Study Protocol

Exploring different composite definitions of responders and non-responders to biologic treatment for severe asthma (FULL BEAM)

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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
AQLQ	Asthma quality of life questionnaire
BD	Bronchodilator
BMI	Body mass index
eCRF	Electronic clinical record form
EMR	Electronic medical record
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in the first second
GETE	Global Evaluation of Treatment Effect
GINA	Global INitiative for Asthma
IgE	Immunoglobulin E
IL13	Interleukin 13
IL4	Interleukin 4
IL5	Interleukin 5
IL5R	Interleukin 5 receptor
ISAR	International Severe Asthma Registry
ISC	ISAR Steering Committee
JAQoL	Jobs and quality of life
LABA	Long-acting bronchodilator inhalers
LAMA	Long-acting muscarinic antagonist
LTOCS	Long-term oral corticosteroids
LTRA	Leukotriene receptor antagonist
NICE	National Institute for Health and Care Excellence
OCS	Oral corticosteroids
OPC	Optimum Patient Care
OPRI	Observational and Pragmatic Research Institute
PEF	Peak expiratory flow
RCT	Randomized control trial
REG	Respiratory Effectiveness Group
T2	Type 2 inflammation
TSLP	Thymic stromal lymphopoetin

1.0 Background

Asthma is a chronic, usually life-long inflammatory disorder of the airways affecting approximately 358 million people worldwide (1). Despite recent advances in treatment options, as many as 50% of affected adults have persistent symptomatic asthma and about 3-10% have severe asthma (2-4). Severe asthma is defined by the Global Initiative for Asthma (GINA) as asthma that is uncontrolled despite maximal optimized therapy and treatment of contributory factors, such as poor inhaler technique and adherence, or that worsens when treatment is decreased (5). Severe asthma results in increased morbidity such as impaired quality of life, loss of pulmonary function and a higher rate of exacerbations and hospitalization (4, 6). This translates into a significant financial burden with an estimated expenditure of €33.9 billion in Europe in 2011; approximately half of which is due to significant work impairment and productivity loss as a result of poor asthma control (7, 8).

In addition to maintenance therapy, long-term treatment with oral corticosteroids (OCS) or frequent, short bursts of OCS are commonly prescribed during an asthma exacerbation to treat the increased inflammatory response which is typically associated with an exacerbation (9, 10). This treatment plays an important role in the long-term severe asthma management and is effective for rapid relief of symptoms to prevent subsequent emergency admission. However, it has been associated with increased morbidity and related healthcare costs (11-13). Specifically, there is a dose-response, risk-association between long-term OCS use and adverse events, such as the onset or progression of osteoporosis, pneumonia, cardio-/cerebrovascular diseases, cataracts, sleep apnoea, depression/anxiety or weight gain (14). Fortunately, patients that are dependent on long-term OCS are eligible to receive novel, monoclonal antibody therapies as clinicians attempt to reduce exacerbation risk and minimize patients' exposure to OCS (10, 15).

The first monoclonal antibody was anti-immunoglobulin E (anti-IgE), which has been introduced more than twenty years ago. This spurred a rapid shift towards targeted therapies for severe asthma, particularly directed at the interleukin-5 inflammatory pathway (anti-IL5) and, more recently, to the interleukin-4 and 13 inflammatory pathways (anti-IL4/IL13). These modalities of therapy have been repeatedly found to be effective in improving asthma-related clinical outcomes such as exacerbation rates, OCS use, asthma symptoms control and lung function (16-28) (Table 1). Although many randomized controlled trials (RCTs) have demonstrated the clinical efficacy and safety of these monoclonal antibodies, their strict inclusion criteria may mean the obtained results only apply to a proportion of the severe

asthma target population. Therefore, the results of these studies may not necessarily reflect the individual response to biologics of patients with severe asthma in a real-world setting.

The response to biologic therapies is variable between patients (27, 29). Biomarkers are used to determine the biologic treatment initiation (15), while the improvements in clinical endpoints such as exacerbation and long-term OCS dose reduction are more pronounced in high baseline blood eosinophil groups (i.e. $\geqslant$300 cells.μL^{-1}) than low eosinophil groups (i.e. <300 cells.μL^{-1}) in studies that performed the comparisons (16, 17, 30). Besides the biomarkers, pooled analyses of two phase III clinical trials have shown that a history of hospitalization, LABA use, higher inhaled corticosteroid dose, higher FeNO and lower FEV1 levels at baseline predicted better response to anti-IgE treatment in terms of percentage reduction in exacerbations (31, 32). In addition, pre-treatment daily prednisone requirement, sinus disease, and late-onset asthma diagnoses were the strongest predictors of sub-optimal response to anti-IL5 treatment (33). However, these pre-treatment characteristics do not fully predict future response (34) and other factors, for instance BMI, socioeconomic status, age, and comorbidities, such as nasal polyposis, allergic rhinitis and chronic rhinosinusitis may also influence response (27, 35, 36). Therefore, gaining a better understanding of these factors could aid in the early identification of patients who are likely to receive benefit from monoclonal antibody therapy.

A universal definition of treatment response remains to be agreed upon. The National Institute for Health and Care Excellence (NICE) has recognized a reduction of exacerbation rate of at least 50% or a clinically reduced dose of long-term OCS as an adequate response, assessed up to 12 months after biologic therapy initiation (37). Currently, physician knowledge or tools like Global Evaluation of Treatment Effect (GETE) (38) are often used to evaluate patient response or treatment continuation. There have been a few real-world studies that have attempted to define responders based on post-biologic improvements in a variety of clinical and functional endpoints with reduction in exacerbations, OCS dose and asthma symptoms control being the most common domains (Table 2). In these studies, the proportion of patients with response ranged from 64% to 83% and time of response assessment ranged from 12 weeks to 1 year (32, 39-44). Furthermore, Delphi-based studies have attempted to operationally define responders and/or super-responders (Table 3). Upham et al. (45) surveyed eighty-one health care professionals (94% pulmonologists or allergists) from 27 countries via a multi-stage Delphi process to compose a super-responder definition. The international consensus-based, definition of super-responder encompassed an improvement of 3 or more domains (minor or major criteria) assessed over a 12-month-period. Perez de Llano et al. (46) developed a score ranging from 0 (worsening) to 100 (best

possible response) based on weighted response in four domains (severe exacerbations, OCS use, symptoms as evaluated by Asthma Control Test (ACT), and bronchial obstruction as assessed by FEV_1 percent predicted).

More recently, Menzies-Gow et al. have proposed a framework for asthma remission for all levels of disease severity as a treatment target based on relevant medical literature in other chronic inflammatory diseases such as rheumatoid arthritis and ulcerative colitis, as well as a modified Delphi survey to garner expert consensus (47) (see Table 3). While previous studies aimed to classify response to treatment by quantifying improvement from pre- to post-biologic initiation therapy, the concept of remission relates to a state or period with low to no disease activity. Its definition in the field of asthma and whether it should be the goal of initiating biologic therapy remains under debate.

Despite the emergence of common domains of treatment response, there is little agreement on clinically useful criteria for identifying real-world responders. To identify responders, clinically relevant markers of treatment response that are unequivocally applicable to all biologics must first be chosen, and then different levels of response characterized and compared. Furthermore, the emerging concept of remission in severe asthma patients remains to be explore in a real-world setting. The International Severe Asthma Registry (ISAR), the largest, real-life data repository of severe asthma cases from 24 countries, offers a unique opportunity to explore response and remission, and characterize patients with across groups using different composite definitions of both.

Table 1. Summary of findings of anti-IL5 and anti-IgE therapies from high quality RCTs*

Study	Design	Exacerbation rate	mOCS Dose	Pre-bronchodilator FEV_1	ACQ and AQLQ
Nair P, et al. 2017 (16)	Benralizumab (Anti-IL5) 28-week, n = 220	⇩ 70-83% vs baseline ⇩ 55-70% vs placebo	⇩ 75% baseline[1] ⇩ 50% placebo[1]	⇧ 210mL baseline ⇧ 105-112mL placebo	⇩ ACQ-6 0.86-1.09 points baseline ⇧ AQLQ 0.90-1.05 points baseline ⇩ ACQ-6 0.24-0.55 points placebo ⇧ AQLQ 0.23-0.45 points placebo
Bleecker ER, et al. 2016 (17)	Benralizumab (Anti-IL5R) 48-week, n = 1205	⇩62-76% vs baseline ⇩21-68% vs placebo[2]		⇧ 120-398mL baseline[2] ⇧ 106-159mL placebo	⇩ ACQ-6 0.89-1.46 points baseline ⇩ ACQ-6 0.08-0.29 points placebo
Chupp GL, et al. 2017 (18)	Mepolizumab (Anti- IL5) 24-week, n = 551				⇩ACQ-5 0.80 points baseline ⇩ACQ-5 0.40 points placebo
Castro M, et al. 2015 (19)	Reslizumab (Anti-IL5) 52-week, n = 953	⇩ 55% vs baseline ⇩ 46% vs placebo		⇧ 220mL baseline ⇧ 110mL placebo	⇩ACQ-7 1.02 points placebo ⇩ACQ-7 0.25 points placebo
Ortega HG, et al. 2014 (20)	Mepolizumab (Anti- IL5) 32-week, n = 576	⇩ 73-78% vs baseline ⇩ 47-53% vs placebo		⇧ 184mL baseline ⇧ 100mL placebo	⇩ACQ-5 0.92-0.94 points placebo ⇩ACQ-5 0.42-0.44 points placebo
Pavord ID, et al. 2012 (21)	Mepolizumab (Anti- IL5) 52-week, n = 621	⇩ 57-67% vs baseline ⇩ 48-52% vs placebo		⇧ 115-140mL baseline ⇧ 15-81mL placebo	⇩ACQ-5 0.75-0.80 points baseline ⇧ AQLQ 0.77- 0.93 points baseline ⇩ACQ-5 0.16-0.27 points placebo ⇧AQLQ 0.05-0.22 points placebo
Hanania NA, et al. 2011 (22)	Omalizumab (Anti-IgE) 48-week, n = 850	⇩ 67% vs baseline ⇩ 25% vs placebo			⇧ AQLQ 1.15 points baseline ⇧AQLQ 0.29 points placebo
Lanier B, et al. 2009[4] (23)	Omalizumab (Anti-IgE) 28-week, n = 627	⇩ 70% vs baseline ⇩ 43% vs placebo			
Holgate ST, et al. 2004 (24)	Omalizumab (Anti-IgE) 52-week, n = 246	⇩ 35-45% vs placebo	⇩ 73.8% baseline[3] ⇩ 23% placebo[3]	⇧ 89-116mL post-BD placebo	
Soler M, et al. 2001 (25)	Omalizumab (Anti-IgE) 28-week, n = 546		⇩ 52-58% placebo	⇧ Predicted FEV_1 3% baseline ⇧ Predicted FEV_1 3% placebo	
Busse W, et al. 2001 (26)	Omalizumab (Anti-IgE) 28-week, n = 525		⇩ 75% baseline (ICS) ⇩ 25% baseline placebo (ICS)	⇧ Predicted FEV_1 4.3% baseline ⇧ Predicted FEV_1 2.9% placebo	

Change % from baseline (absolute difference pre- vs post-biologic) and change % vs placebo (absolute difference drug arm vs placebo). ACQ and AQLQ MCID 0.5 points. Ranges (e.g. 55-70%) reflects the differences in dosage, frequency and baseline biomarkers between the groups of patients.
* Based on assessment from Cochrane review reports (48, 49).
[1]While maintaining asthma control; [2] Eosinophils ≥300 group exacerbation reduction of 45-51% and FEV_1 increase of 345-398mL; [3] Fluticasone ≥50% dose reduction; [4] Study quality unknown.

Table 2. Results of key previous studies measuring responders and non-responders to anti-IL-5 and anti-IgE therapy

			Responder Definition Endpoints					
Study	**Study Design & Population**	**% Responders & Time**	**Exacerbations**	**OCS Dose**	**Asthma Control**	**Quality of Life/Assessment**	**Lung Function**	**Other**
NICE, 2017, Mepolizumab and Reslizumab	Guidelines	at 12 months	≥50% reduction	Clinically significant reduction	Maintain asthma control			
Bousquet J, 2004, Omalizumab (32)	Post-hoc RCT, n = 1070, 55% females, 39 y.	64% at week 16	No exacerbations		Reduction ≥1 level	Increase ≥1 JAQoL	Increase PEF of ≥15	≥1 puffs of rescue medication
Kavanagh JE, 2020, Benralizumab (50)	Retrospective review, n = 130	86% at week 48	≥50% reduction	OR ≥50% reduction				
Kavanagh JE, 2020, Mepolizumab (42)	Retrospective review, n = 99, UK	72.7% responders and 28.3% super-responders at 1-year	≥50% reduction	≥50% reduction (if on)				
Kavanagh JE, 2018, Mepolizumab (40)	Retrospective review, n = 35, 49% females, 55.8y.	77% at week 12		≥50% reduction				
Niven RM, 2016, Omalizumab (39)	Mixed non-interventional, n = 258, 65% female, 44.7y.	82.4% responders at week 16	Physician assessment at week 16[1]					
Braunstahl GJ, 2013, Omalizumab (43)	Observational registry, n = 943, 65% females, 45y.	64.2% responders at week 16				GETE[2] at week 16		
Drick N, 2018 Mepolizumab (41)	Retrospective review	76% responders at 6 months				Improvement of subjective condition[3]	Increase FEV1 12% or ≥ 200 ml	Reduction of blood eosinophils
Gibson PG, 2016, Omalizumab (44)	Web-based registry	83% responders			≥0.5 in ACQ-5			

[1] Based on NICE and SMC criteria which includes exacerbation and OCS dose reduction.
[2] During interview patients were asked by the physician whether their subjective condition under therapy had improved or worsened (yes / no question), patients asked to consider asthma-related symptoms, quality of life (QoL), number of exacerbations and improvement of physical fitness.
[3] Global evaluation of treatment effectiveness (GETE) (38).

Table 3. Summary of Delphi studies defining responders to biologic therapy

		Domains (criteria in order of importance for multiple options)			
Study	Design	Exacerbation	OCS use	Asthma Control	Lung Function
Upham et al. (45)	Super-responder: meet 3 criteria (at least 2 major criteria)	Minor: ≥75% reduction Major: Elimination	Minor: N/A Major: Cessation or weaning of long-term OCS	Minor: Well controlled asthma Major: 2x MCID improvement	Minor: FEV1 500ml improvement Major: N/A
Perez et al. (46)	A response score from 0 to 100 via multiple domains	<50% reduction ≥50% reduction, but ≥1 severe exacerbations No severe exacerbations	<50% reduction Reduction ≥50% but <100% Withdrawal	≥ 3 points for ACT Total score ≥20	Pre-BD FEV1 increase ≥ 100mL FEV1 ≥80% of predicted
Menzies-Gow, Bafadhel et al. 2020 (47)	Framework for asthma remission as a treatment target. Time period ≥12 months	(HCP and patient agreement regarding remission)	No use of systemic corticosteroid therapy	No asthma symptoms	Optimization and stabilization of lung function

2.0 Study Aims and Objectives

2.1 Study Aims

In a real-world setting examine different composite definitions of response and remission following initiation of biologic therapy in adults with severe asthma in relation to patient characteristics before therapy initiation to identify composite measures most useful to assess response and remission in clinical practice.

2.2 Study Objectives

Objective 1: Define the study population

To describe pre-biologic demographic, clinical and functional characteristics of patients initiating biologics, overall and by biologic class.

Objective 2: Quantify levels of response and characterize patients by levels of response

- To operationally assess levels of response to biologics (from non-response to highest level of response) in individual domains and using different composite definitions based on exacerbation rates, long-term oral corticosteroid doses, asthma symptoms control, and lung function;
- To characterize patients by levels of composite definitions of response and compare patient characteristics between levels, overall and by biologic class.

Objective 3: Quantify components of clinical remission and characterize patients according to different definitions

- To operationally assess remission after biologic initiation in individual domains and using different composite definitions based on exacerbation rates, long-term oral corticosteroid use, asthma symptoms control, and lung function;
- To characterize patients by categories of composite definitions of remission and compare patient characteristics between categories, overall and by biologic class.

3.0 Study Design

This study is a registry-based cohort study. The study consists of pre-biologic (baseline) and post-biologic (follow-up) periods (Figure 1). Variables describing the patient baseline demographic and clinical characteristics are obtained during pre-biologic visits, which are prior to or on biologic treatment initiation date. Patient baseline characteristics are available at biologic initiation (eg, age and long-term OCS use), in the year preceding biologic initiation (eg, count of exacerbation episodes), or at any time points pre-biologic initiation (eg, highest blood eosinophil concentration and allergy test results).

Post-biologic period is from biologic initiation date until a follow-up visit closest to a 1-year period with a minimum of 24 weeks of follow-up time (48 weeks for exacerbation rates). ISAR data structure consists of data collected at the time of regular follow-up visits to the doctor, including numbers of exacerbations and change in medication intake (eg, long-term OCS) since the previous visit. In patients who have at least 1 follow-up visit, 80% have post-biologic data available at the 1-year mark +/- 1 month. We aim to use 1-year of follow-up if more than one follow-up visit data is available, thus if a patient had follow-up visits equidistant from before and after 1-year the biologic initiation date, we will use the second follow-up of >1-year in this occasion (maximum 18 months since biologic initiation).

During this post-biologic period, we will assess four asthma clinical and functional endpoints (domains) chosen based on a review of biologic effectiveness studies (Table 1), responder publications (Table 2), and three Delphi based studies (Table 3). The composite definitions will at the minimum consider exacerbations and long-term OCS use. Asthma symptoms control and/or lung function will also be considered.

It should be noted that, while remission can also be defined as a period of time with low to no disease activity (durable remission, on- or off-treatment), this goes beyond the scope of the present project where the disease activity will be assessed at approximately 1-year time after initiating biologics.

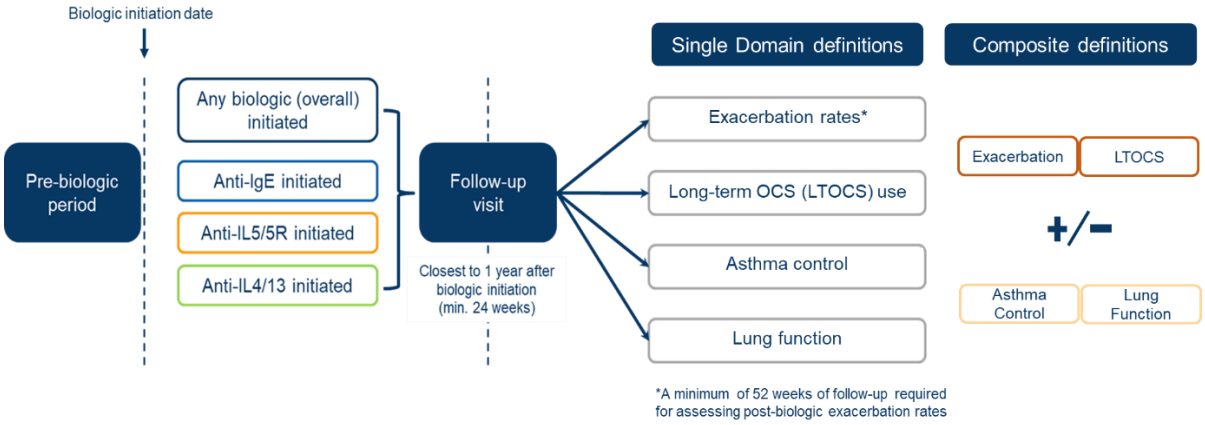

Figure 1. Study design. Note: Patients enrolled in ISAR who initiated anti-TSLP have not yet been followed up.

4.0 Study Population

4.1 Data Sources

Data will be sourced from the International Severe Asthma Registry (ISAR) (51). ISAR is a multi-country, multicentre, observational initiative with retrospective and prospective data collection. Data collection started in 2017 and is currently ongoing. ISAR includes patients ≥18 years old who receive treatment according to GINA Step 5 or experience uncontrolled asthma at GINA Step 4 as per the definition of severe asthma (5, 27). As of July 2022, ISAR had 13,164 patients registered in the database, out of whom 5,961 had a history of biologic treatment. Its strength comes from the collection of patient level, pseudonymous, real-life, standardized (using a core set of agreed variables) data from 24 countries and over 248 sites across the world. Data are collected via electronic Clinical Record Forms (eCRF) made available by a common web-based platform in 14 countries. Another 9 countries collect data using their own eCRF systems, and for the USA data are extracted from electronic medical records (EMR). Data are then processed in a standardized manner to produce overall ISAR datasets.

4.2 Inclusion and Exclusion Criteria

Inclusion Criteria

- Patients who are receiving treatment according to GINA (2020 Criteria) step 5 or are uncontrolled at step 4. Uncontrolled asthma is defined as having severe asthma symptoms or frequent exacerbations (≥2/year) requiring oral corticosteroids;
- Patients prescribed with a biologic (anti-IL5/5R, anti-IgE, anti-IL4/IL13, or anti-TSLP) for the first time;
- Patients 18 years or older at biologic initiation;
- Available registry data prior to or on biologic therapy initiation date for at least one of the studied domains: exacerbation rate (number of episodes in the year preceding biologic initiation), long-term OCS use (at biologic initiation), asthma symptoms control (as assessed closest to biologic initiation in the year preceding to initiation), lung function (as assessed closest to biologic initiation in the year preceding to initiation);
- Available registry data for at least one paired domain at follow-up visit that is closest to a 1-year period (min. 24 weeks for long-term OCS use, asthma symptoms control, and lung function; min. 52 weeks for exacerbations).
  Note: follow-up data for patients enrolled in ISAR who initiated anti-TSLP is not yet available and as such, they are currently not eligible. However, subject to funding and

sufficient numbers, the analysis could be revisited in a year time when this data becomes available.

Exclusion Criteria

- Patients who received bronchial thermoplasty prior to initiating biologics.

5.0 Study Variables and Study Outcome Definitions

While clinical remission will be assessed in all patients irrespective of their status pre-biologic initiation, response can only be assessed in patients impaired when initiating the treatment. Impairment will be defined for each domain independently as: 1) exacerbations: ≥2 exacerbations in the year preceding biologic initiation; 2) long-term OCS use: patients receiving long-term (daily) OCS at biologic initiation; 3) asthma symptoms control: partly or uncontrolled patients at biologic initiation, based on GINA 2020 asthma symptoms control categories (5); 4) lung function: patients <80% FEV1 predicted pre-biologic initiation.

5.1 Individual response/remission domains

5.1.1 Exacerbation rates

Exacerbations during the follow-up will be counted from the day of the biologic initiation to the day closest to the 1-year mark post-initiation. A minimum of 48 weeks of follow-up will be required.

Response definition (in patients with ≥2 exacerbations in the year preceding biologic initiation)

- Non-response: <50% reduction from pre- to post-biologic initiation
- Response: ≥50% reduction from pre- to post-biologic initiation

Post-biologic categories considered for remission definitions (in all patients, irrespective of pre-biologic status)

- ≥1 that required hospitalisation, or ≥3 of any severity
- 2 that did not require hospitalisation
- 1 that did not require hospitalisation
- None

5.1.2 Long-term OCS use

Response definition (in patients receiving long-term OCS at biologic initiation)

- Non-response: <50% reduction in daily dose from pre- to post-biologic initiation
- Response: ≥50% reduction in daily dose from pre- to post-biologic initiation

Post-biologic categories considered for remission definitions (in all patients, irrespective of pre-biologic status)

- >10mg/day
- >5 to 10mg/day
- >0 to 5mg/day
- No long-term OCS use

5.1.3 Asthma symptoms control

Well/partly/uncontrolled categories as defined by GINA 2020 (5) will be used. Whenever ACQ or ACT scores were provided in lieu of GINA categories, conversions will be applied as detailed in section 5.3.

Response definition (in patients uncontrolled or partly controlled pre-biologic initiation)

- Non-response: No improvement or deterioration
- Response: ≥1 category improvement

Post-biologic categories considered for remission definitions (in all patients, irrespective of pre-biologic status)

- Uncontrolled
- Partly controlled
- Well controlled

5.1.4 Lung function

For lung function, post-bronchodilatator FEV1 (absolute value in mL) and FEV1 percent predicted (in %) will be used.

Response definitions (in patients <80% FEV1 predicted pre-biologic initiation)

- Non-response: <100mL increase, no change, or decrease
- Response: ≥100mL to <200mL increase in FEV1
  ≥200mL to <500mL increase in FEV1
  ≥500mL increase in FEV1

As an exploratory analysis, and in an attempt to account for the heterogeneity in patients' geographical location and ethnicity, we will explore different thresholds of relative increase on the FEV1 percent predicted scale.

Post-biologic categories considered for remission definitions (in all patients, irrespective of pre-biologic status)

- <80% FEV1 percent predicted
- ≥80% FEV1 percent predicted

In addition to the definitions provided above, we will explore lung function stability in order to characterize the patients that do not deteriorate over time, which could be considered for both response and remission. Allowing 5% variability on spirometry, the categories will be defined as:

- Deterioration: post-biologic FEV1 <0.95 pre-biologic FEV1
- Stability: post-biologic FEV1 ≥0.95 pre-biologic FEV1

5.2 Composite definitions of response/remission

5.2.1 Response

Eligibility criteria for impairment at biologic initiation and individual domain response definitions described in section 5.1 will be applied for the composite definitions of response. Levels of response will be defined for each composite definition by the number of single domain response criteria met as follows:

1) Exacerbation rates and long-term OCS use

Eligibility criteria: Patients with ≥2 exacerbations in the year preceding biologic initiation & receiving long-term OCS at biologic initiation

Response levels:

- Level 0: meeting none of the response criteria
- Level 1: meeting 1 of the response criteria
- Level 2: meeting both response criteria

2) Exacerbation rates, long-term OCS use, and asthma symptoms control

Eligibility criteria: Patients with ≥2 exacerbations in the year preceding biologic initiation
& receiving long-term OCS at biologic initiation
& being partly or uncontrolled at biologic initiation

Response levels:

- Level 0: meeting none of the response criteria
- Level 1: meeting 1 of the response criteria
- Level 2: meeting 2 response criteria
- Level 3: meeting all 3 response criteria

3) Exacerbation rates, long-term OCS use, asthma symptoms control, and lung function*

Eligibility criteria: Patients with ≥2 exacerbations in the year preceding biologic initiation
& receiving long-term OCS at biologic initiation
& being partly or uncontrolled at biologic initiation
& having FEV1 <80% predicted at biologic initiation

Response levels:

- Level 0: meeting none of the response criteria
- Level 1: meeting 1 of the response criteria
- Level 2: meeting 2 response criteria
- Level 3: meeting 3 response criteria
- Level 4: meeting all 4 response criteria

* The response criteria for improvement in lung function will primarily be an increase of at least 100mL in FEV1. Other criteria will be explored.

In order to explore composite definitions of response in non long-term OCS users, the variables defined above will be computed in this subgroup of patients after excluding the reduction in long-term OCS daily doses, ie 1) reduction in exacerbations and improvement in asthma symptoms control; and 2) reduction in exacerbations, improvement in asthma symptoms, and improvement in lung function. Other combinations of composite definitions of response (eg, improvement in asthma symptoms control and improvement in lung function alone) will also be explored.

5.2.1 Remission

Composite definitions of remission will not impose pre-biologic impairments in any domains. The strict definitions will allow no exacerbation over the year following biologic initiation and no long-term OCS use at approximately 1 year after biologic initiation. The relaxed definitions will allow up to 1 exacerbation (not requiring hospitalisation) and up to 5mg/day of long-term OCS (a dose that can be used in patients who have adrenal insufficiency). Asthma symptoms control and lung function criteria will be progressively added as follows:

1) **Exacerbation rates and long-term OCS use:**

Strict definition:

no exacerbation in the year following biologic initiation
& no long-term OCS use at ~1 year following biologic initiation

Relaxed definition:

≤1 exacerbation (not requiring hospitalisation) in the year following biologic initiation
& long-term OCS ≤5mg/day at ~1 year following biologic initiation

2) **Exacerbation rates, long-term OCS use, and asthma symptoms control:**

Strict definition:

no exacerbation in the year following biologic initiation
& no long-term OCS use at ~1 year following biologic initiation
& partly/well controlled at ~1 year following biologic initiation

Relaxed definition:

≤1 exacerbation (not requiring hospitalisation) in the year following biologic initiation
& long-term OCS ≤5mg/day at ~1 year following biologic initiation
& partly/well controlled at ~1 year following biologic initiation

3) **Exacerbation rates, long-term OCS use, asthma symptoms control, and lung function:**

Strict definition:

no exacerbation in the year following biologic initiation
& no long-term OCS use at ~1 year following biologic initiation
& partly/well controlled at ~1 year following biologic initiation
& FEV1 ≥80% predicted at ~1 year following biologic initiation

Relaxed definition:

≤1 exacerbation (not requiring hospitalisation) in the year following biologic initiation
& long-term OCS ≤5mg/day at ~1 year following biologic initiation

& partly/well controlled at ~1 year following biologic initiation

& FEV1 ≥80% predicted at ~1 year following biologic initiation or stable lung function

5.3 Analytical variables

Table 4. List of variables that will be used for the analysis.

Label	Type	Value	Construct/comments
Meta data[1]			
Calendar year at biologic initiation	Numerical	-	
Follow-up duration (weeks)	Numerical	-	At least 24 weeks and as close as possible to 1 year
Biologic therapy variables[1]			
Type of biologics	Nominal	Anti-IgE, anti-IL5/5R, anti-IL4/13, anti-TSLP	
Biologic therapy maintenance	Binary	0=Switched/stopped 1=Continue	Data indicating a discontinuation of initial biologic in the first year of follow-up
Asthma-related outcome variables[2]			
Exacerbation rates			
Exacerbation rate at biologic initiation	Discrete	-	Number of exacerbations in the year preceding biologic initiation.
Rate of exacerbations requiring hospitalisation at biologic initiation	Discrete	-	Number of exacerbations requiring hospitalisation in the year preceding biologic initiation.
Exacerbation rate at follow-up	Discrete	-	Number of exacerbations during the year following biologic initiation.
Rate of exacerbations requiring hospitalisation at follow-up	Discrete	-	Number of exacerbations requiring hospitalisation during the year following biologic initiation.
Reduction of ≥50% in exacerbation rate between baseline and follow-up	Categorical	Yes No N/A	N/A for patients <2 exacerbations in the year preceding biologic initiation.
Long-term OCS use[2]			
Long-term OCS dose at biologic initiation (mg/day)	Numerical	-	Prednisone-equivalent dosages.
Long-term OCS dose at follow-up (mg/day)	Numerical	-	Prednisone-equivalent dosages.
Reduction of ≥50% in long-term OCS dose between baseline and follow-up	Categorical	Yes No N/A	N/A for patients not receiving long-term OCS at biologic initiation
Asthma symptoms control[2]			
Asthma symptoms control assessment at biologic initiation	Ordinal	Well controlled Partly controlled Uncontrolled	GINA 2020 classification (used by most participating centres). For centres reporting asthma symptoms control assessment based on ACT (52) and/or ACQ (53), algorithms will be used to fit available data to GINA 2020 categories: - ACQ: Mean ACQ ≤0.75: Well controlled 0.75< Mean ACQ <1.5: Partly controlled Mean ACQ ≥1.5: Uncontrolled - ACT: Total ACT >19: Well controlled 15< Total ACT ≤19: Partly controlled Total ACT ≤15: Uncontrolled

Asthma symptoms control assessment at follow-up	Ordinal	Well controlled Partly controlled Uncontrolled	See above.
Improvement in asthma symptoms control between baseline and follow-up	Categorical	Yes No N/A	Yes: Partially or uncontrolled → Well controlled, or Uncontrolled → Partially controlled No: Remain uncontrolled or partially controlled N/A: Patients well controlled at baseline
Lung function[2]			
Post-bronchodilator FEV_1 at biologic initiation (mL)	Numerical	-	
Post-bronchodilator FEV_1 at follow-up (mL)	Numerical	-	
Post-bronchodilator FEV_1 percent predicted at biologic initiation	Numerical	-	
Post-bronchodilator FEV_1 percent predicted at follow-up	Numerical	-	
Change in post-bronchodilator FEV_1 between baseline and follow-up	Categorical	≥500mL increase 200 to 499mL increase 100 to 199mL increase Between 99mL increase and 99mL decrease 100 to 199mL decrease ≥200mL decrease	
Patient characteristics variables			
Demographic characteristics[1]			
Age at biologic initiation (years)	Numerical	-	Attained age in complete years
Sex	Nominal	Female, male	
Ethnicity	Nominal	Caucasian, South East Asian, North East Asian, African, Mixed, Other, Unknown	
Country	Nominal	Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Poland, Portugal, Saudi Arabia, South Korea, Spain, Taiwan, UAE, UK, USA	
Body mass index (BMI) at biologic initiation (kg/m^2)	Numerical	-	Weight in kg/(height in m)^2
Body mass index at biologic initiation in categories	Ordinal	Underweight Normal weight Overweight Obesity class I Obesity class II Obesity class III	Underweight: BMI<18.5 Normal weight: 18.5≤BMI<25 Overweight: 25≤BMI<30 Obesity class I: 30≤BMI<35 Obesity class II: 35≤BMI<40 Obesity class III: BMI>40
Smoking status at biologic initiation	Ordinal	Current smoker, ex-smoker, never smoker	
Asthma clinical features[2]			
Age of asthma onset (years)	Numerical	-	Attained age in complete years at which asthma was diagnosed or symptoms began
Age of asthma onset in categories (years)	Categorical	>25, ≥25	

Asthma duration	Numerical	-	Whole years between age of asthma onset and biologic initiation
Highest blood eosinophil count before biologic initiation (10^9 cells/L)	Numerical	-	
Highest blood IgE count before biologic initiation (IU/mL)	Numerical	-	
Highest FeNO test before biologic initiation (ppb)	Numerical	-	
Allergy test results before biologic initiation	Binary	Positive, negative	From skin prick test or serum test for dust mite, grass mix, cat hair, mould mix, dog hair, aspergillus, weed mix, trees, food mix, animal mix, or other environmental allergens
Asthma-related medication at biologic initiation[2]			
Long-acting muscarinic antagonist (LAMA) in the year preceding biologic initiation	Binary	Yes, no	
Theophylline in the year preceding biologic initiation	Binary	Yes, no	
Leukotriene receptor antagonist (LTRA) in the year preceding biologic initiation	Binary	Yes, no	
Macrolide antibiotic in the year preceding biologic initiation	Binary	Yes, no	
Other steroid sparing agents in the year preceding biologic initiation	Binary	Yes, no	
Other treatment in the year preceding biologic initiation	Binary	Yes, no	
History of comorbidities at biologic initiation			
Allergic rhinitis[2]	Binary	Yes, no	
Chronic rhinosinusitis[2]	Binary	Yes, no	
Nasal polyps[2]	Binary	Yes, no	
Eczema/atopic dermatitis[2]	Binary	Yes, no	
Sleep apnea[3]	Binary	Yes, no	
Anxiety/depression[3]	Binary	Yes, no	
Osteoporosis[3]	Binary	Yes, no	
Diabetes[3]	Binary	Yes, no	
Chronic heart disease[3]	Binary	Yes, no	
Pneumonia[3]	Binary	Yes, no	
Peptic ulcer[3]	Binary	Yes, no	
Pulmonary embolism/ venous thromboembolism[3]	Binary	Yes, no	
Cataract[3]	Binary	Yes, no	
Chronic kidney disease[3]	Binary	Yes, no	
Glaucoma[3]	Binary	Yes, no	
Cerebrovascular accident[3]	Binary	Yes, no	

1. Core ISAR variables.
2. Core ISAR variables, although not necessarily available pre-biologic initiation if biologic initiation occurred before enrolment visit.
3. Effectiveness bolt-on variables, collected by a selection of participating countries.

6.0 Statistical Analysis

6.1 Software

The analysis will be conducted with R version 4.1.0.

6.2 Sample size

As of 21 July 2022, a total of 5,961 patients who initiated biologics are recorded in ISAR.

All patients (objective 3)

Preliminary numbers of patients that will enter the remission analysis (objective 3) are presented in Figure 2. While pre-biologic status for the asthma-related outcomes is not a pre-requisite for the description of remission status, patients with no pre-biologic data overall will be excluded from the analysis as an important part of the project will be to characterize the patients at biologic initiation.

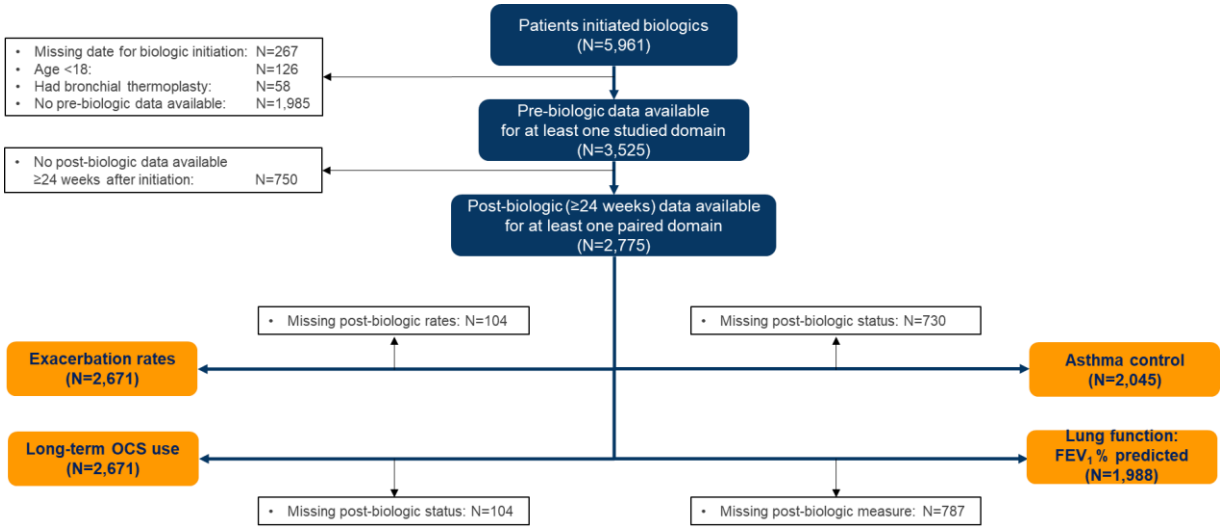

Figure 2. Preliminary flowchart of data availability for patients who initiated any type of biologics as of 21 July 2022. Exclusions are sequential from top to bottom.

In patients impaired at biologic initiation, by single domains and composite definitions of response (objective 2)

Table 5. Preliminary sample size of impaired patients at biologic initiation (numbers presented are patients who were impaired at biologic initiation and with available data at follow-up).

Domains	N
1. Exacerbations (≥2 exacerbation in the year preceding biologic initiation)	1,392
2. Long-term OCS dose (receiving long-term OCS at biologic initiation)	475
3. Asthma symptoms control (uncontrolled or partially controlled at biologic initiation)	1,360
4. Lung function (FEV_1 <80% predicted at biologic initiation)	1,179
1 + 2	313
1 + 2 + 3	264
1 + 2 + 3 + 4	134

6.3 Analysis for objective 1

Objective 1 aims at describing the study population used in objectives 2 and 3. To this end, the pre-biologic asthma-related outcomes will first be described individually and in composite variables. For individual asthma-related outcomes, both continuous and categorical variables will be used. The categories will be based on the eligible criteria used for impairment:

- Exacerbations: ≥2 versus <2
- Long-term OCS use: yes/no
- Asthma symptoms control: partly or uncontrolled versus well controlled
- Lung function: ≥80% versus <80% FEV1 predicted

The distributions will be compared between initiated biologic class using t-tests, Kruskall Wallis tests, or Person's Chi-squared tests as appropriate. The distribution of pre-biologic asthma related outcomes will also be compared between countries (or geographic regions in case of small sample size).

Patient characteristics (see Table 4) will also be described and compared univariately between the initiated biologic classes using appropriate statistical tests based on variable type and distribution.

6.4 Analysis for objective 2

Descriptive analysis

The proportion of patients responding to biologics as defined in section 5 will be computed overall and by biologic classes, for each individual domain and composite definition of response.

Patient characteristics will be described by levels of response using means, standard deviations, medians and interquartile ranges for continuous variables and numbers and percentages for categorical variables.

Trajectories from pre- to post-biologic status will also be described as cross-tabulations, by single domains and composite definitions.

Since the requirements for biologic initiation vary by countries, the above analysis will be stratified by pre-biologic status (eg, no exacerbation, no long-term OCS use, alone or in combination), overall and by country/geographic regions.

Association analysis (composite definitions)

- **Univariate analysis:**
    - The association between patient characteristics, including country/geographic region (see Table 4), and ordinal response levels will be tested by fitting ordinal logistic regressions using response levels as the outcome variable and each patient characteristic individually. Significance will be tested through log-likelihood ratios.
    - Where the proportionality of odds assumption does not hold in the ordinal logistic regressions, binary logistic regressions will be used instead comparing extreme levels to all other levels of response.
    - The comparisons will be performed overall and for each class of biologics separately.
- **Multivariate analysis:**
    - We will use logistic regression techniques in a similar fashion as above, fitting in the same model the patient characteristics that are significant ($p<.05$) in the univariate analysis.
    - The models will be fitted overall and for each class of biologics separately.
    - Optionally, a single model will be fitted adding biologic class in the model together with patient characteristics.

6.5 Analysis for objective 3

Descriptive analysis

The proportion of patients in different definitions of remission at follow-up as defined in section 5 will be computed overall and by biologic classes, for each individual domain and composite definition of response.

Patient characteristics will be described by definitions of remission using means, standard deviations, medians and interquartile ranges for continuous variables and numbers and percentages for categorical variables.

Trajectories from pre- to post-biologic status will also be described as cross-tabulations, by single domains and composite definitions.

Association analysis (composite definitions)

- **Univariate analysis:**
  - The association between patient characteristics, including country/geographic region (see Table 4), and different binary definitions of remission will be tested by fitting binary logistic regressions using remission yes/no as the outcome variable and each patient characteristic individually. Significance will be tested through log-likelihood ratios.
  - The comparisons will be performed overall and for each class of biologics separately.
- **Multivariate analysis:**
  - We will use logistic regression techniques in a similar fashion as above, fitting in the same model the patient characteristics that are significant ($p<.05$) in the univariate analysis.
  - The models will be fitted overall and for each class of biologics separately.
  - Optionally, a single model will be fitted adding biologic class in the model together with patient characteristics.

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

Results from the study will be submitted for publication in asthma focused peer-reviewed scientific journals. We will also consider submitting abstracts for distinct results to relevant international conferences. Authorship will follow the ISAR authorship policy.

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.

Project Steering Committee Member	**Country/Funder**
Jorge Maspero	Argentina
Mark Hew Matthew Peters	Australia
George C. Christoff Todor A. Popov	Bulgaria
Celine Bergeron Mohsen Sadatsafavi	Canada
Carlos A. Torres-Duque	Colombia
Celeste M. Porsbjerg	Denmark
Alan Altraja	Estonia
Lauri A. Lehtimäki	Finland
Arnaud Bourdin Camille Taillé	France
Christian Taube	Germany
Andriana I. Papaioannou Nikolaos G. Papadopoulos	Greece
Sundeep Salvi	India
Richard W. Costello	Ireland
Enrico Heffler Giorgio Walter Canonica	Italy
Takashi Iwanaga	Japan
Mona Al-Ahmad	Kuwait
Désirée Larenas-Linnemann	Mexico
Sverre Lehmann	Norway
Piotr Kuna	Poland
João A. Fonseca	Portugal
Riyad Al-Lehebi	Saudi Arabia
Mariko Koh Siyue	Singapore
Chin Kook Rhee	South Korea
Borja G. Cosio Luis Perez-de-Llano	Spain
Leif Bjermer	Sweden
Diahn-Warng Perng (Steve)	Taiwan
Bassam Mahboub	United Arab Emirates
Andrew N. Menzies-Gow David J. Jackson John Busby Liam G. Heaney Paul E. Pfeffer	United Kingdom
Eileen Wang Michael E. Wechsler	United States
Neil Martin Tham T. Le Trung N. Tran	AstraZeneca

10.0 Research Team

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11.0 Timelines

Action	Timeline
Protocol sign-off	November 2022
Dataset delivery + ADEPT approval	November 2022
Analyses and preliminary results	December 2022
Final study report	February 2023

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