

Study Protocol

Determining elements of remission that predict long term outcomes (**GLISTEN**)

Assessing the comparative value of remission domains in predicting long-term clinical outcomes

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Countries of study	Belgium, Brazil, Bulgaria, Canada, Colombia, Denmark, Ecuador, Estonia, Germany, Greece, Hungary, India, Ireland, Italy, Japan, Korea, Kuwait, Mexico, Norway, Netherlands, Poland, Portugal, Saudi Arabia, Singapore, Spain, Switzerland, 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
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
LLN	Lower limit of normal
LTOCS	Long-term oral corticosteroid
OPC	Optimum Patient Care
OPRI	Observational and Pragmatic Research Institute
OCS	Oral corticosteroids
OLFM	Optimized Lung Function Maintenance
ppFEV1	Percent predicted FEV1

1.0 Background

With the increased use of targeted therapy via monoclonal antibodies in severe asthma, clinical remission has been an evolving concept most frequently defined by symptom control, elimination of oral corticosteroid use, absence of exacerbations, and optimization or stabilization of lung function¹. Recently, expert consensus efforts and large database studies from the international severe asthma registry (ISAR), have contributed to the development of the four-domain definition mentioned above^{2-4,6}. Since 2023, remission as a treatment goal has been adopted by national guidelines with slight variations of the ISAR four-domain criteria. For example, a consensus published by an American College of Allergy, Asthma, and Immunology (ACAAI), American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American Thoracic Society (ATS) workgroup required meeting all six criteria shown below⁵.

- 1). *no exacerbations requiring physician visit, emergency care, hospitalization, and/or systemic steroid for asthma,*
- 2). *no missed work or school over a 12-month period due to asthma-related symptoms,*
- 3). *stable and optimized pulmonary function results on all occasions measured over a 12-month period with a minimum of two measurements during the year,*
- 4). *treatment with ICS only at low-medium doses (or less),*
- 5). *an ACT score >20 (or an AirQ score < 2 or an ACQ score < 0.75) on all occasions measured in the previous 12-month period with a minimum of two measurements during the year,*
- 6). *symptoms requiring one-time reliever therapy no more than once a month.*

As shown by Shackleford et al. (2025), up to 48 definitions of remission have been used across experimental and observational studies, reflecting persistent variability in how clinical remission is conceptualized. This lack of consensus complicates clinical application; however, a more fundamental challenge for health policy adoption may be the inherent tension between

individualized treatment goals such as remission and the population-level outcome measures on which health policy frameworks are typically built. In this study, we set out to determine relative prognostic value of individual criteria of remission on clinical, long-term outcomes (objective 1). This will inform which composite definition of remission is of highest, practical value (objective 2), which will enable the potential adoption of a standard definition amongst stakeholders. For instance, understanding which clinical domain is of highest importance will inform clinicians decision to switch or continue a biologic therapy. Additionally, a more informative criteria of remission can influence regulatory policies to recognize remission as a clinical endpoint of severe asthma which can further facilitate faster regulatory approval and coverage of biologics by payors.

ISAR's global consortium of experts along with its international database of over 14,000 patients on biologic therapy are uniquely positioned to conduct this analysis as it has continued to progress the understanding of remission in severe asthma. Starting with LUMINANT and FULL BEAM studies, the definition of remission and predictors of remission were explored, adding empirical evidence to other global research efforts in this area⁷⁻¹¹. Most recently, the SPOTLIGHT study evaluated the effect of remission on clinical outcomes and showed that graduating to remission within the first year of biologic initiation is associated with better clinical outcomes. For example, patients had 2-5 times less exacerbation rates and greater than 5x higher odds of not using LTOCS for up to 5 years post biologic initiation, when remission was reached within one year of biologic initiation, compared to those who did not achieve remission. Also, compared to patients not in remission during the first year of receiving a biologic, those in remission had 7 to 10 percentage points higher percent predicted FEV1 ($\approx$ 250-350 mL FEV1) in subsequent years (14). However, this latest study has looked at the prognostic value of composite definitions of remission and long-term outcomes. Therefore, here we set out to distinguish which component of remission, along with the appropriate threshold, is most influential in driving long-term clinical outcomes. In this study, we have provisionally chosen absence of exacerbations, lung function stabilization, and optimization

as long-term clinical outcomes of interest as these indicators are both objective measures with up to five years of follow-up data (post-biologic initiation) in ISAR.

2.0 Study Aims and Objectives

2.1 Study Aims

Determine the relative contribution of remission domains and their respective thresholds in predicting long-term outcomes.

2.2 Study Objectives

Objective 1: To determine the relative strength of prediction across individual remission domains and long-term clinical outcomes

Objective 2: To compare the discriminative and predictive performance of different remission definitions in predicting long-term outcomes

3.0 Study Design

This is a registry-based observational longitudinal cohort study that will firstly describe the pre-biologic clinical and demographic characteristics of the study population, which are those with data on all four domains of remission as noted in section 4.2 at index date (1-year post bx initiation) and at least two years of primary outcome (lung function), follow-up data.

3.1 Objective 1

For objective 1, we will examine the relative importance of individual criteria of remission (exacerbations, long-term oral corticosteroids (LTOCS) use, asthma control, and lung function) as per Perez-de-Llano et al (FULL BEAM) in predicting lung function and annualized exacerbation over time periods of 1-, 2-, 3-years since index date. Thus, remission domains assessed at 12 months will compose the exposure and time since then will be the start of the outcome period. Please see figure 1 for key aspects of the study design of objective 1. For a full list of outcomes and respective definitions that will be explored, please see section 5.0.

Objective 1 Exposure: in addition to the clinically relevant FULL BEAM remission domain criteria, to include more information of exacerbation and lung function in assessing its ability to predict outcomes, categorical variables with two thresholds will be used in the analysis for the exposure:

- Exacerbation: 0, 1, ≥ 2
- Lung function: FEV₁ and FEV₁/FVC z-scores < -1.96, -1.96 to < -1.64, ≥ -1.64 ¹
- Asthma control²: well controlled, partly controlled, uncontrolled
- LTOCS: no use, daily dose of ≤ 5 mg, daily dose >5mg prednisolone-equivalent

Objective 1 Outcome:

- Primary – ppFEV₁ z-score
- Secondary – annualized exacerbation rate

¹ Lower limit of normal (LLN) will be used instead of percent of predicted FEV₁ and FEV₁/FVC fixed thresholds in accordance to latest ERS/ATS recommendations (ref: [ERS/ATS Global Lung Function Initiative normal values and classifying severity based on z-scores instead of per cent predicted | European Respiratory Society](#)). A z-score of -1.64 corresponds to the 5th centile value of the reference, healthy population, and a z-score of -1.96 corresponds to the 2.5th centile value.

² Well Controlled, Partly Controlled, or Uncontrolled by working through up to four assessment tools in order of priority: GINA, ACT, ACQ, and AIRQ.

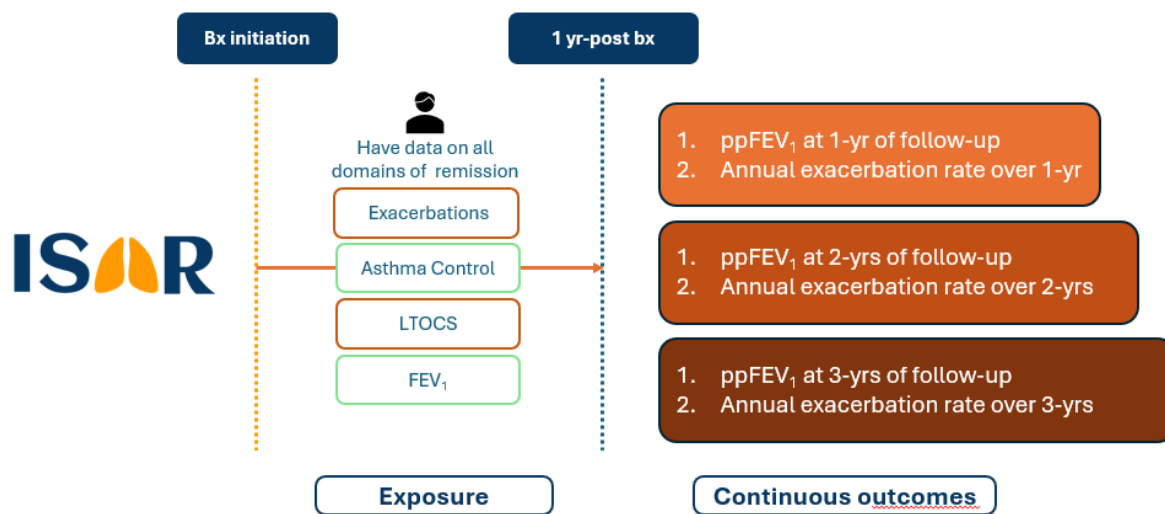


Figure 1 Study design for objective 1

3.2 Objective 2

Secondly, via comparison of Area Under the Curve (AUCs) and Decision Curve Analysis (DCA), objective 2 analysis will assess the discriminative ability of multiple composite remission definitions with clinical benefit considered¹⁶. The definitions considered (examples shown below but not limited to) will be those that include the domains of highest, prognostic value, as determined from objective 1, in predicting both primary (Optimized Lung Function Maintenance (OLFM)) and secondary (OLFM and exacerbation) clinical outcomes as defined in below (also see section 5.2 for outcome definitions (to be confirmed by the study advisory committee)). This will further allow us to explore varying thresholds of domains included in the composite definitions. Figure 2 depicts the study design of objective 2.

Objective 2 Exposure: varying definitions of remission, with different thresholds.

- No LTOCS, 0 exacerbations, well or partly controlled asthma, FEV₁ z-score ≥ -1.64
- No LTOCS, 0 exacerbations, well or partly controlled asthma, FEV₁ z-score ≥ -1.96
- No LTOCS, 0 exacerbations, well controlled asthma, FEV₁ z-score ≥ -1.64
- No LTOCS, 0 exacerbations, well controlled asthma, FEV₁ z-score ≥ -1.96
- No LTOCS, 0 exacerbations, well or partly controlled asthma

Objective 2 Outcomes:

Optimized Lung Function Maintenance (OLFM)

- maintaining lung function stability: no more than $\leq 5\%$ compared to the previous year AND
- achieving optimized lung function: FEV₁ and FEV₁/FVC above the lower limit normal (LLN) 5th percentile (z-score ≥ -1.65)¹⁵. If missing ratio, use FEV₁ LLN.

Absence of Exacerbation: zero annual exacerbations

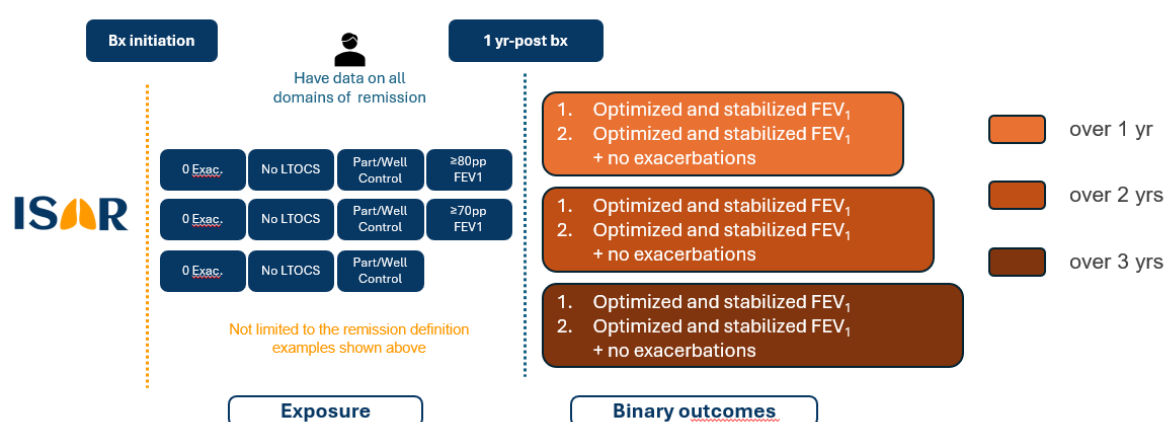


Figure 2 Study design for objective 2

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 asthma⁴. Severe asthma is characterised either by its lack of control despite therapeutic efforts per GINA step 4 or by the necessity for comprehensive treatment as described in step 5 of the GINA guidelines⁵. 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 2018, and as of April 2026, there were 37,612 active participants from 31 countries enrolled into ISAR. Of these enrolled participants, 14,132 have initiated a biologic. The data is comprised of relevant information collected from patients at each visit and extracted medical records. The required visit structure is one annual follow-up visit. 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 for severe asthma, AND
- Date of first biologic initiation AND
- One year of pre-biologic initiation data
- Age 18 years or older at the time of biologic initiation, AND
- Patients that have data on all domains of remission: exacerbations, LTOCS, asthma control and lung function within the first year of biologic initiation, AND
- Patients with at least two years of post-biologic data for lung function

Exclusion criteria

- Biologic received for other conditions (e.g. Urticaria, atopic dermatitis, EGPA, COPD)
This applies only when the complete electronic medical record is shared with ISAR.

Including only those with all domains of remission and at least two years of outcome follow-up data may introduce selection bias as those with all such information may be different from those that do not have complete data. We could assess this by comparing the pre-biologic

characteristics of patients excluded due to insufficient domain data and follow-up time vs those included in the study.

5.0 Study Variables and Study Outcome Definitions

5.1 Patient characteristics

The following data elements that were collected pre-biologic initiation will be used to describe the study population.

Patient characteristics
Sex
Body mass index (BMI)
Ethnicity
Country
Smoking status
Age at asthma onset
Duration of asthma
Highest pre-biologic blood eosinophil count (BEC)
Latest pre-biologic fractional exhaled nitric oxide (FeNO)
Latest pre-biologic serum immunoglobulin E (IgE)
One or more allergen detected from skin prick test and/or serum allergen test
Baseline asthma control (well controlled, uncontrolled, partly-controlled)
Baseline FEV ₁ (post-bronchodilator where available, pre-bronchodilator/on treatment otherwise)
Baseline FEV ₁ percent predicted (calculated from GLI-2022 race neutral equations)
Baseline FVC (post-bronchodilator where available, pre-bronchodilator/on treatment otherwise)
Baseline FEV ₁ /FVC
Baseline Exacerbation rate past 12 months
Eosinophilic grade ¹² - Grade 0: unlikely/non-eosinophilic - Grade 1: least likely - Grade 2: likely - Grade 3: most likely
Comorbidities Potentially T-2 related¹⁵: chronic rhinosinusitis, nasal polyps, allergic rhinitis, eczema / atopic dermatitis
Mean Daily LTOCS dose, mg
Add-on therapies to ICS/LABA - LAMA, LTRA, macrolides, theophylline - ICS medium, high

5.2 Research outcomes

Objective 1

- Primary outcome –

Objective 2

- Primary outcome –
-

6.0 Statistical Analysis

6.1 Sample Size

Per inclusion criteria, the current feasibility for the study population is as shown in figure 2.

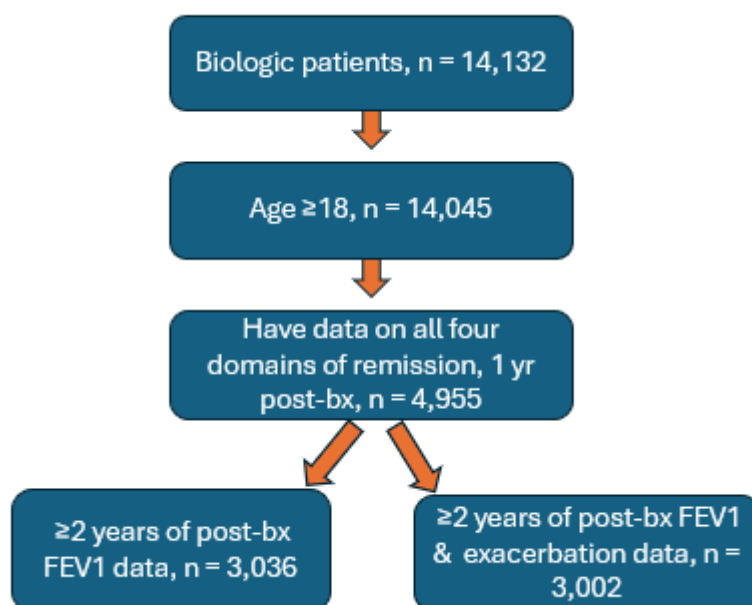


Figure 3 Feasibility

Countries that may contribute at least one patient into the sample:

country	n
Belgium	52
Brazil	9
Bulgaria	2
Canada	74
Colombia	55
Denmark	852
Germany	1

Greece	28
Ireland	11
Italy	712
Japan	29
Kuwait	14
Mexico	48
Norway	59
Poland	29
Portugal	3
Saudi Arabia	30
Singapore	8
South Korea	8
Spain	285
Switzerland	2
Taiwan	46
UK	230
USA	415

6.2 Software

Data management and analysis will be conducted in the R statistical software.

6.3 Objective 1

A dominance analysis approach will be taken to estimate the relative importance of each remission domain (predictors) in relation to the outcomes of interest¹³. Dominance analysis is a statistical method used to quantify the relative importance of predictor variables in a regression model (linear, logistic, or otherwise). Unlike standard regression coefficients, which indicate the direction and magnitude of a predictor's effect holding other variables constant, dominance analysis ranks predictors by their contribution to the model's explanatory power (e.g., R^2 in linear regression). In brief, the contribution of each predictor to the model fit is averaged across all possible subsets of predictors by: 1) comparing all possible submodels (models with subsets of predictors); 2) measuring the increase in model fit when a predictor is added to a submodel; and 3) averaging the increases across all submodels where the predictor could appear.

Linear regressions will be used for modelling FEV₁ measures and negative binomial regressions will be used for modelling annual exacerbation rates. The model fit metrics will be R^2 and the Kullback-Leibler-divergence-based R^2 for linear and negative binomial regressions, respectively.

Minimal adjustment variables will include age at biologic initiation, sex, and country. We will also assess the potential confounding effects of covariates, such as pre-biologic measure of the outcome (lung function or exacerbation), biomarkers, duration of asthma, T2 or OCS-related comorbidities.

6.4 Objective 2

Selected remission definitions with varying thresholds for each domain will be computed as binary variables (remission: yes/no) and used as predictor variables in separate models for each considered outcome. Areas under the curve (AUCs) using the same eligible patients will be computed in order to compare their performance of predicting outcomes. Additionally, the net benefit of each definition from a clinical perspective will be assessed via decision curve analysis. We envision assessing each outcome for three time points: one-year, two years, and three years after biologic initiation. Thus, three models will be computed for each outcome. Sensitivity and specificity will also be compared to explore the differences observed between different remission definitions. Confidence intervals (95%) will be computed for AUCs, sensitivities and specificities and the differences between models will be described.

Patients, who switch or stop biologic, will be retained within the study to mimic an intention to treat analysis. We will explore subgroup analyses excluding those that switched or stopped as this pattern may be due to lack of clinical efficacy and/or other reasons, such as comorbidities, patient preference and access to biologics.

Statistical significance will be assessed at $p < 0.05$.

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 (R3) 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 and/or the ISAR academic network that have volunteered to participate will form the Advisory Group.

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91	Laila Salameh	United Arab Emirates
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Andrew Menzies-Gow

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Senior Data Analyst: Aaron Beastall

11.0 Timelines

Action	Timeline
Contract signature	March 2026
Proposal sign-off	March 2026
Full Protocol delivery	May 2026
Protocol sign-off	June 2026
Dataset delivery	July 2026
Analyses	Sept 2026
Final study report	October 2026
Conference abstract	TBC
Manuscript	TBC

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