/MM/YYYY* |
| | *IgE count* | *Decimal number* |
| **Diagnostics** | *Chest CT scan* | *Normal/Abnormal/Not done* |
| | *Date of chest CT scan* | *DD/MM/YYYY* |
| | *Bone densitometry (DEXA)* | *No/Yes* |
| | *Date of bone densitometry (DEXA)* | *DD/MM/YYYY* |
| **Lung function** | *Pre-bronchodilator $FEV_1$* | *Decimal number* |
| | *Post-bronchodilator $FEV_1$* | *Decimal number* |
| | *Pre-bronchodilator FVC* | *Decimal number* |
| | *Post-bronchodilator FVC* | *Decimal number* |
| | *Predicted $FEV_1$* | *Decimal number (auto-calculated)* |

| | | |
|---|---|---|
| | *Pre-bronchodilator $FEV_1$ (% predicted)* | *Decimal number (auto-calculated)* |
| | *Post-bronchodilator $FEV_1$ (% predicted)* | *Decimal number (auto-calculated)* |
| | *Predicted FVC* | *Decimal number (auto-calculated)* |
| | *Pre-bronchodilator FVC (% predicted)* | *Decimal number (auto-calculated)* |
| | *Post-bronchodilator FVC (% predicted)* | *Decimal number (auto-calculated)* |
| | *$FEV_1$/FVC ratio pre-bronchodilator (%)* | *Decimal number (auto-calculated)* |
| | *$FEV_1$/FVC ratio post-bronchodilator (%)* | *Decimal number (auto-calculated)* |
| | *PC20 methacholine/histamine test* | *No/Yes* |
| | *Date of PC20 test* | *DD/MM/YYYY* |
| | *PC20 test result* | *Decimal number* |
| | *FeNO test* | *No/Yes* |
| | *Date of FeNO test* | *DD/MM/YYYY* |
| | *FeNO test result* | *Decimal number* |
| ***Allergen testing*** | *Environmental allergen test* | *Serum allergen test (CAP, ELISA, RAST)/SPT/not done* |
| | *Serum allergy test: Positive to perennial allergen* | *No/Yes* |
| | *Serum allergy test: Specify positive allergen and result* | *Dust mite (e.g. D. pteronyssinus)/grass mix/cat hair/mould mix/dog hair/Aspergillus/other (please specify)* |
| | *Date of serum allergy test* | *DD/MM/YYYY* |
| | *SPT: Positive to allergen* | *No/Yes* |
| | *SPT: Specify positive allergen and result* | *Grass mix/trees/weed mix/Aspergillus/mould mix/dust mite/food mix/animal mix/cat* |

| | | |
|---|---|---|
| | | *hair/dog hair/other (please specify)* |
| | *Date of SPT* | *DD/MM/YYYY* |
| ***Asthma control***[1] | *GINA Asthma Control Questionnaire* | |
| | *In the past 4 weeks, did the patient have:* | |
| | *Daytime symptoms more than twice per week* | *No/Yes* |
| | *Any activity limitation* | *No/Yes* |
| | *Any nocturnal symptoms/awakening* | *No/Yes* |
| | *Reliever medication use more than twice per week* | *No/Yes* |
| | *Lung function (PEF or $FEV_1$) <80% of predicted or personal best* | *No/Yes* |
| ***Asthma medication*** | *Maintenance oral corticosteroids* | *No/Yes* |
| | *Start date of oral corticosteroids* | *DD/MM/YYYY* |
| | *ICS + LABA combination therapy* | *No*<br>*Budesonide + Formoterol*<br>*Fluticasone furoate + Vilanterol*<br>*Fluticasone propionate + Salmeterol*<br>*Fluticasone propionate + Formoterol*<br>*Mometasone + Formoterol*<br>*Beclomethasone + Formoterol*<br>*Other* |
| | *Start/end date of ICS + LABA combination therapy* | *DD/MM/YYYY* |
| | *ICS (only)* | *No*<br>*Triamcinolone acetonide*<br>*Mometasone furoate*<br>*Fluticasone propionate*<br>*Fluticasone furoate* |

| | | |
|---|---|---|
| | | *Ciclesonide*<br>*Flunisonide*<br>*Budesonide*<br>*Beclomethasone dipropionate*<br>*Other* |
| | *Start/end date of ICS (only) therapy* | *DD/MM/YYYY* |
| | *LABA* | *No*<br>*Formoterol*<br>*Salmeterol*<br>*Indacaterol*<br>*Arformoterol*<br>*Olodaterol*<br>*Other* |
| | *Start/end date of LABA therapy* | *DD/MM/YYYY* |
| | *LAMA* | *No*<br>*Aclidinium*<br>*Tiotropium*<br>*Umeclidinium*<br>*Glycopyrronium*<br>*Other* |
| | *Start/end date of LAMA therapy* | *DD/MM/YYYY* |
| | *Theophyllines* | *No*<br>*Theophylline*<br>*Aminophylline*<br>*Other* |
| | *Start/end date of theophylline therapy* | *DD/MM/YYYY* |
| | *LTRA* | *No*<br>*Zafirlukast*<br>*Montelukast*<br>*Other* |

| | | |
|---|---|---|
| | *Start/end date of LTRA therapy* | *DD/MM/YYYY* |
| | *Anti-IgE treatment* | *No/Yes* |
| | *Start/end date of anti-IgE therapy* | *DD/MM/YYYY* |
| | *Anti-IL-5/IL-5R treatment, other* | *No*<br>*Reslizumab*<br>*Mepolizumab*<br>*Benralizumab*<br>*Other*[2] |
| | *Start/end date of anti-IL-5 therapy* | *DD/MM/YYYY* |
| | *Macrolide antibiotic treatment* | *No*<br>*Azithromycin*<br>*Clarithromycin*<br>*Erythromycin*<br>*Roxithromycin*<br>*Fidaxomicin*<br>*Telithromycin*<br>*Other* |
| | *Start/end date of macrolide antibiotic therapy* | *DD/MM/YYYY* |
| | *Other steroid-sparing agents* | *Free text* |
| ***Adherence*** | *Evidence of poor adherence*[3] | *No*<br>*Yes: Clinical impression*<br>*Yes: Objective measures*<br>*Yes: Prescription records* |
| | *Other factors contributing to severe asthma symptoms*[4] | *Free text* |
| ***Management plan*** | *Current clinical management plan*[5] | *Discharge to local service*<br>*Optimisation of current treatment*<br>*Biologic therapy (specific drug can be found in current medication)*<br>*Bronchial thermoplasty* |

| | | |
|---|---|---|
| | | *Maintenance oral corticosteroids*<br>*Steroid-sparing agent (specific drug can be found in current medication)*<br>*Enter into clinical trial*<br>*Other (please specify)* |

**CAP* immunoCAP test, *CT* computed tomography, *DEXA* dual energy X-ray absorptiometry, *ELISA* enzyme-linked immunosorbent assay, *FeNO* fractional exhaled nitric oxide, $FEV_1$ forced expiratory volume in 1 second, *FVC* forced vital capacity, *GINA* Global Initiative for Asthma, *ICS* inhaled corticosteroids, *IgE* immunoglobulin E, *IL-5* interleukin-5, *ISAR* International Severe Asthma Registry, *LABA* long-acting $\beta_2$-agonist, *LAMA* long-acting muscarinic antagonist, *LTRA* leukotriene receptor antagonist, *PC20* provocative concentration of methacholine/histamine needed to produce a 20% decrease in $FEV_1$, *PEF* peak expiratory flow, *RAST* radio-allergosorbent test, *SPT* skin prick test.

[1]Asthma Control Questionnaire or the Asthma Control Test are optional extras for this category (depending on registry preference).

[2]Other new biologics will be added once approved and in use.

[3]Poor adherence to treatment can be indicated by selecting either (a) or (b):

(a) Clinical impression: opinion of a medical personnel

E.g. i) Impression of 'non-persistence': patient stops taking medication.

ii) Impression of 'non-conformation': patient does not take medication as prescribed.

(b) Prescription records: evidenced by medical records detailing prescriptions being issued and inadequately filled.

E.g. Medication possession ratio (MPR) = (Sum of days' supply for all fills/Number of days) x 100% <80% threshold.

[4]Calls for a trained clinician's perception or opinion on any other external factors (if any) potentially contributing to the severe asthma symptoms.

E.g. Weather (cold air), air pollution, physical activity (exercise-induced asthma symptoms), occupational triggers (workplace irritants, gases, chemical fumes, dust), strong smells (perfumes), prior respiratory infections.

[5]Aims to record the asthma action plan for a patient to review efficacy over time.

E.g. i) Entry into clinical trial: If patient can benefit from a clinical trial drug.

ii) Discharge to local asthma service: If patient has shown alleviated asthma symptoms.

iii) Optimisation of current asthma therapy: If patient's current asthma therapy is titrated for better asthma management.

iv) Bronchial thermoplasty: If patient is eligible to have a surgery to manage their asthma.

v) Biologic therapy: If patient is prescribed biologic therapy.

vi) Others: Asthma education and inhaler use education.

**Table S2**: International Severe Asthma Registry bolt-on variables

| Category | Variables |
|---|---|
| **Safety** | |
| Severe infection | • Infection type<br>• Start and end dates<br>• Outcome of infection<br>• Site of infection |
| Malignancy | • Malignancy history, type, stage, status and diagnosis confirmation<br>• Start and end dates<br>• Outcome of malignancy<br>• Site of malignancy |
| Anaphylactic reaction | • Likely exposure of the reaction<br>• Time to reaction<br>• Date of the reaction<br>• Outcome of the anaphylactic reaction |
| **Effectiveness** | |
| Comorbidities | • Osteoporosis<br>• Osteoporosis: Start date<br>• Circulatory system disease<br>• Circulatory system disease: Type<br>• Circulatory system disease: Start date<br>• Glaucoma or cataract disease<br>• Ocular disease: Type<br>• Ocular disease: Start date<br>• Obstructive sleep apnoea<br>• Obstructive sleep apnoea: Start date<br>• Renal failure<br>• Renal failure: Start date<br>• Depression<br>• Depression: Start date<br>• Anxiety<br>• Anxiety: Start date<br>• Type II diabetes mellitus<br>• Type II diabetes mellitus: Start date<br>• Peptic ulcer<br>• Peptic ulcer: Start date<br>• Pneumonia<br>• Pneumonia: Start date |
| Dosage | • Label dose for oral corticosteroids<br>• Frequency for oral corticosteroids<br>• Label dose for inhaled corticosteroids<br>• Frequency for inhaled corticosteroids |

| | |
|---|---|
| Exacerbation history | • Dates of exacerbations indicated<br>• Type of rescue steroid used with label dose, frequency, start and end dates |
| Medication switching | • Reason for switch in patient's asthma medication/treatment |