Study Protocol

SHINE

Sustainability of response to biologics in severe asthma and predictors of late failure among patients in an international registry

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TITLE	SHINE
Subtitle	Sustainability of response to biologics in severe asthma and predictors of late failure among patients in an international registry
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Study aims and objectives	Aim to use ISAR patient data to characterise late failures—relapses occurring up to three years after remission is achieved at 12 months of biologic therapy. • To describe the frequencies of late failure and the type and extent of domain failure attributed to remission failures • To identify pre- and post-treatment characteristics associated with late failures • To describe persistence of late failures and the potential role of switching biologic agent in regaining remission after late failure
Countries of study	Argentina, Belgium, Brazil, Bulgaria, Canada, Colombia, Denmark, Estonia, Greece, Ireland, Italy, Japan, Kuwait, Mexico, Norway, Poland, Portugal, Saudi Arabia, Singapore, South Korea, Spain, Taiwan, United Arab Emirates (UAE), United Kingdom (UK), United States of America (USA)
Author(s)	Dr William Oswald

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADEPT	Anonymised Data Ethics & Protocol Transparency
BEC	Blood Eosinophil Count
FeNO	Fractional exhaled Nitric Oxide (FeNO)
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
IgE	Immunoglobulin E
ISAR	International Severe Asthma Registry
ISC	ISAR Steering Committee
LTOCS	Long-term oral corticosteroid
OPC	Optimum Patient Care
OPRI	Observational and Pragmatic Research Institute
OCS	Oral corticosteroids
ppFEV1	Percent predicted forced expiratory volume in one second

1.0 Background

Asthma is a common, heterogeneous disease comprising a constellation of respiratory symptoms of varying timing and intensity, such as wheeze, shortness of breath, chest tightness, cough, and limited expiratory airflow (1). In 2021, it was estimated that asthma affects 3.3% of the population or 260 million people worldwide (2), and prevalence by continent ranges from 3.4% in Asia to 8.3% in both North America and Oceania (3). Though asthma prevalence has plateaued in many settings ?in recent years?, it continues to increase in many low- and middle-income countries (4). Despite contributing less than 1% of all mortality, the burden of asthma is high and ranked 23rd among causes of Years Lived with Disability worldwide in 2021 (2).

Severe asthma is defined as “asthma that is uncontrolled, despite adherence with maximal optimised high-dose ICS with LABA treatment and management of contributory factors, or that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations” (asthma attacks) (4,5). Control of asthma symptoms might be possible for most patients through treatment according to two tracks recommended by the Global Initiative for Asthma (GINA) (1,6). Despite adequate treatment, patients with severe asthma face frequent exacerbations (i.e. flare-ups, attacks) and persistent symptoms that require either systemic glucocorticoid bursts or long-term oral glucocorticoid therapy or both (7). Symptoms during an exacerbation include shortness of breath, wheeze, cough, and sputum production; mucus production along with contraction of smooth muscle restrict the airway, which can result in near-fatal or fatal respiratory failure (8). Systemic use of corticosteroid is associated with several adverse effects, not limited to weight gain, osteoporosis and osteonecrosis, diabetes, ocular complications, particularly glaucoma and cataract, cardiovascular effects, and infections, all of which increase the burden of asthma and the cost of its care (4,9). It is now recognized, however, that patients with severe asthma constitute a minority of those with uncontrolled asthma (i.e. one or more of exacerbations, poor symptom control, or impaired lung-function) despite taking high-dose treatment, the majority having treatment barriers, allergen or smoking exposures, viral infections, or comorbidities contributing to poor asthma control (4,7). Among adults with asthma, prevalence of severe asthma is commonly reported to range between 5 and 10% (4,6,10).

Previously only allergic and non-allergic asthma were characterized (11), but improvements in the treatment of severe asthma have occurred alongside recognition of the utility of characterizing the disease’s heterogeneity with endotypes. In contrast to clinical measures, such as reductions in lung function, that are used to characterize a disease’s phenotype and

may have multiple causes, endotypes refer to the distinct molecular mechanisms of subtypes of a disease (8). Blood eosinophils (≥300 cells per µL) and Fractional Exhaled Nitric Oxide (FeNO, ≥25 ppb) are clinical biomarkers of increased type 2 inflammation used to differentiate type-2-high versus type-2-low asthma (4). Type-2-high inflammation is present in childhood-onset, allergic asthma and in adult-onset, severe eosinophilic asthma (7). A subset of type-2-high asthma, allergic asthma represents approximately 70% of all asthma (12). Allergic sensitization to aeroallergens is determined by skin prick test or specific IgE plus exacerbation of asthma or rhinoconjunctivitis symptoms related to a relevant exposure (4). Often associated with obesity, aging, and smoking, asthma in patients with lower levels of type 2 inflammation (non-eosinophilic, sometimes neutrophilic, and metabolic) may be caused by abnormalities in airway smooth muscle or airway hyperresponsiveness and obstruction caused by oxidative stress, interleukin (IL)-17, or neutrophil products (8,11). While type-2-low asthma is less well understood, type-2-high asthma is characterized by high production of type-2 cytokines IL-4, IL-5, and IL-13, which manifest in eosinophil accumulation in lung tissue and mucous production (11).

Biologic therapies leverage our understanding of these specific molecular mechanisms and inflammatory pathways and permit targeted asthma management. Currently, there are four classes of biologic therapies for severe asthma, targeting IgE, the IL-5 pathway, the IL-4/IL-13 pathway , and thymic stromal lymphopoietin (TSLP) (12,13). Omalizumab is a monoclonal antibody (mAb) and is used in cases of IgE-mediated allergic asthma. The cytokine IL-5 is critical to the development and activation of eosinophils and is targeted by three biologics approved for management of severe eosinophilic asthma: Mepolizumab and Reslizumab target ligand IL-5, and Benralizumab binds to IL-5Rα (12). Dupilumab binds to the IL-4Rα subunit, which inhibits both IL-4 and IL-13 signalling related to airway tone and class-switching toward IgE. TSLP is an alarmin, a specific type of cytokine (with IL-33 and IL-25) released by epithelial cells in response to allergens, air pollutants, and viruses, that enhances subsequent inflammation mechanisms (7,12). Targeting TSLP with Tezepelumab and IL-33 with Itepekimab and Astegolimab, as upstream mechanisms, may improve asthma outcomes in a broader patient population, including those with type-2-low severe asthma (7). In addition to their demonstrated efficacy in reducing exacerbations, biologic therapies, specifically Mepolizumab, Benralizumab, and Dupilumab have also been shown to lower dependence on corticosteroids (7), which in turn could lower the burden of associated acute and chronic adverse effects (14).

Use of biologic therapies is increasing, and observed benefits among patients with type-2-high severe asthma have shown the potential of remission being an obtainable goal for asthma

treatment (7,12,15). This recognition has followed two decades of debate on defining what benefits constitute response to biologic therapies, since some recipients show high asthma control, while others see no benefit (16). Remission is a relatively new concept for asthma management, but it is well-defined in other chronic inflammatory conditions like rheumatoid arthritis, Crohn's disease, ulcerative colitis, and systemic lupus erythematosus (15). Drawing from experiences with these other inflammatory diseases, literature review, and expert consensus, four remission subtypes were proposed, contrasting clinical and complete remission both being achieved either on or off treatment (17). Clinical remission typically requires: no use of systemic corticosteroids for exacerbation treatment; no exacerbations and no hospitalizations or emergency department or unscheduled doctor visits for management of asthma exacerbations; and absence of asthma symptoms, as measured using a validated instrument like the Asthma Control Questionnaire (18) or Asthma Control Test (19), or optimisation of lung function (e.g. $FEV_1 \geq 80\%$ predicted). Complete remission requires clinical remission plus normalisation of pathology: no evidence of inflammation; a negative bronchial hyperresponsiveness test; or degree of subepithelial fibrosis (15,17). Clarification of these definitions has facilitated examination of the characteristics of biologic therapy recipients who may or may not respond to treatment in the short-term (20,21), but long-term studies are now needed (22,23).

While severe asthma patients may achieve clinical remission endpoints following biologic treatment, subsequent failures have been observed in real-world studies (12). Remission achievement rates after one year of treatment have been found to vary according to the number of component domains considered within the remission definition, and lower pre-biologic disease severity, shorter asthma duration, and higher BEC were all associated with greater odds of remission at one year (20). A real world study from multiple sites in Italy involving a cohort of patients on Mepolizumab examined several remission definitions and found that 29.7% of patients sustained three-domain remission (exacerbations, LTOCs, symptom control) to two years (24). A real world study from multiple sites in Spain involving a cohort of patients on a single biologic for 24 months found that of 175 patient who responded based on the same definition at 12 months, 51 (29.1%) lost response over time (25). A post hoc analysis of the QUEST and TRAVERSE studies found that 64.4% of patients receiving Dupilumab who achieved a four-domain definition of clinical remission at year 1 sustained remission to year 2 (26). A post hoc analysis of the RELIght study found that 52.5% of patients receiving Mepolizumab had sustained remission from 12 to 24 months, based on a four-domain definition (27). Additional and larger longitudinal studies are needed to determine how frequently clinical remission is maintained over time among severe asthma patients and whether it improves clinical outcomes (20,28). Similarly, identification of the clinical

characteristics of failure at timepoints beyond one year of treatment is necessary, and specifically what characteristics and post-treatment biomarkers, alone or in combination, predict failure at different timepoints (29–31).

2.0 Study Aims and Objectives

2.1 Study Aims

The International Severe Asthma Registry (ISAR) provides a unique data source with information from patients in a variety of settings at timepoints before and after onset of biologic treatment. Here we propose to use these data, specifically from patients in clinical remission (no exacerbations, no or ceasing LTOCS, and controlled asthmal) after 12 months of biologic therapy, to characterise failures to meet one or more clinical remission criteria occurring at later timepoints , which we denote here as “late failures”, and identify factors associated with the occurrence of these events versus sustained remission.

2.2 Study Objectives

Objective 1: To describe frequencies of late failure and the type and extent of domain failure attributed to these remission failures occurring after 12 months of biologic therapy

Objective 2: To identify pre- and post-treatment demographic and clinical characteristics associated with late failure versus sustained remission after 24 months of biologic therapy

Objective 3: To describe persistent failure, from 24 to 36 months, and the potential role of switching or stopping biologic treatment after failure at 24 months in regaining remission.

3.0 Study Design

We will conduct a longitudinal cohort study including data from 25 countries sharing data with ISAR (32–34) from May 1, 2017 to July 27, 2025, for patients, who had data in the central ISAR database as of July 31, 2025. We will identify patients in the registry for our cohort, who have initiated biologic treatment and have at least 2 years of follow-up data after biologic initiation.

For objective 1, among patients in remission at 12 months post-initiation, we will identify all subsequent remission failures at twelve-month intervals. We will then identify and determine the number of domains contributing to the first failure and their extent (i.e. how near or far from achieving remission).

For objective 2, we will estimate the association between the occurrence of a late failure at 24 months and pre-biologic characteristics and other factors such as BEC and FeNO measurements at 12 months and ICS stepdown in combination with removal of LAMA as recorded in the first year of treatment, while adjusting for patient characteristics.

For objective 3, among patients with late failures at 24 months we will describe their subsequent remission trajectory, enumerating subsequent failures and describing biologic treatment patterns.

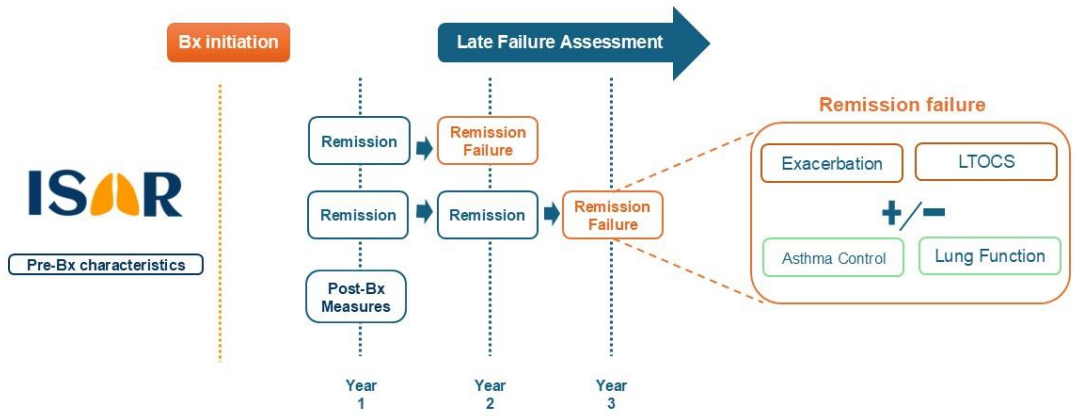

Figure 1 Study design

4.0 Study Population

4.1 Data Sources

The International Severe Asthma Registry (ISAR) is a global, multi-centre project designed to collect ongoing data from patients with severe asthma. To be included in this registry, patients must be 18 years of age or older, visit a participating centre, and have a diagnosis of severe asthma (33). Severe asthma is characterised either by its lack of control despite therapeutic efforts as described in step 4 of the GINA guidelines or by step 5 of the GINA guidelines (1). Patient consent is secured before data collection and the ISAR steering committee provides approval before research using ISAR data can be initiated.

Data collection began in 2017, and as of July 2025, there were 34,965 active participants from 29 countries enrolled into ISAR. Of these enrolled participants, 12,593 have initiated a biologic. The data is comprised of relevant information collected from patients at each visit and extracted medical records. Data is collected at baseline and then at approximate one-year intervals thereafter. The data elements collected and those that are pertinent to this study question are listed in section 5.0.

4.2 Inclusion and Exclusion Criteria

Inclusion Criteria

- Patients receiving a biologic (anti-IgE, anti-IL-5/5R, anti-IL-4Rα, or anti-TSLP), AND
- Age 18 years or older at the time of biologic initiation, AND
- Have available baseline registry data at the time of biologic initiation, AND
- Have data on and meet criteria for remission (no exacerbations, no or ceasing LTOCS use, partly or well-controlled asthma*) at 12 months post-initiation, AND
- Have data available to assess remission at one additional follow up at least 24 months post-initiation

Exclusion Criteria

- Patients who stopped biologics in the first year of follow up, OR
- Patients with insufficient data available to assess remission at least 24 months post-initiation

* Will explore feasibility based on number of patients with available ACQ/ACT measures to allow examination of extent of failure, in which case will loosen definition to only well-controlled asthma

- Patients in remission before initiation of biologic therapy

5.0 Study Variables and Study Outcome Definitions

5.1 Baseline (pre-Biologic) patient characteristics

The following pre-biologic characteristics and measures as collected in ISAR will be used to describe the cohort.

Characteristics	Units/Categories
Country	Country
Age at biologic initiation	Years
Sex	Female, Male
BMI at biologic initiation	kg/m^2
Ethnicity	White, Southeast Asian, Northeast Asian, African, Mixed, Other, Unknown/missing
Smoking status at biologic initiation	Current, Ex-smoker, Never-smoker
Age of asthma onset	Years
Asthma duration	Years
Highest BEC	cells/μL
Latest FeNO	ppb
Latest blood IgE count	IU/mL
Positive SPT or serum specific IgE tests to clinically relevant allergens	Yes/No
Allergic Rhinitis (AR)	Ever/Never
Eczema/Atopic dermatitis	Ever/Never
Chronic Rhinosinusitis (CRS)	Ever/Never
Nasal Polyps (NP)	Ever/Never
History of osteoporosis at biologic initiation	Yes/No
History of anxiety/depression at biologic initiation	Yes/No
Eosinophilic grade	Grade 0 (unlikely/non-eosinophilic); Grade 1 (least likely); Grade 2 (likely); Grade 3 (most likely).

Add on medications to ICS/LABA in the past year	Long-Acting Muscarinic Antagonist (LAMA), Theophylline, Leukotriene Receptor Antagonist (LTRA), Macrolide, LTOCS
ICS daily dose in the past year (GINA 2025)	Low, medium, high
Exacerbation rate	Count in past year
Most recent daily LTOCS dose	Equivalent-prednisone mg
Asthma control	Uncontrolled, partly controlled, well controlled
FEV_1 percent predicted (post-bronchodilator if available, pre-bronchodilator otherwise)	%

5.2 Year 1 characteristics

Characteristics measured at 12 months post-initiation and calculating change from baseline:	Units/Categories
FEV1 percent predicted (post-bronchodilator if available, pre-bronchodilator otherwise)	%
Highest BEC	cells/µL
Latest FeNO	ppb
ICS daily dose in the past year (GINA 2025)	Low, medium, high
LAMA	Yes/No

5.3 Outcomes

The primary outcome of interest will be first failure to meet three-domain remission definition (No exacerbations, no LTOCS use, partly or well-controlled asthma) recorded at a follow up occurring at least 24 months following biologic initiation (20,21). As secondary outcomes, we will also explore the use of an alternative three-domain definition considering lung function in place of symptoms and a four-domain remission definition (20).

Definition component domains are defined as:

- No exacerbation in past 12 months (allowing 48 weeks where a complete year of follow-up isn't available)
- No LTOCS use or ceasing using in past 12 months (allowing 48 weeks where a complete year of follow-up isn't available)
- Well or partly controlled asthma (GINA, ACT, ACQ) as assessed closest to each timepoint (24 weeks to <18 months for the 12-month timepoint, 18 to <30 months for the 24-month timepoint, 30 to <42 months for the 36-month timepoint)
- FEV_1 percent predicted ≥80% as assessed closest to each timepoint (24 weeks to <18 months for the 12-month timepoint, 18 to <30 months for the 24-month timepoint, 30 to <42 months for the 36-month timepoint)

6.0 Statistical Analysis

6.1 Sample Size

All patients meeting study criteria will be included. The table below shows availability of ISAR follow-up data after biologic initiation for all biologic initiators in remission at 12 months based on each given remission definition with at least one consecutive follow-up remission observation, as of July 2025.

Clinical Remission Definition	N
No Exacerbations + No LTOCS Use + Partly/Well Controlled	685
No Exacerbations + No LTOCS Use + No Lung Function Impairment	555
No Exacerbations + No LTOCS Use + Partly/Well Controlled + No Lung Function Impairment	334

6.2 Software

All analyses will be conducted using R version 4.5.1 (r-project.org) in Rstudio (Posit Software, PBC).

6.3 Analysis

Objective 1: To describe frequencies of late remission failures and the type and extent of domain failure attributed to remission failures at each timepoint

We will describe the frequency of domains and the frequency of combinations of domains constituting failures at each time point using histograms. 95% confidence intervals will be calculated using the binomial distribution. To characterize the extent of failure, we will describe the distribution of domain measurements using summary statistics for continuous measures (i.e. number of exacerbations, ppFEV1, LTOCS daily dose, ACT/ACQ scores-as available) and frequencies and proportions for categorical measures (i.e. asthma control classification) for those domains contributing to a failure at a timepoint. We will repeat the analysis using alternate remission definitions.

Objective 2: To identify pre- and post-treatment characteristics associated with failure at each timepoint

To identify predictors associated with late failure, we will examine the study population in remission at 12 months and identify those who fail to meet remission criteria at 24 months. We will compare pre-treatment characteristics (Table 5.1) between patients with late failure at 24 months and patients in sustained remission. We will use logistic regression modelling to estimate the association between pre-treatment characteristics with the occurrence of late failure. For this analysis, continuous measures will be categorised. We will estimate the association between each characteristic and late failure with and without adjustment for sex, index age, and country/centre. In addition, we will estimate the association between characteristics as measured in year 1 and each characteristic's change from baseline (Table 5.2) and the occurrence of late failure at 24 months, with and without adjustment for sex, index age, and country/centre. All models will incorporate robust errors to account for clustering by setting. We will repeat the analysis using alternate remission definitions.

Objective 3: To describe persistence of late failures and the potential role of switching biologic agent after late failure

As a further exploratory analysis and as data permits, we will describe trajectories (frequency of subsequent remission or failures) at later timepoints among patients in remission at 12 months with late failure at 24 months to look at patterns of biologic switching (e.g. within class versus across class) by groups regaining remission or not at 36 months.

6.4 Limitations

As with other registry-based studies, missing data is a limitation, which is compounded by our use of multiple-domain remission definitions, and our data represent information collected for clinical and routine use rather than research. We will explore the impact of missing outcome data and loss to follow-up with the use of different remission definitions. Similar to all observational research, residual confounding and unmeasured confounders may influence our results.

7.0 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 Optimum Patient Care (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.

8.0 Data Dissemination

This novel study is one of the first efforts to harness the power of global real-world data to investigate the long-term outcomes of remission via comparing clinical outcomes post-remission among those succeeding in achieving remission versus those that did not.

Publications:

The findings will be submitted for publication in peer-reviewed journals that focus on respiratory diseases and novel therapies.

Conferences:

Results will also be presented at relevant respiratory medical and scientific conferences, through abstract presentations and/or discussions.

Authorship:

Authorship will be determined in accordance with the ISAR authorship policy as outline in the ISAR publication charter, which has been approved by the ISAR steering committee as well as per the International Committee of Medical Journal Editors (ICMJE) criteria of authorship. Authorship will recognise significant contributions to the study's conception, analysis, and writing.

9.0 Advisory Group

Professor David Price, Chief Investigator for the study, is the chair of the ISAR Steering Committee (ISC). Other members of the committee, as listed in the following table, will form the Advisory Group. This is to be confirmed as per ISC members confirmation and/or nomination in the event they cannot participate.

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10.0 Research Team

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Senior Data Analyst: Aaron Beastall

11.0 Timelines

Action	Timeline
Draft protocol	31-Jul-2025
Final protocol	29-Aug-2025
Dataset creation	1-Sep-2025
Preliminary results (internal)	15-Sep-2025
F2F WG meeting slides and presentation	27-Sep-2025
Full results (internal-outcomes)	10-Nov-2025
Study report	10-Dec-2025

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