OPC Global

Study Protocol (OPCG-2001)

Defining and Characterizing Responders to Biologic TrEAtment in Severe AsthMa Patients (BEAM)

OPERATIONALLY DEFINE RESPONDERS TO BIOLOGIC TREATMENT BY CLINICAL AND FUNCTIONAL ENDPOINTS AND DESCRIBE THEIR CHARACTERISTICS OVERALL AND PER BIOLOGIC CLASS IN A LARGE INTERNATIONAL REGISTRY COHORT STUDY

Date: 04.09.2020

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Title	Defining and Characterizing Responders to Biologic Treatment
Subtitle	Operationally define responders to biologic treatment by clinical endpoints and describe their characteristics overall and per biologic class in a large international registry cohort study.
Protocol version number	2.0
Medicinal product	Not applicable
Product code	Not applicable
Marketing authorisation holder	Not applicable
Marketing authorisation number	Not applicable
Study aims and objectives	Aim: To classify responders to biologic treatment by clinical and functional endpoints and describe their characteristics overall and per biologic drug class Objective 1: To operationally assess response to biologic therapy by clinical and functional endpoints including exacerbations, systemic corticosteroids, asthma control and lung function Objective 2: To describe and compare baseline (pre-therapy) demographic, clinical and functional characteristics of response and non-response groups to overall biologic treatment and by biologic class
Country of study	Canada, USA, Mexico, Colombia, Argentina, the UK, Ireland, Denmark, Germany, Spain, Portugal, Greece, Italy, Bulgaria, South Korea, Japan, Taiwan, Singapore, Kuwait, the UAE, Saudi Arabia
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1. LITERATURE REVIEW

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 up to 6% 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 control and lung function (16-28) **(Table 1)**. Although many Randomized Controlled Trials (RCTs) have demonstrated the clinical effectiveness and safety of these monoclonal antibodies, their strict inclusion criteria and poor external validity 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, and this variation is only partly explained (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. $\geqslant 300\ \mu L^{-}1$) than low eosinophil groups (i.e. $<300\ \mu L^{-1}$) in studies that performed the comparisons (16, 17, 30). However, even patients with lower blood eosinophil levels have significant reductions in exacerbations and are at risk of missing out on the benefits of biologic treatment (17, 27, 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 FEV_1 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 long-term benefit from monoclonal antibody therapy.

As previously stated, 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 (i.e. quality of life) endpoints with reduction in exacerbations, OCS dose and asthma 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, ongoing Delphi-based studies have set out to operationally define responders and/or super-responders **(Table 3).** Upham et al. 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 (45). 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. The Spanish Responder Score Study, currently in development by Perez and colleagues based on patients in the Spanish Severe Asthma Registry, will be a clinical tool to assess response to monoclonal antibodies based on a score from 0 to 100 via multiple core domains that were derived from a literature review and Delphi process. Lastly, Menzies-Gow et al. have proposed a framework for asthma remission for all levels of disease severity as a treatment target by also implementing a modified Delphi survey to garner expert consensus (46) (see Table 3).

Despite the emergence of common domains of treatment response, there is little agreement on clinically useful criteria for identifying real-world responders. The overlap of eligibility for different biologics and/or classes targeting the T2-inflamamtory pathway, further challenges the optimal clinical management of patients receiving biologics [29]. 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. The International Severe Asthma Registry (ISAR), the largest, real-life data repository of severe asthma cases from 23 countries, offers a unique opportunity to assess response and characterize patients with varying levels of response.

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 (47, 48)
[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 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 (49)	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.	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.	A response score from 0 to 100 via multiple domains	<50% reduction ≥50% reduction, but ≥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 (46)	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

1.1. STUDY AIMS

The study aims to classify responders to biologic treatment by clinical and functional endpoints and describe their characteristics overall and per biologic drug class.

1.2. STUDY OBJECTIVES

Objective 1: To operationally assess response to biologic therapy by clinical and functional endpoints including exacerbations, systemic corticosteroids, asthma control and lung function.

Objective 2: To describe and compare baseline (pre-therapy) demographic, clinical and functional characteristics of response and non-response groups to overall biologic treatment and by biologic class.

2. STUDY DESIGN

2.1. DATA SOURCE

Data will be sourced from the International Severe Asthma Registry (ISAR) (50). 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 August 2020, ISAR had 9,211 patients registered in the database, out of which 3,475 had a history of biologic treatment. Its strength comes from the collection of patient level, anonymous, real-life, standardized (using a core set of agreed variables) data from 23 countries and over 248 sites across the world. Primary data are collected via electronic Clinical Record Forms (eCRF) made available by a web-based platform, OpenClinica. The data collection platform is customized for real-life data collection. This ensured the highest data quality feasible via data validation rules at the point of data entry.

ISAR has ethical governance provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG). The registry's scientific merit is ensured by the ISAR Steering Committee (ISC), which is composed of 47 severe asthma specialist or database experts from 25 countries (http://isaregistries.org/).

2.2. STUDY DESIGN

This study is a registry 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 (the first visit date for the UK and Denmark patients). Post-biologic period is from biologic initiation date until a follow-up visit closest to a 1-year period with a minimum of 16 weeks of follow-up time (ERS(34)). ISAR data structure consists of yearly follow-ups, thus majority of follow-up visits occurred at around 1-year mark. We aimed 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. During this post-biologic period, patients' response is evaluated based on four asthma clinical and functional endpoints chosen (i.e. response domains, details found in section 3).

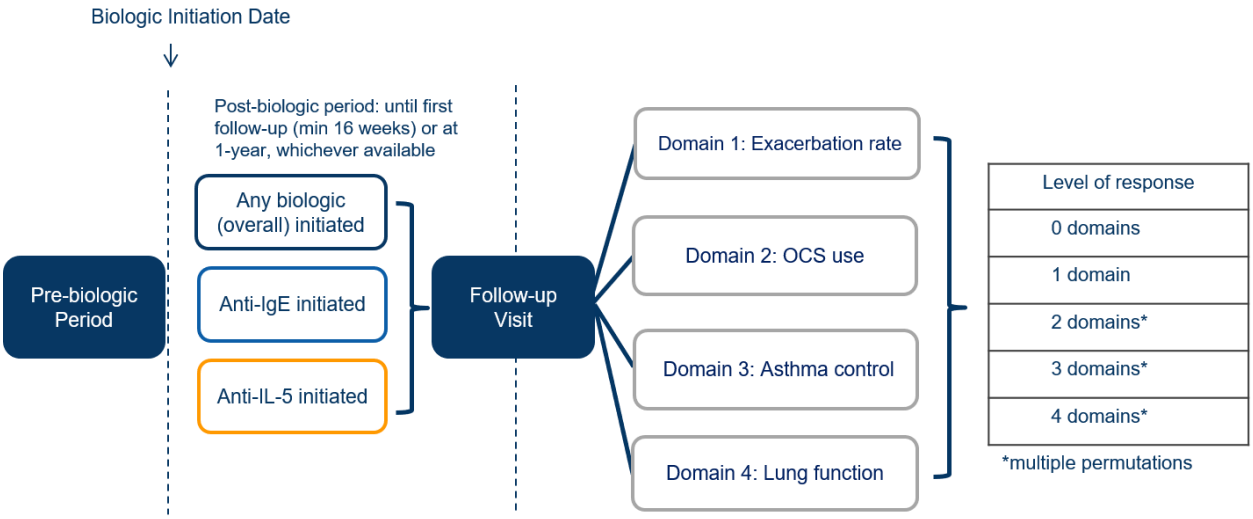

Figure 1. Study design

2.3. STUDY SAMPLE

Patient eligibility criteria for the study is described in **Table 4**. Patients who were included in the International Severe Asthma Registry (ISAR) after they had started biologic treatment will not be included in the study unless pre-treatment data is available.

If patients discontinued or switched a biologic, the reason(s) for doing so will be reported. Previous ISAR studies have reported that the most common reason for discontinuation of biologic is a lack of effectiveness and/or experiencing adverse effects. Thus, patients who switched/stopped their biologic before first post-biologic visit or before 16 weeks (domains cannot be operationally assessed) will be categorized as non-responder.

Table 4. Inclusion and exclusion criteria

• Inclusion criteria: - Patients 18 years or older, who are receiving treatment according to GINA (2018 Criteria) step 5 or are uncontrolled at step 4. Uncontrolled asthma is defined as having severe asthma symptoms or frequent exacerbations requiring systemic corticosteroids. - Patients prescribed with anti-IL5/5R, anti-IgE or anti-IL4/IL13 during study period - Available registry data prior to or on biologic therapy initiation date - Available registry data from biologic initiation date until a follow-up visit that is closest to a 1-year period (min. 16 weeks) or until date of switching/stopping their first biologic - Switched/stopped their first biologic before first follow-up visit or before 16 weeks (as non-response)
• Exclusion criteria: - Patients who received bronchial thermoplasty - Patients who are <18 years old - Patients with a follow-up visit less than 16 weeks after biologic initiation date (without switch/stop)

Patients will be divided into overall biologic use and by biologic class of anti-IgE and anti-IL5:

- Anti-IgE (Omalizumab)
- Anti-IL5 (Reslizumab, Mepolizumab)
- Anti-IL-5R (Benralizumab)
- Anti-IL4/IL13 (Dupilumab)

We will not categorize by biologic class of anti-IL4/IL13 due to low sample size (**Figure 2).** For full feasibility numbers, see **section 4.3.**

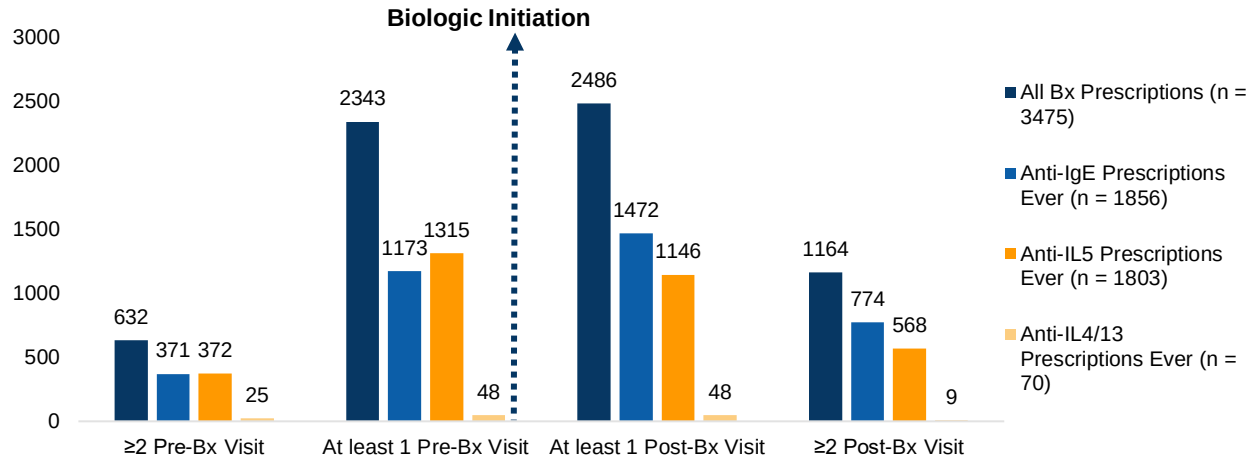

Figure 2. ISAR biologic treatment data structure (August 2020). Not mutually exclusive.

3. STUDY OUTCOMES

Section 3.1. presents the operational definition of biologic response-domains based on the asthma clinical and functional outcomes.

Section 3.2. presents the approach to levels-of-response to biologic treatment as well as operational definition of responders and non-responders based on combined domains from previous section.

Section 3.3. presents exploratory composite definition of response as per previously mentioned Delphi study (Perez et al.).

Section 3.4. presents the list of study domains and their descriptions.

3.1. RESPONSE DOMAINS

Initially, response to a biologic therapy will be evaluated based on improvements of single domains including exacerbation rate, cumulative OCS dose, long-term OCS dose, asthma control and lung function **(Table 5)** from pre- to post-therapy. Single domain criterion will be used to fully utilize ISAR data and capture recognized signs of response especially in patients that do not require long-term OCS treatment or suffer from frequent exacerbations. As noted in the inclusion criteria, to avoid duplication of information, response will be examined for the first biologic only.

Table 5. Criteria of response to biologic treatment based on single domain

Domains (improvement from pre-therapy)	Exacerbation rate	Rescue corticosteroid dose	Long-term OCS dose	Asthma control	FEV1	Percent of predicted FEV1
Exacerbation	≥50% reduction					
Cumulative OCS dose		≥50% reduction				
Long-term OCS			≥50% reduction			
Asthma control				≥1 improvement		
Lung function					≥100mL increase	≥80% of predicted

3.2. LEVEL-OF-RESPONSE

The level of responsiveness will be assessed based on the overlap of the following four domains: exacerbation rate, long-term OCS use, asthma control and lung function **(Figure 3)**. Meeting the criteria of each domain will represent one-level of response and fulfilling the criteria of two domains will be a two-level-response, and so on. Multiple permutations possible for a greater response level of two or more; see **Figure 3** for a depiction.

We will also use the overlap of domains to constitute responder and non-responder to biologic treatment. Not meeting any of the domains regardless of data availability will be considered as non-responders. Patients meeting at least half of the available domains will be considered as responders **(Table 6).**

Table 6. Definition of responder and non-responder based on overlap of domains

	Non-responder	Responder			
Domain	**Level 0**	**Level 1**	**Level 2**	**Level 3**	**Level 4**
Exacerbation rate (≥50% reduction)	None (Or switch/stop before follow-up visit or before 16 weeks)	1/1 1/2	2/2 2/3 2/4	3/3 3/4	4/4
Long-term OCS (≥50% reduction)					
Asthma control (≥1 improvement)					
Lung Function (≥100mL increase)					

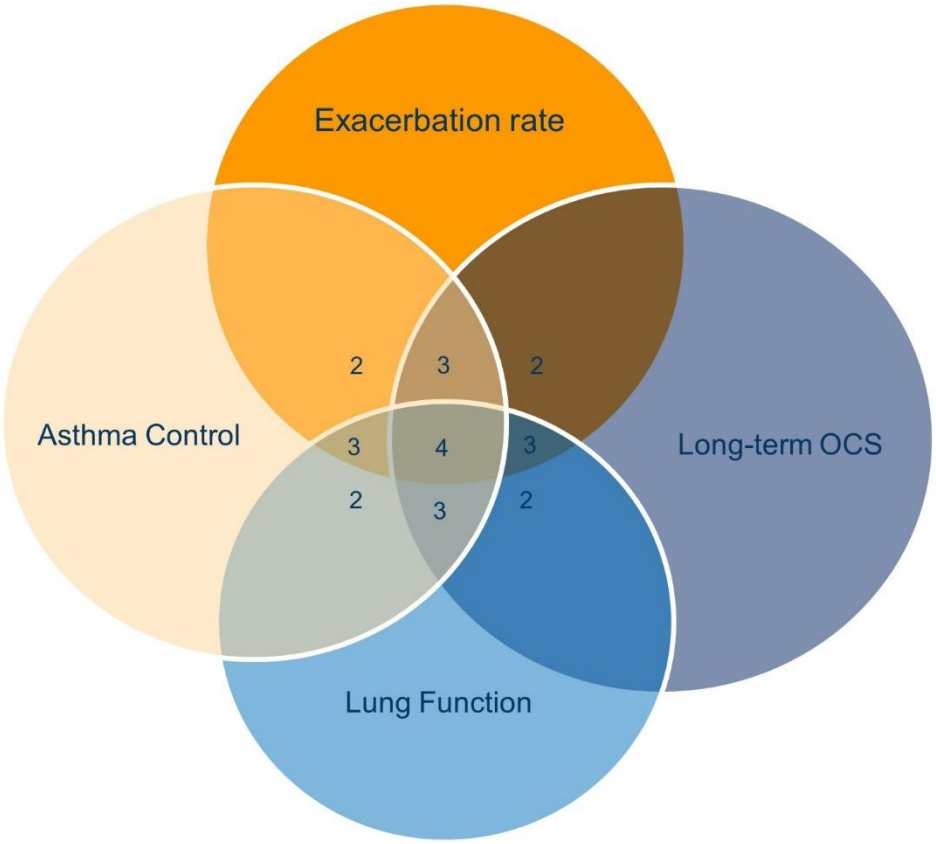

Figure 3. Overlap of four domains and level-of-response permutations

3.3. EXPLORATORY

As an exploratory analysis, we will utilize the "FEOS score" developed by Luis Perez and his colleagues for composite and varying response assessment (Table 3). The score consists of four core items, with different levels of response for each of them: exacerbations, oral corticosteroid maintenance dose, symptoms (evaluated by Asthma Control Test: ACT) and bronchial obstruction (assessed by FEV1 percent of predicted). Exacerbations and oral corticosteroid maintenance dose were weighted most heavily, followed by symptoms and FEV1. As a slight deviation, we will use a combination of GINA-defined asthma control, ACT and ACQ for symptoms. In addition, we will categorize the score to enable descriptive analyses as per objective 2.

3.4. CLINICAL OUTCOMES

The clinical outcomes chosen to assess response are based on a review of biologic effectiveness studies **(Table 1)**, responder publications **(Table 2)**, three Delphi based studies **(Table 3)** and ISAR data availability (Section 4.3). As such four common domains of response were identified: exacerbation reduction/elimination, OCS reduction/elimination, asthma control improvement/well-controlled asthma and lung function improvement or optimization **(Table 3**).

In terms of feasibility, exacerbation count, OCS use, GINA-defined asthma control and lung function are standard ISAR variables collected by all data contributors. See section 4.3 for a feasibility assessment of each study domain.

An asthma exacerbation will be defined as the occurrence of the following events:

- asthma-related hospital attendance/admission; AND/OR
- asthma-related A&E attendance; AND/OR
- an acute oral corticosteroid course of 3 days or more
- Separate recordings of exacerbations within 14 days of each other will be treated as the same exacerbation.

Since not all post-biologic visits fall under 1-year follow-up mark, exacerbation rates will be annualized i.e. exacerbation count divided by the follow-up time completed. Exacerbation counts in majority of pre-biologic (baseline) visits are recorded as “within last year”. However, in cases where baseline visit is not first visit, exacerbation count will be annualized as well.

For patients on OCS, cumulative OCS exposure will include the combined dose of long-term OCS and rescue OCS during the follow-up period. Rescue OCS use is recorded as a total dose used over a specified time and includes prescriptions that have a shorter duration (<14 days). Long-term OCS use is recorded as daily dose in mg and includes prescriptions that have a longer duration (>14 days). Patients who stopped long-term OCS post-therapy without dosage information will be considered as responders for that domain.

For the asthma control domain, due to a battery of asthma control measurement instruments used by ISAR collaborators, a combination of GINA **(Table 7**, used by a majority (70%)**)**,

Asthma Control Test (ACT) (51) and Asthma Control Questionnaire (ACQ) (52) will be used to define three levels: uncontrolled, partly-controlled and controlled.

Table 7. GINA asthma control questionnaire

GINA Criteria	Level of asthma symptom control		
	Controlled	Partly Controlled	Uncontrolled
In the past 4 weeks, has the patient had: • Daytime asthma symptoms more than twice/week? • Any night waking due to asthma? • SABA reliever for symptoms more than twice/week? • Any activity limitation due to asthma? • Predicted post-bronchodilator FEV_1< 80%	None of these	1-2 of these	3 or more of these

4. STUDY VARIABLES

Section 4.1. presents the list of baseline visit (pre-biologic) demographic variables that will be used to describe and compare baseline differences between 'responder' groups (study objective 2).

Section 4.2. presents the list of baseline visit (pre-biologic) and follow-up visit (post-biologic) clinical variables. A change between baseline and follow-up clinical endpoint (domain) values will be used to assess response (study objective 1). In addition, baseline clinical variables including biomarker levels will be used to describe and compare the baseline differences between responder groups (study objective 2).

4.1. DEMOGRAPHIC VARIABLES

Demographics	
Age	Age in completed years.
Sex	Female or Male.
Ethnicity	Caucasian, Asian, African, Mixed and Other (incl. Hispanic and Arabs).
Country	
Body Mass Index (BMI)	The ratio of weight (kg) to squared height (m^2).

Occupation	(String), **categorize** e.g. non-skilled labor, skilled labor, manager, professional.
Smoking Status	Categorised as non-smoker, current smoker or ex-smoker.
Pack years	Number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked.
Asthma History	
Age of Asthma Onset	Age in completed years or months (if less than 1 year) at which asthma was diagnosed or symptoms began.
Asthma duration	Whole years or months (if less than 1 year) at which first asthma diagnosis/symptoms began to the date of entry into the study.
Comorbidities, diagnosed ever	
Allergic rhinitis	
Chronic rhinosinusitis	
Eczema	
Nasal polyps	
Atopic disease	
Osteoporosis	Osteoporosis diagnosis or osteoporotic fracture (hip, wrist, spinal)
Heart failure	
Myocardial Infarction	
Stroke	
Embolism/Thromboembolism	
Glaucoma	
Cataract	
Renal failure	Defined as stage 3-5, or dialysis or renal transplant
Depression	
Anxiety	
T2 diabetes	
Peptic Ulcer	

Pneumonia	
Obstructive sleep apnea	
Number of comorbidities	
Medication History	
Long-term oral corticosteroids (OCS)	No. (%) and average daily dose (mg)
Acute oral corticosteroids	No. (%) and total dose (mg)
Receiving ICS	No. (%) and number of prescriptions and average daily dose.
Receiving SABA	No. (%) and number of prescriptions
Receiving Theophyllines	No. (%) and number of prescriptions
Receiving Respiratory treatment	ICS/LABA, LAMA, LTRA, macrolide, No. (%) and number of prescriptions

4.2. CLINICAL VARIABLES

Clinical Measurements	
Blood eosinophil count	Most recent blood eosinophil count Count of blood eosinophils (cells/ µL).
Blood IgE count	Most recent blood IgE level Count of blood IgE (IU/ml).
Fractional exhaled nitric oxide (FENO) test	Measurements of fractional nitric oxide concentration in exhaled breath, measured in parts per billion (ppb) at a flow rate of 50mL/s.
Pre-bronchodilator FEV_1	FEV_1 measured in litres (L)
Post-bronchodilator FEV_1	FEV_1 measured in litres (L), after administering bronchodilator
Pre-bronchodilator FEV_1 (percentage of predicted)	Measured pre-bronchodilator FEV_1 as % of predicted FEV1
Post-bronchodilator FEV_1 (percentage of predicted)	Measured post-bronchodilator FEV_1 as % of predicted FEV1, after administering bronchodilator

Allergy testing	
Skin prick test	Average wheal diameter (mm)
PC20 challenge test result (53)	Numeric mg/ml (kU/L)
Serum Allergen Test Result (54)	IgE level (kU/L)

Clinical characteristics	
Number of exacerbations	Number of asthma exacerbations defined as events that require urgent action (rescue steroids) on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma
Number of emergency department admissions	Count of emergency department admissions for asthma
Number of hospital admissions	Count of hospital admissions for asthma
Safety Event	Cancer, Serious Infection, Anaphylaxis
Number of invasive ventilations for severe asthma	Count of episodes of invasive ventilation ever
Asthma control	Categorised as controlled, partly controlled or uncontrolled based on GINA, ACT and ACQ.

4.3. FEASIBILITY

In a preliminary analysis of the ISAR severe asthma cohort, 3,475 patients receiving anti-IL5, anti-IgE or anti-IL4/IL13 were identified, out of which 1,363 patients had both pre- and post-biologic visits recorded **(Figure 4).** Similarly, we identified 1,856, 1,803 and 23 users of anti-IgE, anti-IL5 and anti-IL4/IL13, respectively. The feasibility calculations for domains for overall biologic use as well as anti-IgE and anti-IL5 are given below.

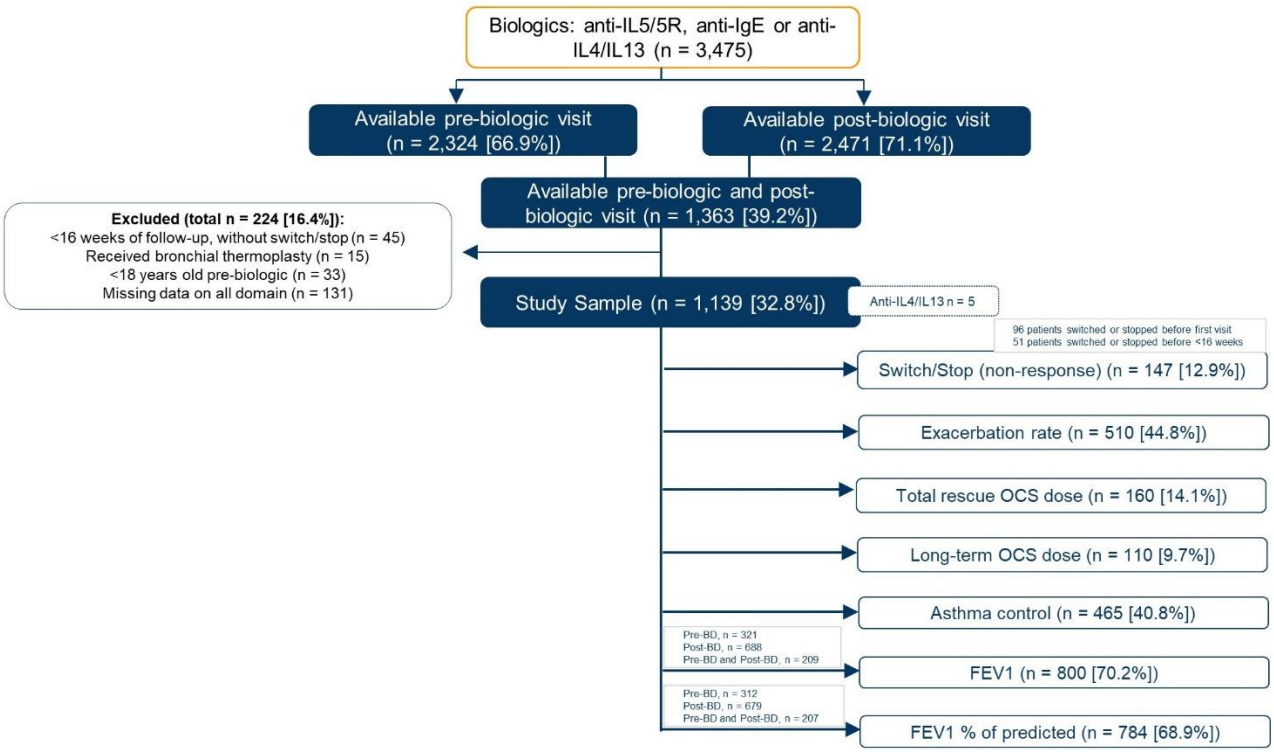

Figure 4. Flowchart of data availability for patients who initiated either anti-IgE, anti-IL5 or anti-IL4/13 therapies (overall biologics)

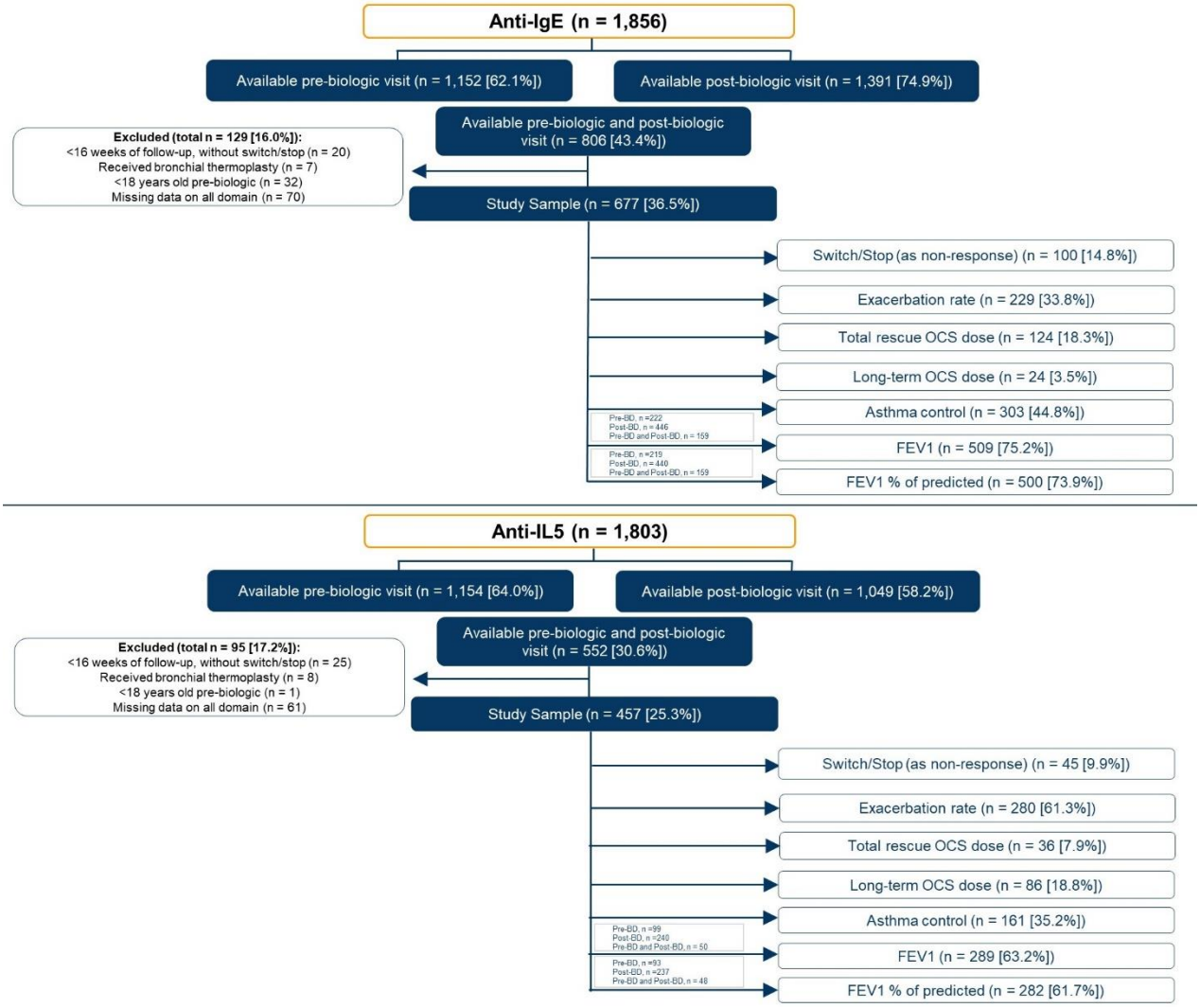

Figure 5. Flowchart of data feasibility for patients who initiated anti-IgE or anti-IL5 therapies

5. STATISTICAL ANALYSIS

Stata version 16+ MP (College Station, TX, USA) will be used to conduct all statistical analyses and data management.

5.1. DESCRIPTIVE STATISTICS

Baseline descriptive characteristics for overall study sample will be reported for all variables listed in **Section 4.** Quantitative change in domains from pre-biologic to post-biologic will be reported and frequency of single-domain response for each domain will be expressed for overall biologic and by biologic class.

As described in section 3.2., responders and non-responders will be defined based on the overlap of the following four domains: exacerbation rate, long-term OCS dose, asthma control and lung function **(Table 5)**. Descriptive statistics of baseline variables including levels of biomarkers and prevalence of comorbidities (**Section 4.1. Demographic Variables** and **Section 4.2. Clinical Variables)** will be provided for non-responder and responder groups for overall biologic use and by biologic class (anti-IL5 and anti-IgE) (study objective 2). Exploratory responder composite groups may also be described.

- Continuous variables will be summarized as: n (non-missing sample size), mean (or median for skewed and ordinal data) and standard deviation or range (minimum-maximum).
- Categorical variables will be presented as frequency and percentage (based on the non-missing sample size) or range (if applicable).
- Tables will be annotated with the total population size including any missing observations (frequency and %).

Graphical presentations such as dot plots, bar graphs or histograms will be also used to better visualize the differences between outcome groups for significant variables ($p<0.05$). To depict the extent of overlap across groups, visuals such as Venn Diagrams will be used.

5.2. ANALYSIS

Baseline (pre-biologic) characteristics (**Section 4.1. Demographic Variables** and **Section 4.2. Clinical Variables)** of chosen responder group will be compared and tested against the non-responder group for statistical significance via Pearson's Chi-square test for comparison of count data and one-way analysis of variance (ANOVA) for continuous variables. Comparisons will be also made between exploratory composite responder groups. Statistical significance will be defined as $p<0.05$. We will use complete case analysis approach for the missing data and report missing data frequency for each variable.

6. REGULATORY AND ETHICAL COMPLIANCE

This study was designed and will be implemented and reported in accordance with the criteria of the “European Network Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

study" 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 www.encepp.eu. Governance will be provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (55).

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 organizations.

Furthermore, all data extracted to be transferred from sites will be hashed and will enter the research database in the form of anonymized patient IDs. The data will be retrieved by OPC data analysts and utilized as an anonymized dataset to perform the analysis according to this protocol.

This study will be performed in compliance with all applicable local and international laws and regulations, including, but not limited to, ICH E6 guidelines for Good Clinical Practices.

7. DATA DISSEMINATION

Results from this study will be submitted in abstract form for ATS 2021, and ERS 2021. The manuscript from this study will be submitted to a severe asthma focused peer-reviewed scientific journal in due course.

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Project Steering Committee Members	Country
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10. TIMELINE

	2020							2021
	Jun	Jul	Aug	Sep	Oct	Nov	Dec	TBD
Protocol Draft								
Dataset Delivery								
ADEPT Approval								
Pilot Results								
Report Writing								
Abstract Submission								
Draft Manuscript								
Publication								

11. APPENDIX

Table 1. Full list of ISAR 95 core variables (50)

Category	Variable field name	Recorded units
Blood/Sputum	Highest blood eosinophil count within the past year	Decimal number
	Date of the highest blood eosinophil count within the past year	DD/MM/YYYY
	Was this the highest blood eosinophil count during an exacerbation event?	No/Yes
	The highest blood eosinophil count within the past year and not during exacerbation	Decimal number
	Date of highest blood eosinophil count within the past year and not during an exacerbation event	DD/MM/YYYY
	Current blood eosinophil count	Decimal number
	Date of current blood eosinophil count	DD/MM/YYYY

	The highest sputum eosinophil count within the past year (percentage)	Decimal number
	Date of the highest sputum eosinophil count within the past year	DD/MM/YYYY
	IgE count	Decimal number
Diagnostics	Chest CT scan	Normal/Abnormal/Not done
	Date of chest CT scan	DD/MM/YYYY
	Bone densitometry (DEXA)	No/Yes
	Date of bone densitometry (DEXA)	DD/MM/YYYY
Lung function	Pre-bronchodilator FEV_1	Decimal number
	Post-bronchodilator FEV_1	Decimal number
	Pre-bronchodilator FVC	Decimal number
	Post-bronchodilator FVC	Decimal number
	Predicted FEV_1	Decimal number (auto-calculated)
	Pre-bronchodilator FEV_1 (% predicted)	Decimal number (auto-calculated)
	Post-bronchodilator FEV_1 (% predicted)	Decimal number (auto-calculated)
	Predicted FVC	Decimal number (auto-calculated)
	Pre-bronchodilator FVC (% predicted)	Decimal number (auto-calculated)
	Post-bronchodilator FVC (% predicted)	Decimal number (auto-calculated)
	FEV_1/FVC ratio pre-bronchodilator (%)	Decimal number (auto-calculated)
	FEV_1/FVC ratio post-bronchodilator (%)	Decimal number (auto-calculated)
	PC20 methacholine/histamine test	No/Yes
	Date of PC20 test	DD/MM/YYYY
	PC20 test result	Decimal number

	FeNO test	No/Yes
	Date of FeNO test	DD/MM/YYYY
	FeNO test result	Decimal number
Allergen testing	Environmental allergen test	Serum allergen test (CAP, ELISA, RAST)/SPT/not done
	Serum allergy test: Positive to perennial allergen	No/Yes
	Serum allergy test: Specify positive allergen and result	Dust mite (e.g. *D. pteronyssinus*)/grass mix/cat hair/mould mix/dog hair/Aspergillus/other (please specify)
	Date of serum allergy test	DD/MM/YYYY
	SPT: Positive to allergen	No/Yes
	SPT: Specify positive allergen and result	Grass mix/trees/weed mix/Aspergillus/mould mix/dust mite/food mix/animal mix/cat hair/dog hair/other (please specify)
	Date of SPT	DD/MM/YYYY
Asthma control[1]	GINA Asthma Control Questionnaire	
	In the past 4 weeks, did the patient have:	
	Daytime symptoms more than twice per week	No/Yes
	Any activity limitation	No/Yes
	Any nocturnal symptoms/awakening	No/Yes
	Reliever medication use more than twice per week	No/Yes
	Lung function (PEF or FEV_1) <80% of predicted or personal best	No/Yes
Asthma medication	Maintenance oral corticosteroids	No/Yes
	Start date of oral corticosteroids	DD/MM/YYYY

	ICS + LABA combination therapy	No Budesonide + Formoterol Fluticasone furoate + Vilanterol Fluticasone propionate + Salmeterol Fluticasone propionate + Formoterol Mometasone + Formoterol Beclomethasone + Formoterol Other
	Start/end date of ICS + LABA combination therapy	DD/MM/YYYY
	ICS (only)	No Triamcinolone acetonide Mometasone furoate Fluticasone propionate Fluticasone furoate Ciclesonide Flunisonide Budesonide Beclomethasone dipropionate Other
	Start/end date of ICS (only) therapy	DD/MM/YYYY
	LABA	No Formoterol Salmeterol Indacaterol Arformoterol Olodaterol Other
	Start/end date of LABA therapy	DD/MM/YYYY

	LAMA	No Aclidinium Tiotropium Umeclidinium Glycopyrronium Other
	Start/end date of LAMA therapy	DD/MM/YYYY
	Theophyllines	No Theophylline Aminophylline Other
	Start/end date of theophylline therapy	DD/MM/YYYY
	LTRA	No Zafirlukast Montelukast Other
	Start/end date of LTRA therapy	DD/MM/YYYY
	Anti-IgE treatment	No/Yes
	Start/end date of anti-IgE therapy	DD/MM/YYYY
	Anti-IL-5/IL-5R treatment, other	No Reslizumab Mepolizumab Benralizumab Other[2]
	Start/end date of anti-IL-5 therapy	DD/MM/YYYY
	Macrolide antibiotic treatment	No Azithromycin Clarithromycin Erythromycin Roxithromycin

		Fidaxomicin Telithromycin Other
	Start/end date of macrolide antibiotic therapy	DD/MM/YYYY
	Other steroid-sparing agents	Free text
Adherence	Evidence of poor adherence[3]	No Yes: Clinical impression Yes: Objective measures Yes: Prescription records
	Other factors contributing to severe asthma symptoms[4]	Free text
Management plan	Current clinical management plan[5]	Discharge to local service Optimisation of current treatment Biologic therapy (specific drug can be found in current medication) Bronchial thermoplasty Maintenance oral corticosteroids Steroid-sparing agent (specific drug can be found in current medication) Enter into clinical trial Other (please specify)

CAP immunoCAP test, *CT* computed tomography, *DEXA* dual energy X-ray absorptiometry, *ELISA* enzyme-linked immunosorbent assay, *FeNO* fractional exhaled nitric oxide, FEV_1 forced expiratory volume in 1 second, *FVC* forced vital capacity, *GINA* Global Initiative for Asthma, *ICS* inhaled corticosteroids, *IgE* immunoglobulin E, *IL-5* interleukin-5, *ISAR* International Severe Asthma Registry, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *LTRA* leukotriene receptor antagonist, *PC20* provocative concentration of methacholine/histamine needed to produce a 20% decrease in FEV_1, *PEF* peak expiratory flow, *RAST* radio-allergosorbent test, *SPT* skin prick test.

[1]Asthma Control Questionnaire or the Asthma Control Test are optional extras for this category (depending on registry preference).

[2]Other new biologics will be added once approved and in use.

[3]Poor adherence to treatment can be indicated by selecting either (a) or (b):

(a) Clinical impression: opinion of a medical personnel

E.g. i) Impression of 'non-persistence': patient stops taking medication.

ii) Impression of 'non-conformation': patient does not take medication as prescribed.

(b) Prescription records: evidenced by medical records detailing prescriptions being issued and inadequately filled.

E.g. Medication possession ratio (MPR) = (Sum of days' supply for all fills/Number of days) x 100% <80% threshold.

[4]Calls for a trained clinician's perception or opinion on any other external factors (if any) potentially contributing to the severe asthma symptoms.

E.g. Weather (cold air), air pollution, physical activity (exercise-induced asthma symptoms), occupational triggers (workplace irritants, gases, chemical fumes, dust), strong smells (perfumes), prior respiratory infections.

[5]Aims to record the asthma action plan for a patient to review efficacy over time.

E.g. i) Entry into clinical trial: If patient can benefit from a clinical trial drug.

ii) Discharge to local asthma service: If patient has shown alleviated asthma symptoms.

iii) Optimisation of current asthma therapy: If patient's current asthma therapy is titrated for better asthma management.

iv) Bronchial thermoplasty: If patient is eligible to have a surgery to manage their asthma.

v) Biologic therapy: If patient is prescribed biologic therapy.

vi) Others: Asthma education and inhaler use education.

Table 2: International Severe Asthma Registry bolt-on variables

Category	Variables
Safety	
Severe infection	• Infection type • Start and end dates • Outcome of infection • Site of infection
Malignancy	• Malignancy history, type, stage, status and diagnosis confirmation • Start and end dates • Outcome of malignancy • Site of malignancy
Anaphylactic reaction	• Likely exposure of the reaction • Time to reaction • Date of the reaction • Outcome of the anaphylactic reaction
Effectiveness	
Comorbidities	• Osteoporosis • Osteoporosis: Start date • Circulatory system disease • Circulatory system disease: Type • Circulatory system disease: Start date • Glaucoma or cataract disease • Ocular disease: Type • Ocular disease: Start date • Obstructive sleep apnoea • Obstructive sleep apnoea: Start date • Renal failure • Renal failure: Start date • Depression • Depression: Start date • Anxiety • Anxiety: Start date • Type II diabetes mellitus • Type II diabetes mellitus: Start date • Peptic ulcer • Peptic ulcer: Start date • Pneumonia • Pneumonia: Start date
Dosage	• Label dose for oral corticosteroids • Frequency for oral corticosteroids • Label dose for inhaled corticosteroids • Frequency for inhaled corticosteroids

Exacerbation history	• Dates of exacerbations indicated • Type of rescue steroid used with label dose, frequency, start and end dates
Medication switching	• Reason for switch in patient's asthma medication/treatment

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