Study Protocol

Characteristics of type 2 asthma phenotypes and OCS use in ISAR (STAR)

A study of the prevalence of type 2 asthma and the association between OCS use (intermittent OCS use versus long-term OCS use) and asthma clinical characteristics in the International Severe Asthma Registry

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TITLE	Characteristics of type 2 asthma phenotypes and OCS use in ISAR (STAR)
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Study aims and objectives	**Study aims:** To characterise patients by asthma phenotypes and OCS use prior to initiation of biological treatment **Study objectives:** **Objective 1**: To describe patients 18 years of age or older with GINA 4/5 asthma, enrolled in ISAR, by OCS use and biomarker distribution, type 2 characteristics and individual biomarkers, prior to biologic initiation **Objective 2**: To describe the population of patients 18 years of age or older, with GINA 4/5 asthma, enrolled in ISAR, who present with low eosinophilic phenotypes and long-term OCS use prior to biologic initiation
Countries of study	22 countries: Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Korea, Kuwait, Mexico, Poland, Portugal, Saudi Arabia, Spain, Taiwan, United Arab Emirates (UAE), United Kingdom (UK), United States of America (USA)
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LIST OF ABBREVIATIONS

Abbreviation or special term	**Explanation**
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADEPT	Anonymised Data Ethics & Protocol Transparency
AD	Atopic dermatitis
AR	Allergic rhinitis
Anti-IgE	Anti-immunoglobulin E
Anti-IL4/13	Anti-interleukin 4/13
Anti-IL5/5R	Anti-interleukin 5/5-receptor
BEC	Blood eosinophil count
COPD	Chronic obstructive pulmonary disease
CRS	Chronic rhinosinusitis
EOE	Eosinophilic oesophagitis
FeNO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroids
IgE	Serum immunoglobulin E
IQR	Interquartile range
ISAR	International Severe Asthma Registry
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
LTOCS	Long-term oral corticosteroids
NP	Nasal polyps
OCS	Oral corticosteroids
OPC	Optimum Patient Care
OPRI	Observational and Pragmatic Research Institute
ppb	Parts per billion
SCS	Systemic corticosteroids
SD	Standard deviation

1.0 Background

An estimated 5-10% of the asthma population suffers from severe asthma, defined by the European Respiratory Society and American Thoracic Society's 2014 guidelines as asthma that requires high-dose inhaled corticosteroid (ICS) treatment plus a second controller and/or oral corticosteroids (OCS) to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy (1). A variety of cellular pathways are activated in patients with severe asthma. Allergy, eosinophilic inflammation, and airway epithelial dysregulation have each been implicated in the pathogenesis of severe asthma (2).

According to the Global Initiative for Asthma (GINA) 2021 recommendations, Type 2 inflammation is found in the majority of people with asthma, is characterized by raised blood eosinophils (BEC) or fractional exhaled nitric oxide (FeNO), and is generally refractory to high-dose ICS in patients with severe asthma (3). GINA states that the possibility of refractory type 2 inflammation should only be considered if any of the following are found while the patient is taking high-dose ICS or daily OCS:

- Blood eosinophils ≥150/µL, and/or
- FeNO ≥20 ppb, and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen-driven (3).

Further to GINA recommendations, previous studies from the Observational and Pragmatic Research Institute (OPRI) have assessed the prevalence of the eosinophilic phenotype in patients with asthma, as well as the association between eosinophilic asthma phenotypes and asthma outcomes.

An evidence-based eosinophil gradient algorithm was developed by expert consensus to categorize patients from the International Severe Asthma Registry (ISAR) according to their likelihood of their eosinophilic phenotype, using characteristics such as high BEC, long-term OCS (LTOCS) use, raised FeNO, nasal polyps and adult-onset asthma (Table 1) (4). The eosinophilic phenotype was predominant in severe asthma: 83.8% of patients were most likely eosinophilic and 1.6% of patients were non-eosinophilic (4). Patients with eosinophilic severe asthma were more likely to have poorer lung function and adult-onset asthma than those with non-eosinophilic severe asthma (4). This study was thought to have influenced the change in GINA's statements on the prevalence of eosinophilic asthma: in 2020, GINA stated that Type 2 inflammation is found in ~50% of people with severe asthma; in 2021, GINA recognised that Type 2 inflammation is found in the majority of people with severe asthma (3).

Table 1. Characterisation of eosinophilic and noneosionphilic phenotypes and the proportion of patients with these phenotypes in ISAR (4)

Highest BEC Available (cells/μL)[a]	Treatment or Clinical Characteristic	Eosinophilic Phenotype	Prospective ISAR Population (N = 1,716) [Original Algorithm]		Prospective ISAR Population (N = 1,716) [Original Algorithm Minus Age of Onset]		Prospective ISAR Population (N = 1,716) [Original Algorithm Minus FENO]	
			No. (%)	(%)	No. (%)	%	No. (%)	%
≥ 300		Grade 3: most likely	1,196 (69.7)	83.8	1,196 (69.7)	82.6	1,196 (69.7)	82.7
Anti-IL5		Grade 3: most likely	178[b] (10.4)		178[b] (10.4)		178[b] (10.4)	
≥ 150-< 300	Long-term OCS	Grade 3: most likely	37 (2.2)		37 (2.2)		37 (2.2)	
	Presence of ≥ 2 of the following: NP, FENO ≥ 25 ppb, or adult onset[c] (no long-term OCS)	Grade 3: most likely	27 (1.6)		7 (0.4)		8 (0.5)	
	Either NP, FENO ≥ 25 ppb or adult onset (no long-term OCS)	Grade 2: likely	67 (3.9)	3.9	45 (2.6)	2.6	71 (4.1)	4.1
	No NP, elevated FENO, adult onset, or long-term OCS	Grade 1: least likely	27 (1.6)	1.6	69 (4.0)	4.0	42 (2.4)	2.4
< 150	Long-term OCS	Grade 2: likely	75 (4.4)	4.4	75 (4.4)	4.4	75 (4.4)	4.4
	Either NP, FENO ≥ 25 ppb or adult onset (no long-term OCS)	Grade 1: least likely	81 (4.7)	4.7	40 (2.4)	2.4	64 (3.7)	3.7
	No NP, elevated FENO, adult onset, or long-term OCS	Grade 0: unlikely (non-eosinophilic)	28 (1.6)	1.6	69 (4.0)	4.0	45 (2.6)	2.6

The predominance of the eosinophilic phenotype was also observed across all asthma severities when the ISAR eosinophil gradient algorithm was applied to a primary care cohort in the UK (5). 72.5% of patients had most likely or likely eosinophilic phenotypes and 5.6% of patients were non-eosinophilic (5). Patients with most likely eosinophilic asthma tended to have more comorbidities, poorer asthma control, and greater healthcare resource use than those with non-eosinophilic asthma (5). These findings suggest that asthma phenotyping should become part of routine clinical practice in primary care (5). Patients with eosinophilic asthma phenotypes may benefit from earlier intervention with Type 2 targeted treatments, including ICS and steroid-sparing therapies such as biologics (5).

In an OPRI study funded by Regeneron/Sanofi, it was demonstrated that 56-60% of UK primary care patients with asthma across all GINA steps received a medical diagnosis of at least one other co-existing type 2 inflammatory disease (6). Patients with asthma had co-existing Type 2 inflammatory diseases in three distinct clusters: 1) food allergy and anaphylaxis; 2) chronic rhinosinusitis and NP; 3) allegic rhinitis, eczema, allergic conjunctivitis and urticaria (6). Furthermore, increased co-existing type 2 inflammatory disease burden (greater number of co-existing Type 2 comorbidities) was associated with increased likelihood of experiencing ≥2 asthma exacerbations and decreased likelihood of achieving asthma control (6). This highlighted the clinical importance of assessing Type 2 comorbidity burden in patients with moderate-to-severe asthma (6).

While Type 2 targeted treatments currently exist for severe eosinophilic or allergic asthma, effective treatments are lacking for noneosinophilic asthma (7). Patients with non-Type 2 asthma are characterized by the absence of eosinophilia and poor response to standard asthma treatments such as ICS, which could result in greater disease severity and poorer asthma control (7). Pathways hypothesized to result in noneosinophilic asthma include neutrophilic inflamation, Th1 inflammation, Th17 inflammation and corticosteorid insensitivity

(8). The phenotyping of noneosinophilic asthma is essential to identify treatable traits and enable the delivery of precision medicine to these patients (7).

In addition, OPRI research on chronic obstructive pulmonary disease (COPD) in UK primary care patients has shown that BEC <150 cells/µL was associated with poorer outcomes, including hospital admission within a few days of COPD exacerbation and short-term readmission after discharge (9). Furthermore, patients with low BEC had poorer response to OCS than those with higher BEC (9). These findings suggest that the characterisation of patients with low BEC, such as through the identification of biomarkers and clinical features, could support treatment choice and improve their asthma outcomes (9).

OPRI's research has shed light on the predominance of eosinophilic severe asthma and the problem of low eosinophilic phenotypes in respiratory disease. Nevertheless, there is opportunity to enhance our understanding of the Type 2 characteristics (i.e., biomarkers and concomitant disease) and OCS use (i.e., intermittent OCS use versus long-term OCS use) of severe asthma patients prior to biologic initiation. This would help severe asthma specialists identify treatable traits and patients suitable for biologic treatment. Furthermore, current understanding of low eosinophilic phenotypes in severe asthma is limited; therefore the characterization of severe asthma patients with BEC <150 cells/µL would facilitate the delivery of precision medicine to these patients.

OPRI holds a unique partnership with The International Severe Asthma Registry (ISAR), which enrols patients 18 years of age or older who are receiving GINA 2018 Treatment Step 5, or who have uncontrolled asthma (defined as frequent severe exacerbations requiring OCS or severe asthma symptoms) while receiving GINA 2018 Treatment Step 4. ISAR has a unique database of over 13,000 patients with severe asthma (retrospectively and prospectively captured), drawn from 25 countries worldwide, which can be used to conduct retrospective and prospective real-world database studies. Therefore, ISAR provides sufficient statistical power to characterize severe asthma patients by Type 2 characteristics and OCS use, as well as those with BEC <150 cells/µL.

2.0 Study Aims and Objectives

2.1 Study Aims

To characterise patients by asthma phenotype, endotypes and OCS use prior to initiation of biological treatment.

2.2 Study Objectives

Objective 1: To describe patients 18 years of age or older with GINA 4/5 asthma, enrolled in ISAR, by OCS use and biomarker distribution, Type 2 characteristics and individual biomarkers, prior to biologic initiation.

Objective 2: To describe the population of patients 18 years of age or older, with GINA 4/5 asthma, enrolled in ISAR, who present with low eosinophilic phenotypes and who have long-term OCS use prior to biologic initiation.

3.0 Study Design

The study will aim to better understand the unmet needs of patients with severe asthma and to assess whether there are missed opportunities for personalised medicine. It will stimulate discussion with key opinion leaders regarding guidelines reform and future research needs in the severe asthma space.

Objective 1: A **retrospective cross-sectional cohort study**, including adults with severe asthma enrolled in ISAR (from 2018 to 2022) prior to biologic initiation, described by OCS use and biomarker distribution, Type 2 characteristics and individual biomarkers. The data will be assessed to classify patients and characterise the prevalence of three distinct patient cohorts:

1. No intermittent OCS use prior to biologic initiation, and
2. Intermittent OCS use prior to biologic initiation, and
3. Long-term OCS use prior to biologic initiation.

Objective 2: A **retrospective cross-sectional cohort study** to characterise adults with severe asthma enrolled in ISAR (from 2018 to 2022) prior to biologic initiation with low eosinophils (<150 cells/µL) and long-term OCS use.

For Objectives 1 and 2, the date of first biologic initiation at or post-ISAR enrollment will be used as the index date.

4.0 Study Population

4.1 Data Sources

ISAR is a collaborative initiative comprising existing and new registries that builds on data from multiple nations and regions and increases the statistical power and comparability of data (10). It is the first global adult severe asthma registry to be established and holds data on the following key variables for classifying study populations for this study question:

Type 2 Comorbidities (history of diagnoses at the index date [date of first biologic initiation at or post-ISAR enrolment)

- Eczema
- Allergic rhinitis
- Chronic rhinosinusitis with or without recognized nasal polyps diagnosed by pulmonologists/allergists
- Nasal polyps

Type 2 Biomarkers (highest available measurements before and on the date of biologic initiation)

- Blood eosinophil counts
- IgE count
- FeNO

Type 2 Allergy Testing (most recent allegen test information before and on the date of biologic initiation)

- Specific IgE test
- Skin prick test.

ISAR also contains variables on demographics, diagnostic measurements, therapy and asthma clinical characteristics, which are detailed in Section 5.0.

4.2 Inclusion and Exclusion Criteria

Patients will be included from the participating existing and newly created local or regional registries in ISAR.

Inclusion Criteria:

- Patients, 18 years of age or older at the index date (date of first biologic initiation at or post-ISAR enrolment), with a diagnosis of severe asthma which requires treatment with GINA 2018 recommended medications (11):
    - GINA Treatment Step 4 (medium- or high-dose ICS-LABA therapy) and uncontrolled asthma (poor symptom control with or without frequent exacerbations [≥2/year] requiring OCS or serious exacerbations [≥1/year] requiring hospitalization) OR
    - GINA Treatment Step 5 (with or without add-on LAMA or biologic therapy)
- Registry data for a minimum of one year after asthma phenotype classification
- Initiation of first biologic treatment at or post-enrollment into ISAR.

For Objective 2, an additional criterion is BEC <150 cells/µL (highest BEC measurement at or before biologic initiation).

Exclusion Criteria:

- Received bronchial thermoplasty
- Receiving biologics at or after enrollment into ISAR and had missing biologic initiation date, or had no pre-biologic assessment.

5.0 Study Variables and Definitions

The following variables will be used to derive an analysis dataset suitable for the objectives of the study.

5.1 Patient demographic and clinical characteristics to be described in Objectives 1 and 2

For Objective 1, demographic and clinical characteristics will be described for GINA Steps 4/5 patients with no, intermittent and long-term OCS use. For Objective 2, demographic and clinical characteristics will be described for GINA Steps 4/5 patients with BEC<150 cells/µL (highest BEC measurement at or before biologic initiation) and long-term OCS use.

Patient demographics	
Age	Age in completed years at the index date (date of first biologic initiation at or post-ISAR enrolment).
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 (most recent status before starting biologics)
Comorbidities (history of diagnoses at the index date [date of first biologic initiation at or post-ISAR enrolment])	
Type 2 comorbidities	Number of comorbidities reported from the following list: Allergic Rhinitis, Chronic Rhinosinusitis with or without recognized nasal polyps diagnosed by pulmonologists/allergists, Eczema, Nasal Polyps, Eosinophilic Esophagitis (EOE)[1]
OCS-related comorbidities	Number of comorbidities reported from the following list: Anxiety, Depression, Osteoporosis, Type II Diabetes, Peptic Ulcer, Pneumonia, Obstructive Sleep Apnea, Renal Failure, Heart Failure, Myocardial Infarction, Venous Thromboembolism/ Pulmonary Embolism, Cataract, Glaucoma
Comorbidities that mimick or exacerbate asthma	Chronic obstructive pulmonary disease (COPD)[2]
Biomarkers (highest available measurements before and on the date of biologic initiation)	

[1] As EOE is not part of ISAR's core variable set, the availability of data for this variable will be limited
[2] As COPD is not part of ISAR's core variable set, the availability of data for this variable will be limited

Blood eosinophil count	Count of blood eosinophils (cells/µL). Categorised as: BEC <150 cells/µL, BEC ≥150 - <300 cells/µL, BEC ≥300 - <500 cells/µL and BEC ≥500 cells/µL.
Blood IgE level	Blood level IgE (IU/mL). Categorised as: IgE <30 IU/mL, IgE ≥30 - <75 IU/mL and IgE ≥75 IU/mL.
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. Categorised as: FeNO <20 ppb and FeNO ≥20 ppb; FeNO <25 ppb and FeNO ≥25 ppb.
Lung function and allergen tests (most recent lung function and allergen test information before and on the date of biologic initiation)	
Predicted FEV1	Predicted value of forced expiratory volume in the first second of expiration (L).
Post-bronchodilator FEV1	Measured forced expiratory volume in the first second of expiration, after the use of a bronchodilator (L).
Postbronchodilator FEV1 (% predicted)	Measured forced expiratory volume in the first second of expiration, after the use of a bronchodilator (L) as a percentage (%) of predicted FEV1 value
Predicted FVC	Predicted value of forced vital capacity (FVC) in the first second of expiration (L).
Postbronchodilator FVC (% predicted)	Measured forced vital capacity, after the use of a bronchodilator (L) as a percentage (%) of predicted FVC value
Post-bronchodilator FVC	Forced vital capacity, after the use of a bronchodilator (L).
Post-bronchodilator FEV1/FVC Ratio	Measured FEV1 as a ratio of measured FVC.
Skin Prick Test	Positive skin prick test
Specific IgE Test	Positive specific IgE test
Therapy in addition to ICS/LABA (at the index date [date of first biologic initiation at or post-ISAR enrolment])	
Long-term OCS	Long-term (maintenance) oral corticosteroids (OCS) - OCS use for a duration of >90 days (3 months) prior to the index date (date of first biologic initiation at or post-ISAR enrolment)
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
LAMA	Prescription for LAMA (add-on therapy to ICS/LABA)
LTRA	Precription for LTRA (add-on therapy to ICS/LABA)
LAMA + LTRA	Prescripton for LAMA + LTRA (add-on therapy to ICS/LABA)
Theophylline	Prescription for theophylline (add-on therapy to ICS/LABA)
Asthma control	

Number of asthma exacerbations	Number of exacerbations requiring rescue steroids in the year prior to index date (date of first biologic initiation at or post-ISAR enrolment)
Asthma control in the past 4 weeks	Categorised as controlled, partly controlled, or uncontrolled according to the GINA Asthma Control Criteria/Asthma Control Questionnaire (ACQ-6)/Asthma Control Test (ACT)
Cumulative dose of oral corticosteroids in the last 90 days	Label Dose X Frequency x 90 days of long-term OCS
Total dose of oral corticosteroids	Label Dose X Frequency X Duration of Use for long-term OCS and rescue steroids in the year prior to index date (date of first biologic initiation at or post-ISAR enrolment)
Healthcare resource utilization	
Number of hospital admissions	Annualized number of hospital admissions in the year prior to index date (date of first biologic initiation at or post-ISAR enrolment)
Number of emergency room visits	Annualized number of emergency room visits in the year prior to index date (date of first biologic initiation at or post-ISAR enrolment)

5.2 Prevalence of Type 2 characteristics by OCS use to be described in Objective 1

The prevalence of Type 2 characteristics, as defined by biomarkers or concomitant Type 2 disease, will be presented for patients with GINA 4/5 asthma:

- No intermittent OCS use
- Intermittent OCS use
- Long-term OCS use

Prevalence of Type 2 asthma as defined by BEC/ FeNO / IgE biomarker combinations	• BEC ≥150 cells/µL OR FeNO ≥ 20 ppb • BEC ≥150 cells/µL OR FeNO ≥ 25 ppb • BEC <150 cells/µL AND FeNO ≥ 20 ppb • BEC <150 cells/µL AND FeNO ≥ 25 ppb • BEC <150 cells/µL AND FeNO < 20 ppb • BEC <150 cells/µL AND FeNO < 25 ppb • BEC ≥150 cells/µL AND FeNO < 20 ppb • BEC ≥150 cells/µL AND FeNO < 25 ppb • BEC ≥150 cells/µL AND FeNO > 20 ppb • BEC ≥150 cells/µL AND FeNO > 25 ppb • BEC ≥150 cells/µL OR FeNO ≥ 20 ppb OR Total IgE ≥30 IU/mL • BEC ≥150 cells/µL OR FeNO ≥ 25 ppb OR Total IgE ≥30 IU/mL •
Prevalence of Type 2 asthma as	• Nasal Polyps (NP) • Atopic Dermatitis (AD)

defined by concomitant Type 2 disease[3]	• Allergic Rhinitis (AR) • Chronic rhinosinusitis (CRS) with or without recognized nasal polyps diagnosed by pulmonologists/allergists • Eosinophilic Esophagitis (EOE) • NP or AD or AR or CRS or EOE

6.0 Statistical Analysis

6.1 Sample Size

The final sample size will depend on the number of individuals with available data on biomarkers, OCS use and Type 2 comorbidities.

6.2 Software

Analysis will be undertaken in STATA and R. Datasets will be received from the data analytics team in CSV, which can be easily imported into both STATA and R.

6.3 Analysis

The distributions of pre-biologic visit dates before the index date (date of first biologic initiation at or post-ISAR enrolment), and before the index date plus 42 days, will be described for patients who initiated their first biologic treatment at or post-enrolment into ISAR.[4]

Approach to analyses of variables:

- **Age**: at the index date (date of first biologic initiation at or post-ISAR enrolment)
- **Comorbidities**: history of diagnoses at the index date (date of first biologic initiation at or post-ISAR enrolment)
- **Biomarkers**: highest available measurements before and on the date of biologic initiation
- **Lung function and allergen tests**: most recent information before and on the date of biologic initiation
- **Therapy**: at the index date (date of first biologic initiation at or post-ISAR enrolment)

Objective 1:
As this is a descriptive analysis no inferential statistics will be performed. Continuous variables will be summarised using means, standard deviations (SD), medians and interquartile ranges (IQR). Categorical variables will be shown as number and percentage (%). Summary results will be presented separately for the 'no intermittent OCS use', 'intermittent OCS use' and 'long-term OCS use' cohorts.

[3] As EOE is not part of ISAR's core variable set, the availability of data for this variable will be limited
[4] Up to six weeks are allowed for the entry of data regarding biologic initiation. Although data from a patient may be entered into an electronic medical record upon clinical attendance, the data is not submitted into the electronic case report form in ISAR until up to six weeks later, in some cases.

Objective 2:
As this is a descriptive analysis no inferential statistics will be performed. Continuous variables will be summarised using means, standard deviations (SD), medians and interquartile ranges (IQR). Categorical variables will be shown as number and percentage (%). Summary results will be presented separately for the 'long-term OCS use' cohort.

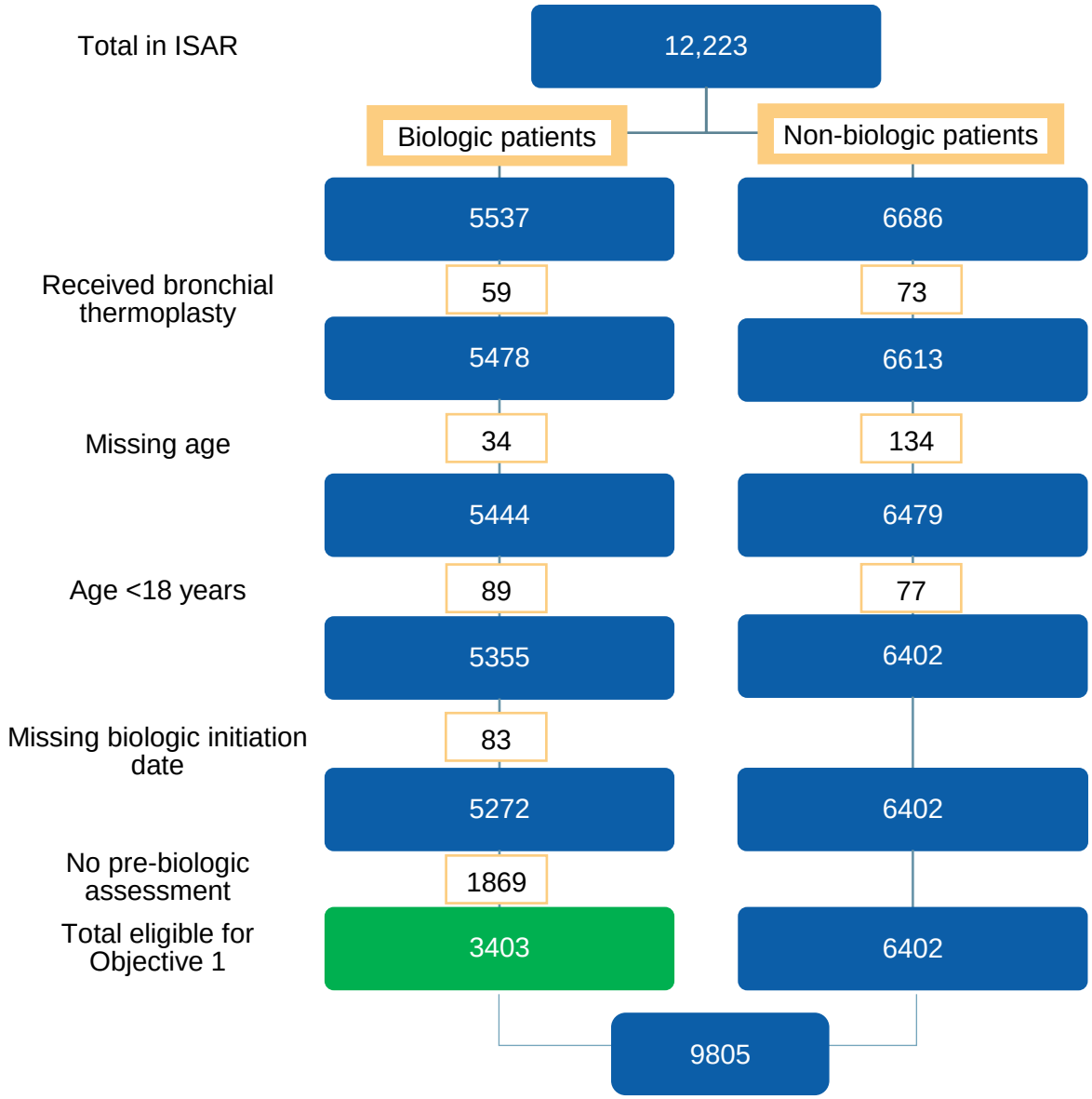
The templates for the results tables are given in Appendix 1.

7.0 Feasibility Assessment

An initial analysis of the International Severe Asthma Registry showed 12,223 patients across 22 countries available for data.

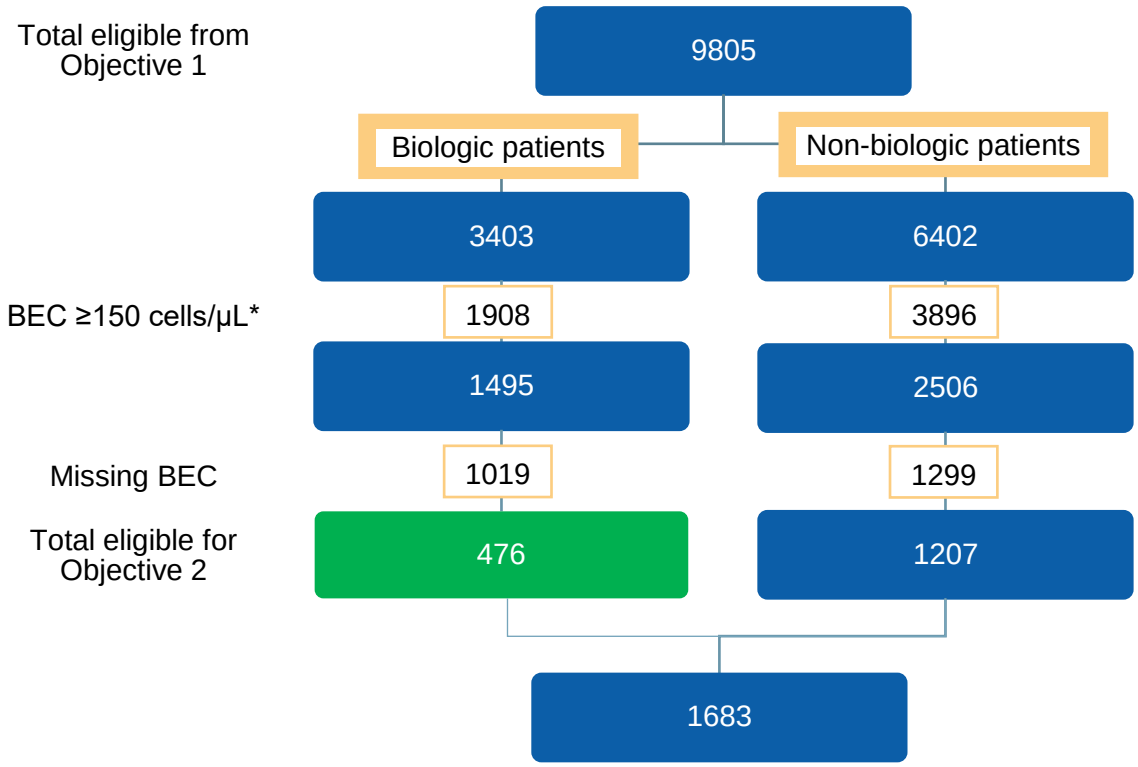
For Objective 1, 61.5% (n=3,403) of 5,537 patients receiving biologics were available for analysis after excluding those aged <18 years, had received bronchial thermoplasty, had no pre-biologic assessment, or had missing data on age and biologic initiation date.

Patient flow for Objective 1



For Objective 2, 14% (n=476) of 3,403 patients receiving biologics from Objective 1 were available for analysis as they had BEC <150 cells/µL (highest BEC measurement pre-biologic initiation), after excluding those with missing BEC.

Patient flow for Objective 2



*Highest BEC measurement pre-biologic initiation

8.0 Regulatory and Ethical Compliance

This study was designed and shall be implemented and reported in accordance with the criteria of the "European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)" and follows the ENCePP Code of Conduct (EMA 2014). Once a final version of the protocol has been agreed and reviewed by the advisory group, this study will be registered with ENCePP (www.encepp.eu).

ISAR is approved by the Health Research Authority for clinical research use, and governed by the Anonymised Data Ethics & Protocol Transparency (ADEPT) Committee. We will submit the finalised version of this protocol to the ADEPT committee (https://www.regresearchnetwork.org/adept-committee/) for approval.

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 organisations. Further, all data extracted to be transferred from sites will be hashed and will enter the research database in the form of anonymised patient IDs. The data will be retrieved by OPC data analysts and utilised as an anonymised dataset to perform the analysis according to protocol. This 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.

9.0 Data Dissemination

The results will be disseminated to the public through publications in peer reviewed journals, alongside abstract presentations at relevant conferences. Authorship will be determined through the ISAR authorship policy.

10.0 Advisory Group

Professor David Price, Chief Investigator for the study, is the chair of the ISAR Steering Committee (ISC). Other members of the ISC, as listed in the following table, will form the Advisory Group.

Project Steering Committee Member	**Country/Funder**
Jorge Maspero	Argentina
Mark Hew	Australia
Matthew Peters	
Peter G. Gibson	
George C. Christoff	Bulgaria
Todor A. Popov	
Mohsen Sadatsafavi	Canada
Celine Bergeron	
Carlos A. Torres-Duque	Colombia
Celeste M. Porsbjerg	Denmark
Nikolaos G. Papadopoulos	Greece
Andriana I. Papaioannou	
Sundeep Salvi	India
Richard W. Costello	Ireland
Enrico Heffler	Italy
Giorgio Walter Canonica	
Takashi Iwanaga	Japan
Chin Kook Rhee	South Korea
Mona Al-Ahmad	Kuwait
Désirée Larenas-Linnemann	Mexico
Piotr Kuna	Poland
João A. Fonseca	Portugal
Riyad Al-Lehebi	Saudi Arabia
Borja G. Cosio	Spain
Luis Perez-de-Llano	
Diahn-Warng Perng (Steve)	Taiwan
Bassam Mahboub	UAE
Andrew N. Menzies-Gow	UK
David J. Jackson	
John Busby	
Liam G. Heaney	
Paul E. Pfeffer	
Eileen Wang	USA
Michael E. Wechsler	
Jason Wang	Regeneron/Sanofi
Rebecca Gall	
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11.0 Research Team

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12.0 Timelines

Action	Timeline
Contract signature	11/02/2022
Literature search & draft protocol	05/04/2022
Full Protocol delivery	15/07/2022
Protocol sign-off	17/10/2022
Dataset delivery + ADEPT approval	28/11/2022
Analyses	16/01/2022
Final study report	13/02/2022
Study report sign-off	27/02/2023
Conference abstract	TBC
Manuscript	TBC

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14.0 Appendices

14.1 Proposed results tables for Objective 1

Demographic and clinical characteristics of patients with GINA 4/5 asthma according to patterns of OCS use

	No Intermittent OCS use); N=xx	Intermittent OCS use); N=xx	Long-term OCS use, N=xx
GINA Treatment Step (at ISAR enrolment)			
GINA 2018 Step 4 and uncontrolled asthma, n (%)			
GINA 2018 Step 5, n (%)			
Gender			
Non-missing, n (%)			
Female, n (%)			
Age (at the date of first biologic initiation at or post-ISAR enrolment)			
Non-missing, n (%)			
Mean (SD)			
18-34, n (%)			
35-54, n (%)			
55-79, n (%)			
≥80, n (%)			
BMI			
Non-missing, n (%)			
Underweight (<18.5), n (%)			
Normal (≥18.5-<25), n (%)			
Overweight (≥25 - <30), n (%)			
Obese (≥30), n (%)			
Smoking status			
Non-missing, n (%)			
Current smokers, n (%)			
Ex-smokers, n (%)			
Never-smoked, n (%)			
Age of asthma onset (years)			
Non-missing, n (%)			
Mean (SD)			
<18, n (%)			
≥18, n (%)			
OCS-related comorbidities (history of diagnoses at the index date [date of first biologic initiation at or post-ISAR enrolment])			
Non-missing, n (%) Anxiety, n (%)			
Non-missing, n (%) Depression, n (%)			
Non-missing, n (%) Osteoporosis, n (%)			
Non-missing, n (%) Type II diabetes, n (%)			

Non-missing, n (%) Peptic ulcer, n (%)			
Non-missing, n (%) Pneumonia, n (%)			
Non-missing, n (%) Obstructive sleep apnoea, n (%)			
Non-missing, n (%) Renal failure, n (%)			
Non-missing, n (%) Heart failure, n (%)			
Non-missing, n (%) Myocardial infarction, n (%)			
Non-missing, n (%) Venous thromboembolism/ pulmonary embolism, n (%)			
Non-missing, n (%) Cataract, n (%)			
Non-missing, n (%) Glaucoma, n (%)			
Comorbidity that mimicks/exacerbates asthma (history of diagnoses at the index date [date of first biologic initiation at or post-ISAR enrolment])			
Non-missing, n (%) COPD, n (%)			
Biomarkers (highest available measurement before and on the date of biologic initiation)			
BEC (cells/µL), non-missing n (%)			
<150, n (%)			
≥150 - <300, n (%)			
≥300 - <500, n (%)			
≥500, n (%)			
IgE (IU/mL), non-missing n (%)			
<30, n (%)			
≥30 - <75, n (%)			
≥75, n (%)			
FeNO (ppb), non-missing n (%)			
<20, n (%)			
≥20, n (%)			
<25, n (%)			
≥25, n (%)			
Lung function and allergen tests (most recent information before and on the date of biologic initiation)			
Post-BD FEV_1 % predicted, non-missing n (%) Mean (SD)			
Post-BD FVC % predicted, non-missing n (%) Mean (SD)			
Post-BD FEV_1/FVC, non-missing n (%) Mean (SD)			

<0.7, n (%)			
Skin prick test, non-missing n (%)			
Positive skin prick test, n (%)			
Specific IgE test, non-missing n (%)			
Positive specific IgE test, n (%)			
Therapy in addition to ICS/LABA (at the date of first biologic initiation at and post-ISAR enrolment)			
Long-term OCS, non-missing n(%) Long-term OCS, n (%)			
Anti-IgE, n (%)			
Anti-IL5/5R, n (%)			
Anti-IL4/13, n (%)			
Add-on to ICS/LABA			
LAMA, non-missing n(%) LAMA, n(%)			
LTRA, non-missing n(%) LTRA			
LAMA + LTRA, non-missing n(%) LAMA + LTRA			
Theophylline, non-missing n(%) Theophylline			
Asthma Control*			
Asthma control, non-missing n (%)			
Not controlled, n (%)			
Partially controlled, n (%)			
Well controlled, n (%)			
Asthma exacerbations, non-missing n (%)			
Mean (SD)			
Median (IQR)			
0, n (%)			
1, n (%)			
2, n (%)			
3, n (%)			
≥4, n (%)			
Total annual OCS dose, non-missing n (%) Mean (SD)			
Healthcare resource utilization			
ED visit, non-missing n (%)			
Mean (SD)			
0, n (%)			
1, n (%)			

≥2, n (%)			
Hospitalization, non-missing n (%)			
Mean (SD)			
0, n (%)			
1, n (%)			
≥2, n (%)			

GINA 2018 recommendations[1] were used to classify patient cohorts:

- GINA Treatment Step 4 (medium- or high-dose ICS-LABA therapy) and uncontrolled asthma (poor symptom control ± frequent exacerbations [≥2/year] requiring OCS or serious exacerbations [≥1/year] requiring hospitalization) OR
- GINA Treatment Step 5 (with or without add-on LAMA or biologic therapy).

*Asthma control is defined in ISAR using either GINA ACA[2], ACQ[3,4,5] or ACT[6,7]:

- Well controlled: GINA ACA 0 "yes"; mean ACQ ≤0.75; total ACT >19
- Partially controlled: GINA ACA 1-2 "yes"; 0.75< mean ACQ <1.5; 15< total ACT ≤19
- Not controlled: GINA ACA 3-4 "yes"; mean ACQ ≥1.5; total ACT ≤15.

GINA ACA[2]: In the past 4 weeks, has the patient had:

- Daytime asthma symptoms more than twice/week?
- Any night waking due to asthma?
- Reliever needed for symptoms more than twice/week?
- Any activity limitation due to asthma?

Non-missing data refers to the number (and percentage) of patients who have available data for the specific variable(s), and serves as the denominator for the calculation of patient proportions in the categories shown.

ACA: asthma control assessment; ACQ: Asthma Control Questionnaire; ACT: Athma Control Test; BD: bronchodilator; BEC: blood eosinophil count; BMI: body mass index; ED: emergency department; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; ICS: inhaled corticosteroid; IgE: Immunoglobulin E; ISAR: International Severe Asthma Registry; LAMA: long-acting muscarinic receptor antagonist; LABA: long-acting β_2-agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid; SD: standard deviation.

[1]*Global Initiative for Asthma (GINA). GINA difficult-to-treat and severe asthma in adolescent and adult patients - Diagosis and management [Internet]. 2018 Nov [cited 2022 Mar 24]. Available from: https://ginasthma.org/wp-content/uploads/2018/11/GINA-SA-FINAL-wms.pdf*
[2]*Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention [Internet]. 2019 [cited 2022 April 22]. Available from: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf*
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[4]*Werner CU et al. NPJ Pri Care Resp Med 2017;27:64*
[5]*Juniper EF et al. Eur Respir J. 1999;14:902-907*
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[7]*Schatz M et al. J Allergy Clin Immunol 2006;117:549-556*

Prevalence of Type 2 characteristics of patients with GINA 4/5 asthma according to patterns of OCS use

	No Intermittent OCS use; N=xx	Intermittent OCS use; N=xx	Long-term OCS use, N=xx
Biomarkers (highest available measurement before and on the date of biologic initiation)			
BEC (cells/µL) **or** FeNO (ppb), non-missing n (%)			
BEC ≥150 **or** FeNO ≥20, n (%)			
BEC ≥150 **or** FeNO ≥25, n (%)			
BEC (cells/µL) **and** FeNO (ppb), non-missing n (%)			
BEC <150 **and** FeNO ≥20, n (%)			
BEC <150 **and** FeNO ≥25, n (%)			
BEC <150 **and** FeNO <20, n (%)			
BEC <150 **and** FeNO <25, n (%)			
BEC ≥150 **and** FeNO <20, n (%)			
BEC ≥150 **and** FeNO <25, n (%)			
BEC ≥150 **and** FeNO >20, n (%)			
BEC ≥150 **and** FeNO >25, n (%)			
BEC (cells/µL) **or** FeNO (ppb) **or** IgE (IU/mL), non-missing n (%)			
BEC ≥150 **or** FeNO ≥20 **or** IgE ≥30, n (%)			
BEC ≥150 **or** FeNO ≥25 **or** IgE ≥30, n (%)			
Type 2 comorbidities (history of diagnoses at the index date [date of first biologic initiation at or post-ISAR enrolment)			
Non-missing, n (%) NP, n (%)			
Non-missing, n (%) Atopic dermatitis (AD), n (%)			
Non-missing, n (%) Allergic rhinitis (AR), n(%)			
Non-missing, n (%) Chronic rhinosinusitis (CRS) with or without recognized nasal polyps diagnosed by pulmonologists/allergists, n(%)			
Non-missing, n (%) Eosinophilic esophagitis (EOE), n(%)			

Non-missing (for NP and AD and AR and CRS and EOE), n (%) NP or AD or AR or CRS or EOE, n(%)			

GINA 2018 recommendations[1] were used to classify patient cohorts:

- GINA Treatment Step 4 (medium- or high-dose ICS-LABA therapy) and uncontrolled asthma (poor symptom control ± frequent exacerbations [≥2/year] requiring OCS or serious exacerbations [≥1/year] requiring hospitalization) OR
- GINA Treatment Step 5 (with or without add-on LAMA or biologic therapy).

Non-missing data refers to the number (and percentage) of patients who have available data for the specific variable(s), and serves as the denominator for the calculation of patient proportions in the categories shown.

AD: atopic dermatitis; AR: allergic rhinitis; BEC: blood eosinophil count; COPD: chronic obstructive pulmonary disease; CRS: chronic rhinosinusitis; EoE: eosinophilic esophagitis; FeNO: fractional exhaled nitric oxide; IgE: Immunoglobulin E; NP: nasal polyps

[1]*Global Initiative for Asthma (GINA). GINA difficult-to-treat and severe asthma in adolescent and adult patients - Diagosis and management [Internet]. 2018 Nov [cited 2022 Mar 24]. Available from: https://ginasthma.org/wp-content/uploads/2018/11/GINA-SA-FINAL-wms.pdf*

14.2 Proposed results table for Objective 2

Demographic and clinical characteristics of patients of patients with GINA 4/5 asthma and with BEC <150 cells/µL and with long-term OCS use

	Long-term OCS use, N=xx
GINA Treatment Step (at ISAR enrolment)	
GINA 2018 Step 4 and uncontrolled asthma, n (%)	
GINA 2018 Step 5, n (%)	
Gender	
Non-missing, n (%)	
Female, n (%)	
Age (at the date of first biologic initiation at or post-ISAR enrolment)	
Non-missing, n (%)	
Mean (SD)	
18-34, n (%)	
35-54, n (%)	
55-79, n (%)	
≥80, n (%)	
BMI	
Non-missing, n (%)	
Underweight (<18.5), n (%)	
Normal (≥18.5-<25), n (%)	
Overweight (≥25 - <30), n (%)	
Obese (≥30), n (%)	
Smoking status	

Non-missing, n (%)	
Current smokers, n (%)	
Ex-smokers, n (%)	
Never-smoked, n (%)	
Age of asthma onset (years)	
Non-missing, n (%)	
Mean (SD)	
<18, n (%)	
≥18, n (%)	
Type 2 comorbidities (history of diagnoses at the index date [date of first biologic initiation at or post-ISAR enrolment])	
Non-missing, n (%) NP, n (%)	
Non-missing, n (%) Atopic dermatitis (AD), n (%)	
Non-missing, n (%) Allergic rhinitis (AR), n(%)	
Non-missing, n (%) Chronic rhinosinusitis (CRS) with or without recognized nasal polyps diagnosed by pulmonologists/allergists, n(%)	
Non-missing, n (%) Eosinophilic esophagitis (EOE), n(%)	
Non-missing (for NP and AD and AR and CRS and EOE), n (%) NP or AD or AR or CRS or EOE, n(%)	
OCS-related comorbidities (history of diagnoses at the index date [date of first biologic initiation at or post-ISAR enrolment])	
Non-missing, n (%) Anxiety, n (%)	
Non-missing, n (%) Depression, n (%)	
Non-missing, n (%) Osteoporosis, n (%)	
Non-missing, n (%) Type II diabetes, n (%)	
Non-missing, n (%) Peptic ulcer, n (%)	
Non-missing, n (%) Pneumonia, n (%)	
Non-missing, n (%) Obstructive sleep apnoea, n (%)	
Non-missing, n (%) Renal failure, n (%)	
Non-missing, n (%) Heart failure, n (%)	
Non-missing, n (%) Myocardial infarction, n (%)	
Non-missing, n (%)	

Venous thromboembolism/ pulmonary embolism, n (%)	
Non-missing, n (%) Cataract, n (%)	
Non-missing, n (%) Glaucoma, n (%)	
Comorbidity that mimicks/exacerbates asthma (history of diagnoses at the index date [date of first biologic initiation at or post-ISAR enrolment])	
Non-missing, n (%) COPD, n (%)	
Biomarkers (highest available measurement before and on the date of biologic initiation)	
IgE (IU/mL), non-missing n (%)	
<30, n (%)	
≥30 - <75, n (%)	
≥75, n (%)	
FeNO (ppb), non-missing n (%)	
<20, n (%)	
≥20, n (%)	
<25, n (%)	
≥25, n (%)	
Lung function and allergen tests (most recent information before and on the date of biologic initiation)	
Post-BD FEV_1 % predicted, non-missing n (%) Mean (SD)	
Post-BD FVC % predicted, non-missing n (%) Mean (SD)	
Post-BD FEV_1/FVC, non-missing n (%) Mean (SD)	
<0.7, n (%)	
Skin prick test, non-missing n (%)	
Positive skin prick test, n (%)	
Specific IgE test, non-missing n (%)	
Positive specific IgE test, n (%)	
Therapy in addition to ICS/LABA (at the date of first biologic initiation at or post-ISAR enrolment)	
Long-term OCS, non-missing n(%) Long-term OCS, n (%)	
Anti-IgE, n (%)	
Anti-IL5/5R, n (%)	
Anti-IL4/13, n (%)	
Add-on to ICS/LABA	
LAMA, non-missing n(%) LAMA	
LTRA, non-missing n(%) LTRA	
LAMA + LTRA, non-missing n(%) LAMA + LTRA	
Theophylline, non-missing n(%) Theophylline	
Asthma Control*	
Asthma control, non-missing n (%)	
Not controlled, n (%)	

Partially controlled, n (%)	
Well controlled, n (%)	
Asthma exacerbations, non-missing n (%)	
Mean (SD)	
0, n (%)	
1, n (%)	
2, n (%)	
3, n (%)	
≥4, n (%)	
Total annual OCS dose, non-missing n (%) Mean (SD)	
Healthcare resource utilization	
ED visit, non-missing n (%)	
Mean (SD)	
0, n (%)	
1, n (%)	
≥2, n (%)	
Hospitalization, non-missing n (%)	
Mean (SD)	
0, n (%)	
1, n (%)	
≥2, n (%)	

GINA 2018 recommendations[1] were used to classify patient cohorts:

- GINA Treatment Step 4 (medium- or high-dose ICS-LABA therapy) and uncontrolled asthma (poor symptom control ± frequent exacerbations [≥2/year] requiring OCS or serious exacerbations [≥1/year] requiring hospitalization) OR
- GINA Treatment Step 5 (with or without add-on LAMA or biologic therapy).

*Asthma control is defined in ISAR using either GINA ACA[2], ACQ[3,4,5] or ACT[6,7]:

- Well controlled: GINA ACA 0 "yes"; mean ACQ ≤0.75; total ACT >19
- Partially controlled: GINA ACA 1-2 "yes"; 0.75< mean ACQ <1.5; 15< total ACT ≤19
- Not controlled: GINA ACA 3-4 "yes"; mean ACQ ≥1.5; total ACT ≤15.

GINA ACA[2]: In the past 4 weeks, has the patient had:

- Daytime asthma symptoms more than twice/week?
- Any night waking due to asthma?
- Reliever needed for symptoms more than twice/week?
- Any activity limitation due to asthma?

Non-missing data refers to the number (and percentage) of patients who have available data for the specific variable(s), and serves as the denominator for the calculation of patient proportions in the categories shown.

ACA: asthma control assessment; ACQ: Asthma Control Questionnaire; ACT: Athma Control Test; AD: atopic dermatitis; AR: allergic rhinitis; BD: bronchodilator; BEC: blood eosinophil count; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRS: chronic rhinosinusitis; ED: emergency department; EoE: eosinophilic esophagitis; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; ICS: inhaled corticosteroid; IgE: Immunoglobulin E;

ISAR: International Severe Asthma Registry; LAMA: long-acting muscarinic receptor antagonist; LABA: long-acting β_2-agonist; LTRA: leukotriene receptor antagonist; NP: nasal polyps; OCS: oral corticosteroid; SD: standard deviation.

[1]*Global Initiative for Asthma (GINA). GINA difficult-to-treat and severe asthma in adolescent and adult patients - Diagosis and management [Internet]. 2018 Nov [cited 2022 Mar 24]. Available from: https://ginasthma.org/wp-content/uploads/2018/11/GINA-SA-FINAL-wms.pdf*
[2]*Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention [Internet]. 2019 [cited 2022 April 22]. Available from: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf*
[3]*QoLTech. Asthma Control Questionnaire (ACQ) [Internet]. [Cited 2022 April 25]. Available from: https://www.qoltech.co.uk/acq.html.*
[4]*Werner CU et al. NPJ Pri Care Resp Med 2017;27:64*
[5]*Juniper EF et al. Eur Respir J. 1999;14:902-907*
[6]*Quality Metric. Asthma Control Test: A User's Guide [Internet]. 2008 Dec [cited 2022 April 25]. Available from: https://astar-register.org/wp-content/uploads/sites/284/2018/08/Asthma-Control-Test-ACT-User27s-Guide_2009.pdf*
[7]*Schatz M et al. J Allergy Clin Immunol 2006;117:549-556*