Study Protocol

Assessing the impact of remission on long-term clinical outcomes of patients with severe asthma (SPOTLIGHT)

An assessment of the long-term impact of remission

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12.11.2024

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TITLE	**Assessing the impact of remission at 12-months on long-term clinical outcomes of patients with severe asthma (SPOTLIGHT)**
Subtitle	An assessment of the long-term impact of remission at 12-months post-initiation of biologic therapy
Protocol version number	V 0.2
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Product code	Not applicable
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Study aims and objectives	To evaluate the impact of clinical remission among patients with severe asthma • Objective 1: To describe the remission-relapse patterns and the patient characteristics of various patterns • Objective 2: To investigate the effect of remission on long-term clinical outcomes of asthma between those, who graduate to remission compared to those that do not
Countries of study	Argentina, Belgium, Brazil, Bulgaria, Canada, Colombia, Denmark, Estonia, France, Greece, India, Ireland, Italy, Japan, Korea, Kuwait, Mexico, Norway, Poland, Portugal, Saudi Arabia, Singapore, 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
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 FEV1

1.0 Background

Disease remission has been described as the state of low to no disease activity for an extended period of time in cancer and chronic inflammatory diseases, such as rheumatoid arthritis[16]. Remission can be induced by therapy or achieved spontaneously. In adult severe asthma, with the arrival and increased use of targeted therapy via monoclonal antibodies, the possibility and aim of complete or partial remission has surfaced as well. According to the European Respiratory Society and the American Thoracic Society task force severe asthma is defined as asthma that requires high-dose inhaled corticosteroids plus a second controller and/or oral corticosteroids (OCS) to remain controlled or asthma that continues to be uncontrolled despite therapy[14].

As a first step, there have been multiple efforts to define remission in severe asthma. Although a universal consensus on the definition of remission has not been reached, clinical, inflammatory, partial and complete remission are types of definitions that have been recently explored. For this project, we will focus on *clinical remission with therapy*. Menzies-Gow et al., Upham et al. and Canonica et al. conducted modified Delphi surveys to define clinical remission[1,2,3]. Upham et al. provided a 'super response' definition that involved improvement in three or more of the four clinical domains of asthma (exacerbation, asthma control, lung function, long-term oral corticosteroid use) over 12 months. Menzies-Gow et al. proposed a framework for clinical remission with treatment as (1) absence of significant symptoms by validated instrument, (2) lung function optimization/stabilization, (3) patient/provider agreement regarding remission, and (4) no use of systemic corticosteroids for 12 months or more. Canonica et al.'s modified Delphi presented a criterion for on-treatment, complete (the absence of the need for oral corticosteroids, symptoms, exacerbations or attacks, and pulmonary function stability) and partial (the absence of the need for oral corticosteroids, and two of three criteria: the absence of symptoms, exacerbations or attacks, and pulmonary stability) clinical remission. Therefore, current, expert-driven definition of remission has been

a composite of multiple domains, involving a criterion that requires achievement of three or more of the clinical domains of asthma at one-year post-initiation of a biologic, four being the most common[17]. With such a range of definitions, the proportion of patients with severe asthma that are obtaining remission in the real-world ranged from 18% to 47% (using a four domain definition) [6,7,8,9,10,17]

Thus far, real-world cohort studies of severe asthma have evaluated the prevalence of remission using various definitions mentioned above at multiple time points post-initiation, with 12-month post-initiation being the most common[17]. However, the effect of remission on clinical outcomes at one or two years after remission is achieved is not clear. In rheumatoid arthritis where biologics have been used for over 30 years, tapering of biologic drugs and even cessation of therapy is considered after remission[11]. Therefore, it is important to understand how clinical outcomes of asthma behaves upon remission so that clinical management plans and/or goals of severe asthma post-remission can be informed and updated.

The aim of this study is to first investigate the remission-relapse patterns that patients enrolled in the international severe asthma registry experience after one-, two- and three-years of achieving remission as clinical remission can be lost over time. We will compare the asthma outcome of those that reach remission at one year post-initiation and results will be compared to those that do not achieve remission. This will inform clinicians' and patients' long-term expectations once a patient arrives at remission at 12-months and which aspects of the disease pathology and burden should be carefully monitored and managed.

For this study, we will use the remission definition used by Perez-de-Llano et al: 0 exacerbations/year and no long-term oral corticosteroid (LTOCS) plus either partly/well controlled asthma or predicted percent predicted forced expiratory volume in one second (pp FEV1) ≥80% after twelve-months of biologic initiation. We will also conduct sensitivity analyses

using three (LTOCS, control, exacerbation) versus four domain (+lung function) definition of remission.

2.0 Study Aims and Objectives

2.1 Study Aims

To assess the long-term impact of remission at 12-months post-initiation on clinical outcomes of asthma

2.2 Study Objectives

Objective 1: To describe the patterns of remission and the patient characteristics of various patterns of remission

Objective 2: To investigate the effect of remission on long-term clinical outcomes of asthma between those that graduate to remission compared to those that do not

3.0 Study Design

This is a prospective cohort study describing the patterns of remission and profile the patients of each remission-pattern-group (objective 1, see section). Also, the long-term effects of remission on clinical outcomes (objective 2). For objective 1, remission will be assessed at 12 months, 24 months, and 36 months post-initiation as we plan to describe patterns of remission by time for a global severe asthma cohort.

For objective 2, we will assess long-term (up to 48 months post initiation) clinical outcomes of asthma (e.g. exacerbation) amongst those who graduate to remission at 12 months vs. those that do not graduate to remission at 12 months from starting a biologic using two severe asthma registries (ISAR (global) and CHRONICLE (US only)). Clinical outcomes will be assessed at 12 months from starting a biologic (for non-graduating patients) and at 24 and 36 months (and longer if data permits) for both graduating and non-graduating patients. For a full list of outcomes and respective definitions that will be explored, please see section 5.0. If sample size is adequate, a benralizumab-specific subgroup analysis will be conducted.

Furthermore, for objective 2, first time of remission assessment (twelve months post-initiation) will be the index date and time since remission assessment date will be the start of the outcome period for both groups. To further clarify, the deemed graduates and non-graduates are derived only from the first-remission assessment conducted at 12 months post-initiation. Thus, for objective 2, we will not look at the effect of remission on clinical outcomes across graduates and non-graduates from remission assessed beyond the point of 12-months post initiation.

Please see figure 1 for key aspects of the SPOTLIGHT study design. As noted in the background section, we will use the composite definition of remission as published by Perez-de-Llano et al in the American Journal of Respiratory and Critical Care Medicine. We will also conduct sensitivity analyses using three (LTOCS, control, exacerbation) versus four domain (+lung function) definition of remission.

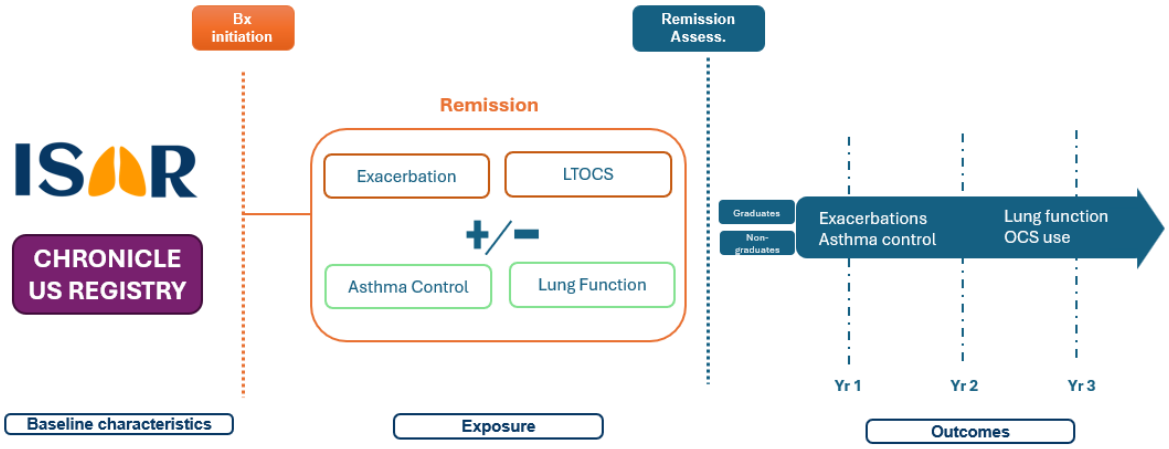

Figure 1 Study design

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[4]. Severe asthma is characterised either by its lack of control despite therapeutic efforts, or by the necessity for comprehensive treatment as described in steps 4 and 5 of the GINA guidelines[5]. 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 October 2024, there were 33,472 active participants from 28 countries enrolled into ISAR. Of these enrolled participants, 11,504 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.

CHRONICLE is a non-interventional, US, severe asthma registry that has collected data since February 2018. Adult (18 years or older) patients receiving a biologic or those who remain uncontrolled despite high-dosage inhaled corticosteroids and additional controllers are included in the registry. At inception, ISAR and CHRONICLE aligned on a core set of variables to allow for merging of a large study dataset. Like ISAR, CHRONICLE collects clinical outcome and patient reported outcomes annually. As of October 2024, there were 2687 patients that were prescribed a biologic and had at least 12 months of follow-up data on remission domain (exacerbation, asthma control, LTOCS, lung function).

4.2 Inclusion and Exclusion Criteria

Inclusion Criteria

- Patients receiving a biologic, AND
- Age 18 years or older at the time of biologic initiation, AND
- Patients with two year of post-biologic data for at least exacerbation and long-term oral corticosteroids (LTOCS) plus either lung function or asthma control
- Biologic therapy received primary for severe asthma

Exclusion criteria

- Biologic received for other conditions (e.g. Urticaria, atopic dermatitis, EGPA)

5.0 Study Variables and Study Outcome Definitions

5.1 Patient characteristics

The following data elements that were collected the pre-biologic will be used to describe those that did and did not achieve remission after 12 months of biologic initiation.

Patient characteristics
Sex
Age at time of remission (index date) or one year after bx initiation (non-graduates)
Body mass index (BMI)
Ethnicity
Country
Smoking status
Age at asthma onset
Duration of asthma
Highest pre-biologic blood eosinophil count (BEC)
Highest pre-biologic fractional exhaled nitric oxide (FeNO)
Highest pre-biologic serum immunoglobulin E (IgE)
One or more allergies detected from skin prick test and/or serum allergy test
Baseline asthma control
Baseline FEV_1 (post-bronchodilator)
Baseline FEV_1 percent predicted
Baseline FVC (post-bronchodilator)
Baseline FVC percent predicted
Baseline Exacerbation rate
Eosinophilic grade[12] Grade 0: unlikely/non-eosinophilic Grade 1: least likely Grade 2: likely Grade 3: most likely
Comorbidities Potentially T-2 related[15]: 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 low, medium, high

5.2 Research outcomes

Objective 1

Patterns of remission

	Months post Bx initiation (post-index + 12)		
	12	**24**	**36**
Stable	✓	✓	✓
Semi-sustained	✓	✓	×
Unsustained	✓	×	×
Relapse-remitting	✓	×	✓

Objective 2

Clinical outcomes of asthma

- LTOCS
- Exacerbations/year
- Lung function
- Asthma control
- Persistence of remission at 2 yrs
- Persistence of remission at 2 and 3 yrs

6.0 Statistical Analysis

6.1 Sample Size

Availability of ISAR follow-up data after biologic initiation for all biologic initiators, as of September 2024. CHRONICLE to be added.

Remission definitions as per Perez de-Llano	< 1 yr follow-up	1 yr follow-up	1 + 2 yr follow-up	1 + 2 +3 yr follow-up
Exacerb. + LTOCS	2753	2882	1565	985
Exacerb. + LTOCS + control	2482	2608	1312	790
Exacerb. + LTOCS + FEV1	2253	2265	1104	608
Exacerb. + LTOCS + control + FEV1	2068	2096	977	519

Availability of ISAR follow-up data after biologic initiation for Benralizumab initiators, as of November 2024. CHRONICLE to be added. This is for a potential Benra-specific subgroup analysis.

Remission definitions as per Perez de-Llano	< 1 yr follow-up	1 yr follow-up	1 + 2 yr follow-up	1 + 2 +3 yr follow-up
Exacerb. + LTOCS	493	494	259	165
Exacerb. + LTOCS + control	428	440	216	128
Exacerb. + LTOCS + FEV1	354	369	157	82
Exacerb. + LTOCS + control + FEV1	321	337	132	63

6.2 Software

Data management and analysis will be conducted in statistical software: Stata and/or R.

6.3 Objective 1

Remission graduates – pattern of remission

- The pattern of remission will be visually described via river plots. To clarify, we plan to show the moving proportion of patients who achieve remission at 12 months, who subsequently succeed and fail remission at later time points (vertical node) by time (horizontal node).
- As noted in the study design section, to facilitate this we will assess remission at 12-month intervals, therefore 24, 36, 48+ months post biologic initiation (1, 2, 3+ years post first remission assessment).

Remission pattern	Months post Bx initiation (post-index + 12)		
	12	24	36
Stable	✓	✓	✓
Semi-sustained	✓	✓	×
Unsustained	✓	×	×
Relapse-remitting	✓	×	✓

- Baseline patient characteristics (Section 5.1) for each remission-pattern group, such as those mentioned above, will be described. Contingency table analyses will be conducted to assess when differences across remission-pattern groups are statistically significant.
- Furthermore, for the remission-graduates, we will describe the pattern of attrition during 0-12, 12-24 months, and more than 24 months post first remission assessment date in the manner shown below. This exercise will inform us of the most common clinical domain of failure. Patients may show one of the following patterns up to 2 years from initial remission (3 years from biologic initiation):

    - Proportion with failure of one domain (specify the parameter)
    - Proportion with failure of two domains (specify the parameters)
    - Proportion with failure of three domains (specify the parameters)
    - Proportion with failure of all four domains (specify the parameters)

6.4 Objective 2

Remission graduates and non-graduates – impact of remission on clinical outcomes

- Baseline patient characteristics (Section 5.1) for graduating and non-graduating patients will be tabulated and compared using standardised mean differences (SMD).
- After describing the baseline patient characteristics, we will report the proportion of patients that arrive at the following destinations (categorical variables) or mean values (continuous variables) at the timeframe of 12-months, 24-months and 36-months past first-remission assessment year among graduates and non-graduates of on-treatment clinical remission:

    - **Lung function**
        - Continuous
            - FEV1
            - Percent predicted FEV1
                - If there are multiple recordings of lung function per year, the highest measurement will be used
        - Categorical

        - ≥ 80% ppFEV1
        - < 80% ppFEV1
- **Exacerbation**
    - 0 exacerbations in the last year
    - Greater than 0 exacerbations in the last year
        - 1 exacerbation in the last year
        - 2-3 exacerbations in the last year
        - 4+ exacerbations in the last year
- **LTOCS**
    - no use of LTOCS
    - Greater than 0 dd of LTOCS
- **Asthma control**
    - Partly/well controlled asthma
    - Reported poorly controlled asthma

For each timepoint (24, 36, and 48 months post biologic initiation), associations between the outcome and presence or absence of remission at 12 months post biologic initiation will be explored using linear, logistic or negative binomial regression. This will show whether remission at 12 months is key to successful clinical outcomes in later follow-up.

Linear regression – Highest FEV_1 in the last year, highest percent predicted FEV_1 in the last year

Logistic regression – ≥ 80% ppFEV1, 0 exacerbations in the last year, no use of LTOCS in the last year, partly/well controlled asthma

Negative binomial regression – Number of exacerbations in the last year

In each regression, remission at 12 months will be included as an explanatory variable (unadjusted analyses).

Each regression will be repeated adjusting for covariates likely to be prognostic for remission (baseline values of FEV_1, asthma control, exacerbation rate, asthma duration, use of LTOCS, and diagnosis of depression or obesity). Baseline patient characteristics with an SMD >0.1 between the remission graduate and non-graduate groups will also be considered as adjustment factors. The effect of having remission at 12 months will be tested be repeating these regressions with and without remission at 12 months as an explanatory variable and comparing these using a likelihood ratio test. This will show whether remission has an effect

on the outcomes over and above that due to differences in baseline characteristics. (Note: this approach is used rather than interpreting the coefficient for remission directly in the adjusted analyses due to its multicollinearity with some of the baseline characteristics).

Patients who switch or stop biologic treatment will be included in all analyses. For example, if a patient stopped the first biologic and restarted/switched to another biologic where the gap between biologic therapies is less than 6 months, the follow-up period will be anchored to the first biologic initiation date. Those that stopped a biologic and restarted/switched after 6 months or more of a period of non-bx therapy, the initiation or index date will reset with the second biologic that was continued for more than one year.
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 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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51	Michael E. Wechsler	United States
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53	Lakmini Bulathsinhala	OPC
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10.0 Research Team

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Senior Statistician: John Townend

Senior Data Analyst: Aaron

Medical Writer: David Neil

11.0 Timelines

Action	Timeline
Contract signature	March 2024
Proposal sign-off	March 2024
Full Protocol delivery	October 2024
Protocol sign-off	December 2024
Dataset delivery	February 2025
Analyses	April 2025
Final study report	May 2025
Conference abstract	TBC
Manuscript	TBC

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