Study Report

SHINE

Relapse and its predictors among ISAR patients in remission 12 months after initiating biologics (SHINE)

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Countries of study	Belgium, Brazil, Bulgaria, Canada, Colombia, Denmark, Greece, Ireland, Italy, Japan,

	Kuwait, Mexico, Norway, Poland, Portugal, Saudi Arabia, Singapore, South Korea, Spain, Taiwan, United Arab Emirates (UAE), United Kingdom (UK), United States of America (USA)
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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ACQ	Asthma control questionnaire
ACT	Asthma control test
ADEPT	Anonymised Data Ethics & Protocol Transparency
BMI	Body mass index
CI	Confidence interval
ENCePP	European Network Centres for Pharmacoepidemiology and Pharmacovigilance
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
GINA	Global initiative for asthma
GLI	The Global Lung Function Initiative
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
IL4R	Interleukin 4 receptor
IL5	Interleukin 5
IL5R	Interleukin 5 receptor
ISAR	International Severe Asthma Registry
ISC	ISAR Steering Committee
LABA	Long-acting bronchodilator inhalers
LAMA	Long-acting muscarinic antagonist
LTOCS	Long-term oral corticosteroids
LTRA	Leukotriene receptor antagonist
MCID	Minimal Clinically Important Difference
OCS	Oral corticosteroids
OPRI	Observational and Pragmatic Research Institute
OR	Odds ratio
Q1, Q3	1^{st} quartile, 3^{rd} quartile
REG	Respiratory Effectiveness Group
SD	Standard deviation
T2	Type 2 inflammation
TSLP	Thymic stromal lymphopoietin

1.0 Executive Summary

This study aimed to examine patterns and predictors of relapse among ISAR patients in clinical remission for 12 months following initiation of biologic therapy. We considered relapse as failure to meet one or more clinical remission definition criteria, occurring after 12 months of biologic therapy. We primarily defined clinical remission based on three domains: no asthma exacerbations, no LTOCS use, and reported well or partly controlled symptoms in the previous 12 months, but we also examined an alternate three-domain definition considering lung function in place of symptoms and a four-domain remission definition including both symptom control and lung function. Specifically, we aimed: 1) to describe frequencies and timing of relapse and the type and extent of domain failure attributed to relapses occurring after 12 months of biologic therapy; 2) to identify pre- and post-treatment demographic and clinical characteristics associated with relapse versus sustained remission at 24 months post-initiation of biologic therapy; and 3) to compare frequency of switching or stopping biologic treatment among patients with an observed first relapse versus those with sustained remission.

Using our primary three-domain definition, the overall percentage of patients experiencing relapse remained stable over time, ranging from 20.2% at 24 months to 23.2% at 60 months post-initiation, with similar percentages of patients changing status at each timepoint. Restricting the analysis to first observed relapses, we found that 50% of patients in remission after 12 months remained in remission beyond 48 months of follow-up, using either three-domain definition, and beyond 36 months, using the stricter four-domain definition. These relapses were most frequently attributed to a single domain. For both three-domain definitions, the occurrence of any exacerbations was the most frequent domain failure; while for the four-domain definition, the most frequent domain failure was <80% percent predicted FEV1. Using our primary three-domain remission definition, among relapses attributable to exacerbations, 75% involved a single exacerbation. Relapses attributable to symptom control showed considerable worsening of symptoms as, among patients with ACT or ACQ results, we calculated the median absolute difference from remission to relapse to be approximately three times the minimal clinically important difference for each respective scale. Although limited by small population numbers, we found that patients who experienced continued relapse in the year after their first relapse often did so by failing in the same remission domain and that patients who relapsed as a result of exacerbation more frequently regained remission in the following year than those who relapsed due to symptom control and exacerbation or lung function.

We used logistic regression modelling to estimate the association of pre- and post-biologic patient and clinical characteristics with the occurrence of relapse at 24 months among patients in remission at 12 months based on three-domain clinical remission. Pre-biologic predictors of increased odds of relapse included female sex, ever smoking, duration of asthma, allergic rhinitis, and starting on an anti-IgE biologic. We found that patients with a pre-biologic BEC ≥1000 cells/μL, and pre-biologic FeNO concentration >20 ppb had lower odds of relapse. In our analysis of characteristics measured 12 months post-biologic initiation and relapse at 24 months, we found that patients with ≥80% percent predicted FEV1 had lower odds of relapse compared to those with <80%. Patients with post-biologic BEC ≥100 cells/μL had higher odds of relapse compared to those with <100 and patients with a smaller relative percent change in BEC from pre-biologic levels had higher odds of relapse. Patients with more modest FeNO suppression <34% compared to ≥34% from pre-biologic levels had increased odds of relapse. Patients on medium dose ICS at 12 months post-biologic initiation had increased odds of relapse compared to patients on high dose ICS, but we did not find an association between change in ICS dose from pre-biologic to 12 months post-biologic and relapse. Approximately, 4% of patients in remission at 12 months switched biologic therapy between 12 and 24 months, though none stopped. This switching was associated with increased odds of relapse, but this finding may reflect adaptation of treatment in response rather than a cause of relapse, as they were assessed over the same period of time.

2.0 Background

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

Among adults with asthma, prevalence of severe asthma is commonly reported to range between 5 and 10% (4–6). Severe asthma is defined as “asthma that is uncontrolled, despite adherence with maximal optimised high-dose ICS with LABA treatment and management of contributory factors, or that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations” (asthma attacks) (4,7). Control of asthma symptoms might be possible for most patients through treatment according to two tracks recommended by the Global Initiative for Asthma (GINA) (1,5). Despite adequate treatment, patients with severe asthma face frequent exacerbations (i.e. flare-ups, attacks) and persistent symptoms that require either systemic glucocorticoid bursts, long-term oral glucocorticoid therapy, or both (8). Symptoms during an exacerbation include shortness of breath, wheeze, cough, and sputum production; mucus production along with contraction of smooth muscle restrict the airway, which can result in near-fatal or fatal respiratory failure (9). Systemic use of corticosteroid is associated with several adverse effects including weight gain, osteoporosis and osteonecrosis, diabetes, ocular complications, particularly glaucoma and cataract, cardiovascular effects, and infections, all of which increase the burden of asthma and the cost of its care (4,10).

Previously, only allergic and non-allergic asthma were characterized (11), but improvements in the treatment of severe asthma have occurred alongside recognition of the utility of characterizing the disease’s heterogeneity with endotypes. In contrast to clinical measures, such as reductions in lung function, that are used to characterize a disease’s phenotype and may have multiple causes, endotypes refer to the distinct molecular mechanisms of subtypes of a disease (9). Blood eosinophils (≥300 cells per µL) and fractional exhaled nitric oxide (FeNO, ≥25 ppb) are clinical biomarkers of increased type 2 inflammation used to differentiate

type-2-high versus type-2-low asthma (4). Type-2-high inflammation is frequently present in childhood-onset, allergic asthma and in adult-onset, severe eosinophilic asthma (8). A subset of type-2-high asthma, allergic asthma represents approximately 70% of all asthma (12). Allergic sensitization to aeroallergens is determined by skin prick test or specific IgE plus exacerbation of asthma or rhinoconjunctivitis symptoms related to a relevant exposure (4). Often associated with obesity, aging, and smoking, asthma in patients with lower levels of type 2 inflammation (non-eosinophilic, sometimes neutrophilic, and metabolic) may be caused by abnormalities in airway smooth muscle or airway hyperresponsiveness and obstruction caused by oxidative stress, interleukin (IL)-17, or neutrophil products (9,11). While type-2-low asthma is less well understood, type-2-high asthma is characterized by high production of type-2 cytokines IL-4, IL-5, and IL-13, which manifest in eosinophil accumulation in lung tissue and mucous production (11).

Biologic therapies leverage our understanding of these specific molecular mechanisms and inflammatory pathways and permit targeted asthma management. Currently, there are four classes of biologic therapies for severe asthma, targeting IgE, the IL-5 pathway, the IL-4/IL-13 pathway, and thymic stromal lymphopoietin (TSLP) (12,13). Omalizumab is a monoclonal antibody (mAb) and is used in cases of IgE-mediated allergic asthma. The cytokine IL-5 is critical to the development and activation of eosinophils and is targeted by three biologics approved for management of severe eosinophilic asthma: mepolizumab and reslizumab target ligand IL-5, and benralizumab binds to IL-5Rα (12). Dupilumab binds to the IL-4Rα subunit, which inhibits both IL-4 and IL-13 signalling related to airway tone and class-switching toward IgE. TSLP is an alarmin, a specific type of cytokine (with IL-33 and IL-25) released by epithelial cells in response to allergens, air pollutants, and viruses, that enhances subsequent inflammation mechanisms (8,12). Targeting TSLP with Tezepelumab, as upstream mechanisms, may improve asthma outcomes in a broader patient population, including those with type-2-low severe asthma (8). In addition to their demonstrated efficacy in reducing exacerbations, biologic therapies, specifically mepolizumab, benralizumab, dupilumab, and tezepelumab, have also been shown to lower dependence on corticosteroids (8,14), which in turn could lower the burden of associated acute and chronic adverse effects (15).

Use of biologic therapies is increasing, and observed benefits among patients with type-2-high severe asthma have shown the potential of remission being an obtainable goal for asthma treatment (8,12,16). This recognition has followed two decades of debate on defining what benefits constitute response to biologic therapies, since some recipients show high asthma

control, while others see no benefit (17). Remission is a relatively new concept for asthma management, but it is well-defined in other chronic inflammatory conditions like rheumatoid arthritis, Crohn's disease, ulcerative colitis, and systemic lupus erythematosus (16). Drawing from experiences with these other inflammatory diseases, literature review, and expert consensus, four remission subtypes were proposed, contrasting clinical and complete remission both being achieved either on or off treatment (18). Clinical remission typically requires: no use of systemic corticosteroids for exacerbation treatment; no exacerbations and no hospitalizations or emergency department or unscheduled doctor visits for management of asthma exacerbations; and absence of asthma symptoms, as measured using a validated instrument like the Asthma Control Questionnaire (19) or Asthma Control Test (20), or optimisation of lung function (e.g. $FEV_1 \geq 80\%$ predicted). Complete remission requires clinical remission plus normalisation of pathology: no evidence of inflammation; a negative bronchial hyperresponsiveness test; or degree of subepithelial fibrosis (16,18). Clarification of these definitions has facilitated examination of the characteristics of biologic therapy recipients who may or may not respond to treatment in the short-term (21,22), but long-term studies are now needed (23,24).

While severe asthma patients may achieve clinical remission endpoints following biologic treatment, subsequent failures have been observed in real-world studies (12). Remission achievement rates after one year of treatment have been found to vary according to the number of component domains considered within the remission definition, and lower pre-biologic disease severity, shorter asthma duration, and higher BEC were all associated with greater odds of remission at one year (21). A real-world study from multiple sites in Italy involving a cohort of patients on Mepolizumab examined several remission definitions and found that 29.7% of patients sustained three-domain remission (exacerbations, LTOCs, symptom control) to two years (25). A real-world study from multiple sites in Spain involving a cohort of patients on a single biologic for 24 months found that of 175 patients, who responded based on the same definition at 12 months, 51 (29.1%) lost response over time (26). A post hoc analysis of the QUEST and TRAVERSE studies found that 64.4% of patients receiving Dupilumab who achieved a four-domain definition of clinical remission at year 1 sustained remission to year 2 (27). A post hoc analysis of the RELIght study found that 52.5% of patients receiving Mepolizumab had sustained remission from 12 to 24 months, based on a four-domain definition (28). Additional and larger longitudinal studies are needed to determine how frequently clinical remission is maintained over time among severe asthma patients and whether it improves clinical outcomes (21,29). Similarly, identification of the clinical

characteristics of relapse at timepoints beyond one year of treatment is necessary, and specifically what characteristics and post-treatment biomarkers, alone or in combination, predict relapse at different timepoints (30–32).

3.0 Study Aims and Objectives

3.1 Study Aim

The International Severe Asthma Registry (ISAR) provides a unique data source with information from patients in a variety of settings at timepoints before and after onset of biologic treatment. Here we propose to use these data, specifically from patients in clinical remission according to at least one definition (no exacerbations, no or ceasing LTOCS, and controlled asthma) after 12 months of biologic therapy, to characterise failures to meet one or more clinical remission criteria occurring at later timepoints, which we denote here as relapse, and identify factors associated with the occurrence of these events versus sustained remission up to 24 months.

3.2 Study Objectives

Objective 1: To describe frequencies of relapse and the type and extent of domain failures attributed to relapses occurring after 12 months of biologic therapy

Objective 2: To identify pre- and post-treatment demographic and clinical characteristics associated with relapse versus sustained remission at 24 months post-initiation of biologic therapy

Objective 3: To compare frequency of switching or stopping biologic treatment among patients with an observed first relapse versus those with sustained remission

4.0 Methods

4.1 Data Source

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

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

4.2 Study Design

We conducted a longitudinal cohort study including data from 25 countries sharing data with ISAR (33–35) between May 1, 2017 and July 27, 2025. We identified patients in the registry for our cohort, who have initiated biologic treatment and have at least 2 years of follow-up data after biologic initiation.

For objective 1, among patients in clinical remission according to at least one definition at 12 months post-initiation, we identified all subsequent relapses at twelve-month intervals. We then determined the time to and the number of domains contributing to the first observed relapse and their extent (i.e. how near or far from achieving remission). Among patients who experienced a relapse, we examined the frequency of continued relapse in the 12 months following their first relapse and the contributing domains.

For objective 2, we estimated the association between the occurrence of a relapse at 24 months and patient characteristics, while adjusting for patient characteristics and setting.

For objective 3, among patients in remission at 12 months post-initiation, we examined biologic treatment trajectories and contrasted the frequency of stopping or switching between patients with and without an observed relapse.

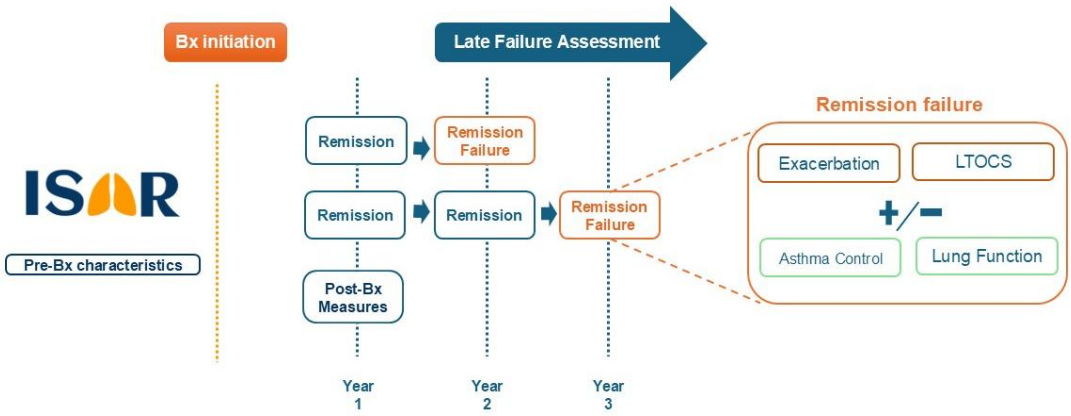

Figure 1. Study design.

4.3 Inclusion and exclusion criteria

Inclusion Criteria

- Patients receiving a biologic (anti-IgE, anti-IL-5/5R, anti-IL-4Ra, or anti-TSLP), AND
- Age 18 years or older at the time of biologic initiation, AND
- Have available baseline registry data at the time of biologic initiation, AND
- Have data on and meet criteria for at least one clinical remission definition at 12 months post-initiation, AND
- Have data available to assess remission at one additional follow up at least 24 months post-initiation

Exclusion Criteria

- Patients with insufficient data available to assess remission at least 24 months post-initiation
- Patients with a recorded stop or change in type of biologic therapy in the first 12 months

4.4 Regulatory and Ethical Compliance

We designed, implemented, and reported this study in accordance with the criteria of the "European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)" and followed the ENCePP Code of Conduct (EMA 2014) (EUPAS1000000788). ISAR is

approved by the Health Research Authority for clinical research use and governed by the Anonymised Data Ethics & Protocol Transparency (ADEPT) Committee. SHINE study protocol was approved by the ADEPT committee (https://www.regresearchnetwork.org/adept-committee/) (ADEPT1025). All sites entered 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. All extracted site data were hashed and entered the research database with anonymised patient IDs. We performed this study in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices.

5.0 Study Variables and Study Outcome Definitions

5.1 Pre-biologic patient characteristics

We used the following pre-biologic demographic and clinical characteristics as collected in ISAR to describe the cohort.

Table 1. Patient pre-biologic demographic and clinical characteristics.

Characteristics	Units/Categories
Geographic setting	Country and site
Biologic initiation date	Date
Biologic class	Anti-IL5/5R, Anti-IgE, Anti-IL4Ralpha, Anti-TSLP
Age at biologic initiation	Years
Sex	Female, Male
Ethnicity	Caucasian, African, Southeast Asian, Northeast Asian, Mixed, Other
Smoking status at biologic initiation	Current, Ex-smoker, Never-smoker
BMI at biologic initiation	kg/m^2
Obese (BMI ≥30 kg/m^2)	Yes/No
Exacerbations In Past Year	Count in past year
LTOCS Use in Past Year	Yes/No
Most Recent Asthma Control in Past Year	Uncontrolled, partly controlled, well controlled

	In ISAR, GINA 2020 classification is collected by most participating ISAR centres (0 = Well controlled; 1–2 = Partly controlled; 3–4 Uncontrolled). For centres reporting asthma symptom control assessment based on ACT (Nathan et al., 2004) and/or ACQ (Juniper et al., 1999), algorithms were 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			
Most Recent Percent Predicted FEV_1 In Past Year (%)	FEV_1 percent predicted (post-bronchodilator if available, pre-bronchodilator otherwise), %			
Most Recent FEV_1/FVC Ratio in Past Year	FEV_1/FVC			
Age at asthma onset	Years			
Asthma duration	Years			
Highest Blood Eosinophil Count	cells/µL			
Latest serum total IgE concentration	IU/mL			
Latest FeNO concentration	ppb			
Positive SPT or serum specific IgE tests to clinically relevant allergens	Yes/No			
Eosinophilic grade	Grade 0 (unlikely/non-eosinophilic); Grade 1 (least likely); Grade 2 (likely); Grade 3 (most likely).			
ICS daily dose in the past year (BDP-equivalent mcg/day)	Low ≤500, medium >500 - 1000, high ≥1000			
Inhaled corticosteroid (mcg/day)		Low	Medium	High

Beclometasone dipropionate (standard particles)*	≤500	>500–<1000	≥1000
Beclometasone dipropionate (extra-fine particles)*	≤200	>200–<400	≥400
Budesonide*	≤400	>400–800	>800
Ciclesonide (extra fine particles)	80–160	>160–320	>320
Fluticasone furoate*	<200	≥200	
Fluticasone propionate*	≤250	>250–500	>500
Flunisolide+	≤1000	>1000–2000	>2000
Mometasone furoate (standard particle)	200–400	>400	

Add on medications to ICS/LABA in the past year	Long-Acting Muscarinic Antagonist (LAMA), Leukotriene Receptor Antagonist (LTRA), Theophylline, Macrolide
Allergic Rhinitis (AR)	Ever/Never
Chronic Rhinosinusitis (CRS) with or without nasal polyps (+/-NP)	Ever/Never
Chronic Rhinosinusitis with nasal polyps (CRSwNP)	Ever/Never
Eczema/Atopic dermatitis	Ever/Never
History of osteoporosis	Yes/No
History of anxiety and/or depression	Yes/No

5.2 Year 1 characteristics

Table 2. Patient year 1 clinical characteristics.

Characteristics measured at 12 months post-initiation and calculating change from baseline:	Units/Categories
Most Recent Percent Predicted FEV_1 In Past Year (%)	FEV_1 percent predicted (post-bronchodilator if available, pre-bronchodilator otherwise), %
Most Recent Blood Eosinophil Count	cells/μL
Most Recent FeNO Concentration	ppb
ICS daily dose in the past year (GINA 2025)	BDP-equivalent mcg/day; Low ≤500, medium >500 - 1000, high ≥1000
Long-Acting Muscarinic Antagonist (LAMA) use	Yes/No

Switch biologic class	Yes/No

5.3 Outcomes

The primary outcome of interest will be first failure to meet three-domain remission definition (No exacerbations, no LTOCS use, partly or well-controlled asthma) recorded at a follow up occurring at least 24 months following biologic initiation (21,22). As secondary outcomes, we will also explore the use of an alternative three-domain definition considering lung function in place of symptoms and a four-domain remission definition in the study populations with information available for the respective definition (21).

Remission component domains are defined as:

- No exacerbation in past 12 months (allowing 48 weeks where a complete year of follow-up isn't available)
- No LTOCS use or ceasing use in past 12 months (allowing 48 weeks where a complete year of follow-up isn't available)
- Well or partly controlled asthma (GINA, ACT, ACQ) as assessed closest to each timepoint (24 weeks to <18 months for the 12-month timepoint, 18 to <30 months for the 24-month timepoint, 30 to <42 months for the 36-month timepoint)
- FEV_1 percent predicted ≥80% as assessed closest to each timepoint (24 weeks to <18 months for the 12-month timepoint, 18 to <30 months for the 24-month timepoint, 30 to <42 months for the 36-month timepoint). Reference equations: GLI 2022 race-neutral equations (36).

6.0 Statistical Analysis

6.1 Objective 1

To describe frequencies of relapse and the type and extent of domain failure attributed to relapses occurring after 12 months of biologic therapy

We visualized patterns of remission and relapse using histogram and alluvial plots (37) and calculated the percentage of patients in remission or relapse at each follow-up timepoint in addition to the frequency with which patients experienced a change in remission status (i.e. relapse) or not between follow-up timepoints. We calculated survival time, i.e. the time to first observed relapse, and sustained remission probability using the Kaplan-Meier method and described using histograms the frequency of failure in each domain or combination of domains

contributing to these first observed relapses. To characterize the extent or severity of remission failure, we described the distribution of measurements of domains contributing to a first relapse using summary statistics. Among patients who experienced relapse, we compared the frequency of continued relapse versus regaining remission in the year following first relapse between domains contributing to the first relapse using Pearson's chi-squared tests. We repeated analyses using alternate clinical remission definitions.

6.2 Objective 2

To identify pre- and post-treatment demographic and clinical characteristics associated with relapse versus sustained remission at 24 months post-initiation of biologic therapy

To identify factors associated with relapse at 24 months post-initiation of biologic therapy, we examined the study population in remission at 12 months and identified those who subsequently failed to meet clinical remission criteria at 24 months, i.e. experienced relapse. We measured the association between pre-biologic demographic and clinical characteristics (Table 1) with the occurrence of relapse at 24 months using logistic regression models to estimate odds ratios with 95% confidence intervals. We estimated the association between each characteristic and relapse with and without adjustment for sex, index age, setting (country/site), and initial biologic class. In addition, we estimated the association between clinical characteristics as measured in the first 12 months post-initiation and certain characteristics' change from pre-biologic levels (Table 2) and occurrence of relapse at 24 months, with and without adjustment for sex, index age, setting, and initial biologic class (continuous measures were also adjusted for pre-biologic measurements). We estimated the association between the relative percent change in BEC and FeNO measurements from pre- to post-initiation and relapse, categorising the measure of change using thresholds approximating the median observed change. Similarly, we examined the association of change in ICS dose from pre- to post-initiation as either an increase or decrease versus no change, and the change in LAMA use. Finally, we used longitudinal biologic treatment records to assign therapy switches or stops to 12-month follow-up intervals and estimated the association between any switch in therapy between 12 and 24 months post-initiation and relapse. All models incorporated robust errors to account for clustering by setting and excluded patients on anti-TSLP biologic therapy because of small numbers.

6.3 Objective 3

To compare frequency of switching or stopping biologic treatment among patients with an observed first relapse versus those with sustained remission

For each clinical remission definition, we compared the proportion of patients with biologic class switching or stopping recorded at any timepoint up to the first observed relapse or study exit between patients in remission at 12 months with and without any recorded relapse using Pearson's Chi-squared test.

6.4 Software

We conducted all analyses using R version 4.6.0 (r-project.org) in Rstudio (Posit Software, PBC).

7.0 Results

7.1 Patient disposition

A description of the number of biologic initiator patients considered for and included in the study is provided in **Error! Reference source not found.**Table 3. Of 11,798 ISAR patients, a total of 8,357 patients (70.8%) were initially eligible. Further exclusions based on the availability of sufficient follow-up (at least 2 consecutive years post-initiation) information for each of the clinical remission definitions and excluding patients who switched or stopped biologic in the first 12 months reduced the numbers of eligible patients to 713 for the three-domain definition with symptom control, 591 for the three-domain definition with lung function, and 352 for the four-domain definition.

7.2 Description of the study population

Pre-biologic characteristics of 952 ISAR patients included in analyses on at least one of the remission definitions are described in Table 4. This population was 58.8% female (560/952) with a median age of 56.6 years. Included patients were from 24 geographical settings across 23 countries, most frequently from Denmark 32.6% (310/952), Italy 27.6% (263/952), and National Jewish Health in the United States of America 10.6% (101/952). Biologic therapy in the overall study population began between 2008-07-21 and 2023-02-22 and was most frequently an anti-IL5 (390/952, 41.0%). Among patients with available information, 34.1% (322/945) previously or currently smoked, and 24.3% (228/940) were obese, with a BMI ≥30 kg/m^2. Patients meeting a clinical remission definition within 12 months of starting biologic therapy had experienced a median of 2.0 exacerbations in the year prior to initiating biologic therapy (IQR 1.0, 4.0), 16.9% used LTOCS in the past year (125/738), 60.3% reported uncontrolled asthma symptoms (315/522), and 52.2% most recently had a percent predicted FEV_1 <80% (328/628).

Overall, the distributions of most characteristics were similar between populations with sufficient follow-up information for each of the remission definitions (Table 5). Across definitions, included patients were, again, most frequently from Denmark, followed by Italy, though the population with information for the three-domain definition with lung function had a higher percentage of patients from National Jewish Health in the United States. The study population with sufficient information on the three-domain definition with symptom control had a lower percentage of uncontrolled symptoms in the past year than populations with sufficient

information on the other definitions. The study populations with sufficient information on the three-domain definition with lung function and the four-domain definition had better indicators for lung function, including median percent predicted FEV_1, the percentage with percent predicted FEV_1 <80%, and most recent FEV_1/FVC ratio.

7.3 Objective 1

Figure 2 shows remission and relapse status over time in the population in remission at 12 months post-initiation based on the three-domain clinical remission definition, including no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma. As shown by the percentages along the bottom of the figure, percentage of patients experiencing relapse amongst those with data available at each timepoint remained stable over time, ranging from 20.2% at 24 months to 23.2% at 60 months post-initiation. The percentage of patients in remission in the previous year and subsequently relapsing also remained stable over time, ranging from 20.2% from 12 to 24 months to 13.7% from 24 to 36 months.

In the study population with information on the three-domain clinical remission definition including lung function and the four-domain clinical remission definition, percentage of patients experiencing relapse at each timepoint was higher but consistent with primary definition and remained stable over time, ranging from 25.5% at 24 months to 29.3% at 60 months for the three-domain definition (Figure 3) and from 27.6% at 24 months to 25.7% at 60 months for the four-domain definition (Figure 4). The percentage of patients with available information relapsing between timepoints was similar at approximately 20%, using either clinical remission definition involving lung function.

Restricting analysis to only first observed relapses allowed us to estimate the sustained remission probability at each follow-up timepoint and determine the median time until first relapse for each definition (Figure 5, Figure 6, Figure 7, Table 6). For both three-domain definitions, median time without relapse was 60 months, while for the four-domain definition, median time without relapse was 48 months.

Among observed first relapses, we described the frequency of failure within each domain or combination of domains by clinical remission definition (Figure 8, Figure 9, Figure 10). Using the three-domain remission, defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma (Figure 8), of 222 observed first relapses, 98 (44.1%) first

relapses were attributable to exacerbations alone, 75 (33.7%) were attributable to reported uncontrolled symptoms alone, and 40 (18.0%) were attributable to both exacerbations and uncontrolled symptoms. Only 4.1% first relapses (9/222) were attributed to the use of LTOCS, and 5 of these relapses also involved exacerbations. Among 143 observed first relapses involving exacerbations, 75% of patients experienced a single exacerbation during the follow-up period (Table 7). Among 119 observed first relapses involving uncontrolled symptoms and with available information on ACQ or ACT, the median absolute difference in symptom scores from remission in the first 12 months to relapse was 1.3 (Q1 0.8, Q3 1.8) for ACQ and 8.5 (Q1 6.0, Q3 10.2) (Table 7).

Similar numbers of exacerbations and symptom control differences were observed when using the other remission definitions. Using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and no lung function impairment, among 109 observed first relapses involving lung function, the median difference from remission in the first 12 months to relapse was -11.6 (Q1 -16.8, Q3 -7.0) percentage points, and a similar difference was observed using the four-domain definition (Table 7).

Among patients who experienced a first relapse and had available information on clinical remission in the next year, we compared the frequency of achieving remission versus experiencing continued relapse by the domain criteria attributed to their first relapse (Figure 11). Our post-hoc analysis showed that continued relapse in our limited population may be more frequent when symptoms are uncontrolled rather than due to exacerbations. Continued relapse frequency differed by combination of failed remission criteria in first relapse, excluding "Other pattern" due to small counts ($X^2(df = 2) = 11.24$, $p = 0.004$). Using our primary clinical remission definition, pairwise comparisons (Fisher's Exact Test, Bonferroni-corrected $\alpha = 0.017$) showed patients whose first relapse was attributed to one or more exacerbations more frequently achieved remission (30/42, 71.4%) in the following year compared to patients whose first relapse was attributed to uncontrolled symptoms and one or more exacerbations (6/20, 30.0%, p=0.003) and more frequently compared to patients whose first relapse was attributed to uncontrolled symptoms, though the latter did not achieve statistical significance after correction for multiple comparisons (21/47, 44.7%, p=0.018). We found no difference in remission frequency following relapse due to uncontrolled symptoms with or without exacerbations (p=0.291)

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Though population numbers are small (Figure 11), among patients with continued relapse and whose first relapse was attributed to exacerbations with or without uncontrolled symptoms, exacerbations were the most frequent domain attributed to their continued relapse. Similarly, among patients whose first relapse was attributed to uncontrolled symptoms, symptom control was the domain most frequently attributed to their continued relapse.

We also observed a significant difference in the percentage of patients in the year following their first relapse who achieved remission or continued relapse by the domain pattern attributed to first relapse, excluding patients exhibiting a less frequently observed pattern, i.e. "Other pattern" using the three-domain remission definition including lung function (Figure 12, p = 0.027). Specifically, patients whose first relapse was attributed to one or more exacerbations alone more frequently achieved remission (34/54, 63.0%) in the following year compared to patients whose first relapse was attributed to lung function (17/47, 36.2%, p = 0.010). This comparison did not reach statistical significance in this population based on the four-domain clinical remission definition (Figure 13, p = 0.488).

7.4 Objective 2

Towards objective 2, we modelled the association of pre-biologic patient and clinical characteristics with the occurrence of relapse at 24 months among patients in remission at 12 months based on three-domain clinical remission (
Figure *14*), defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma. Adjusting for age, sex, and setting, being female was associated with 1.64 times the odds of relapse observed among males (95% CI 1.24, 2.17), and ever smoking increased the odds of relapse by 1.70 times (95% CI 1.21, 2.38). Longer asthma duration (≥25 years, OR 1.50, 95% CI 0.99, 2.26) and ever having allergic rhinitis (OR 1.64, 95% CI 1.01, 2.67) were associated with higher odds of relapse at 24 months, adjusting for age, sex, and setting. Using a biologic therapy targeting Type 2 inflammation versus an anti-IgE biologic were all associated with lower odds of relapse at 24 months, though with only the anti-IL5R reaching significance (OR 0.38, 95% CI 0.17, 0.86), adjusting for age, sex, and setting. A pre-biologic highest BEC ≥1000 cells/μL (OR 0.45, 95% CI 0.28, 0.71) and pre-biologic most recent FeNO ≥20 ppb (20 – <40, OR 0.42, 95% CI 0.28, 0.64; ≥40, OR 0.61 95% CI 0.49, 0.76) were associated with lower odds of relapse at 24 months, adjusting for age, sex, and setting. The relationship between pre-biologic Type 2 inflammation markers and later relapse is likely

mediated by the selection of biologic therapy, and including biologic class in the model attenuated the observed associations towards the null but did not remove the association completely (Table 8).

We analysed clinical characteristic and treatments at 12 months after biologic initiation and change from pre-biologic measures (Table 9) among the population with information on the three-domain remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma. Among 416 patients, 266 (63.9%) had a percent predicted FEV_1 in the first 12 months ≥80%. Median most recent BEC at 12 months was 100.0 cells/μL (Q1 40.0, Q3 362.5), and 53.4% of patients with information from both timepoints (186/348) had at least a 75% reduction in BEC at 12 months compared to pre-biologic. Median most recent FeNO concentration at 12 months was 22.6 ppb (Q1 14.0, Q3 38.8), and the median difference in FeNO at 12 months compared to pre-biologic was -32.5 (Q1 -62.4, Q3 9.8). Of 513 patients with post-biologic initiation ICS dosage information, 436 (85.0%) had no change in ICS dose at 12 months versus pre-biologic, and the median dose at 12 months was 1200.0 BDP-equivalent mcg/day (Q1 800.0, Q3 2000.0). Of 702 patients, 335 (47.7%) reported LAMA use at 12 months. Among 588 patients with post-initiation biologic treatment information, 24 (4.1%) were found to have switched between 12 and 24 months, but no patients were reported to have stopped their biologic therapy.

We then modelled the association of these 12-month clinical characteristics and treatments with the occurrence of relapse at 24 months (Figure 15, Table 10), using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma. We found that 12-month percent predicted FEV_1 ≥80% versus <80% was associated with lower odds of relapse at 24 months (OR 0.53, 95% CI 0.36, 0.77), adjusting for age, sex, setting, initial biologic class, and pre-biologic FEV_1 percent predicted. Patients with a 12-month BEC ≥100 cells/μL had three times the odds of relapse at 24 months versus patients with a 12-month BEC <100 cells/μL (OR 3.04, 95% CI 1.27, 7.26). After adjusting for biologic class and pre-biologic BEC in addition to age, sex, and setting, we found that a percent reduction <75% in BEC or no change or increase in BEC from pre-initiation to 12 months post-initiation was associated with increased odds of relapse at 24 months (>-75%–<0% OR 2.93, 95% CI 1.12, 7.67; ≥0% OR 2.26, 95% CI 0.92, 5.57) versus a reduction of ≥75%. FeNO concentration measured closest to 12-months post-initiation was not associated with relapse at 24 months. A <34% reduction in FeNO concentration compared to a ≥34% reduction was associated with increased odds of relapse at 24 months (OR 2.06, 95% CI 1.47, 2.88). We

also observed an association of no change or increase in FeNO concentration at 12-month with relapse at 24 months compared to a ≥34% reduction (OR 1.54, 95% CI 1.06, 2.23), though this association was attenuated down towards the null after adjustment for age, sex, biologic class, and pre-biologic FeNO concentration (OR 1.29, 95% CI 0.60, 2.77). Patients on a medium ICS dose versus a high dose had higher odds of relapse at 24 months (OR 1.83, 95% CI 1.17, 2.86), after adjusting for age, sex, setting, biologic class, and pre-biologic ICS dose. We did not observe an association between change in pre-biologic to 12-month ICS dose or LAMA use with relapse at 24 months. Patients who switched biologic between 12 and 24 months had higher odds of relapse at 24 months than those who continued on the same treatment (OR 2.58, 95% 1.09, 6.10).

As a post hoc analysis we restricted our modelling analyses to patients initially on each of the four main classes of biologic therapy: anti-IgE; anti-IL4Ralpha; anti-IL5; and anti-IL5R. The distributions of twelve-month clinical characteristics for patients on each biologic class are presented in Table 11. No 12-month characteristics were significantly associated with relapse at 24 months among patients initially on an anti-IgE biologic (Table 12). Among patients on an anti-IL4Ralpha biologic, percent predicted FEV1 ≥80% (Table 13, OR 4.35, 95% CI 2.08, 9.06) and LAMA use (Table 13, OR 3.23, 95% CI 1.40, 7.46) were associated with increased odds of relapse at 24 months, adjusting for age, sex, setting, and pre-biologic measures. Among patients on an anti-IL5 biologic, percent predicted FEV1 ≥80% (Table 14, OR 0.43, 95% CI 0.24, 0.76) and LAMA use (Table 14 OR 0.18, 95% CI 0.04, 0.73) were associated with lower odds of relapse at 24 months, while BEC ≥100 versus <100 (Table 14, OR 4.31, 95% CI 1.16, 15.96) and Medium versus Low ICS dose (Table 14, OR 3.31, 95% CI 1.46, 7.50) were associated with higher odds of relapse at 24 months, adjusting for age, sex, setting, and pre-biologic measures. Among patients on an anti-IL5R biologic, FeNO ≥20 versus <20 (Table 15, OR 0.07, 95% CI 0.02, 0.22) and Medium versus Low ICS dose (Table 15, OR 0.55, 95% CI 0.34, 0.90) were associated with lower odds of relapse at 24 months, adjusting for age, sex, setting, and pre-biologic measures.

7.5 Objective 3

Among patients in remission at 12 months with and without a recorded relapse, as *post hoc* analysis, we compared the frequency of biologic switching or stopping at any point of follow-up (Table 16). Regardless of clinical remission definition used, we found a higher proportion of having stopped biologic treatment at any point after 12 months among patients who

experienced a relapse in comparison with right-censored patients, but the small population limits our interpretation of these statistical findings. We did not observe this difference for switching of biologic after 12 months.

8.0 Summary and Discussion

In the current study, we leveraged the size and scope of ISAR to examine patterns and predictors of relapse among patients in clinical remission for 12 months following initiation of biologic therapy. We primarily defined clinical remission based on three domains: no asthma exacerbations, no LTOCS use, and well or partly controlled symptoms in the previous 12 months. We found that the percentage of patients meeting clinical remission criteria and relapse frequency were stable over time, and relapses after 12 months were most frequently attributed to a single remission domain. We identified pre- and post-biologic demographic and clinical characteristics associated with relapse at 24 months.

Our first objective aimed to describe frequencies of relapse and the type and extent of domain failure attributed to relapses occurring after 12 months of biologic therapy. Towards this, we used alluvial plots to visualise the percentage of patients meeting clinical remission criteria or not at subsequent follow-up timepoints among patients in clinical remission for 12 months following initiation of biologic therapy. This analysis revealed that while the overall percentage of patients in remission or relapse remained stable over time, there was considerable change in status between timepoints with patients relapsing or regaining remission. In particular, the percentage of patients in remission in the previous year and subsequently relapsing remained stable over time, regardless of the clinical remission definition used and at a similar rate as observed in other studies (26–28). To explore further, we restricted our analysis to first relapses to examine the time to event, as others have used for remission (38), and found that 50% of patients remain in remission beyond 48 months of follow-up, using our primary definition, and beyond 36 months using the strict four-domain definition, including both reported symptoms and lung function.

For each of these first relapses, we also examined in which domain or combination of domains the patient failed to meet remission criteria. We found that, regardless of the clinical remission definition used, these first relapses or “late failures” were most frequently attributed to a single domain. For both of the three-domain definitions, the occurrence of any exacerbations was the most frequent domain for which remission was not achieved for that period. Using the same three-domain definition, Dacal-Rivas et al. also found exacerbations alone, and then in addition to symptom control, to be the first and second most common manifestations of relapse (26). Further, in our work, using the four-domain definition, the most frequent domain failure was lung function, i.e. not achieving percent predicted FEV_1 ≥80%. Dacal-Rivas et al. chose not to incorporate lung function in their remission definition as they considered some bronchial

obstruction to be acceptable in practice if other therapeutic objectives are achieved (26). We attributed very few relapses to LTOCS use, and in these cases, the relapse was often due to LTOCS use in addition to the occurrence of exacerbations. We also examined the extent of failure in each domain for relapses attributed to that domain and found similar results across remission definitions. Using our primary three-domain remission definition, among relapses attributable to exacerbations, 75% involved a single exacerbation. These single exacerbations may have been caused by a viral respiratory infection, the most common trigger of exacerbations (39–41). Among viral causes of exacerbations, rhinoviruses, the agent of the "common cold", are the most frequent (39). Examination of exacerbation dates to look for seasonal variation could support or refute the conclusion that these exacerbations are infection-related events. Among patients on an anti-IL5/5R biologic, viral infections have been associated with low measurements of FeNO during exacerbations, which in turn have shown less improvement to OCS treatment with respect to lung function and symptom control (41,42). Relapses based on symptom control criteria involved considerable worsening of symptoms as, among those with ACT or ACQ results, we calculated the median absolute difference for ACQ to be 1.3 and for ACT to be 8.5—approximately three times the minimal clinically important difference for each respective scale (43). A MCID does not exist for percent predicted FEV_1, but relapses based on lung function involved a >10% decline in predicted lung function, using either the three- or four-domain definition. Exploring what happened to patients in the year following their first relapse provides important further information. Although limited by small population numbers, we found that patients who experienced continued relapse often did so by failing in the same remission domain and that patients who relapsed as a result of exacerbation more frequently regained remission in the following year.

Towards our second objective, we modelled the association between pre-biologic demographic and pre- and post-biologic clinical characteristics and occurrence of relapse between 12 and 24 months. Our findings align with those from other studies on relapse and remission (26,28,29,44). Pre-biologic predictors of increased odds of relapse included female sex, ever smoking, duration of asthma, allergic rhinitis, and starting on an anti-IgE biologic. We found that patients with shorter disease duration, pre-biologic BEC ≥1000 cells/μL, and pre-biologic FeNO concentration >20 ppb had lower odds of relapse. Patients with more recent onset of disease in addition to elevated biomarkers may exhibit adult-onset, intrinsic asthma that was suitably targeted by a biologic targeting eosinophils (45); conversely, patients with longer duration of disease and allergic rhinitis—traits of the allergic (extrinsic) phenotype—may also have been initially prescribed an anti-IgE biologic, which was the first available

biologic for asthma, but may be better suited to an alternative therapy (26). Interestingly, adjusting for biologic class, we still found increased odds of relapse among patients with longer disease duration, which may represent patients with irreparable pulmonary damage (46), and with more moderate pre-biologic BEC. This possibility is also shown in our analysis of 12-month characteristics and relapse at 24 months. Similar to Dacal-Rivas et al., we found that patients with ≥80% percent predicted FEV_1 had lower odds of relapse, compared to those with <80%. Patients with post-biologic BEC ≥100 cells/μL compared to those with <100 and patients with a smaller relative percent change in BEC measures from pre-biologic levels had higher odds of relapse, adjusting for age, sex, setting, initial biologic class, and pre-biologic levels. While 12-month FeNO levels were not associated with subsequent relapse, patients with more modest reductions from pre-biologic levels had increased odds of relapse.

In our study population, among those with information available, approximately 4% of patients had a switch in biologic therapy recorded between 12 and 24 months. We observed a strong association of biologic switch with higher odds of relapse between 12 and 24 months post-initiation. It is important to note, however, that switching or stopping between 12 and 24 months corresponds with the same period of time during which relapse at 24 months is assessed, so this relationship could represent a change in therapy made in response to failings in one or more of the clinical remission domains rather than an actual determinant of relapse. Towards our third objective with the aim of contributing to the sparse evidence on the relationship between biologic switching or stopping and remission (26,46), we compared frequencies of these patterns at any timepoint between patients with an observed first relapse and those without. Patients with an observed relapse more frequently had a stop in biologic therapy recorded, but we observed no difference in switching frequency. Stopping, or switching, therapy could be undertaken in response to a relapse and is considered a marker of treatment failure, so this limited evidence of an association could also reflect reverse causality.

As with other registry-based studies, missing data is a limitation, which is compounded by our use of multiple-domain remission definitions. Our study was limited to patients with sufficient follow-up and data completeness to examine long-term remission trends, which may limit generalisability, if the excluded patients differ systematically from our analysis population. Our data also represent information collected for clinical and routine use rather than research, and similar to all observational research, residual confounding and unmeasured confounders may influence our results.

9.0 Conclusion

In conclusion, we have described the frequency of late clinical remission failures, or relapses, occurring after remission was achieved during 12 months of biologic therapy. We have identified in which domains failure to reach remission thresholds contributed to these relapses and measured the severity of failure in each and explored how subsequent remission trajectories differ depending on which domain failure contributed to initial relapse. Our modelling identified both demographic and clinical predictors of relapse between 12 and 24 months, identifying that markers of residual Type 2 inflammation may correspond with increased occurrence of relapse. Finally, we examined the role of switching and stopping of biologic therapy using two approaches, but our conclusions from this work were limited by the study design and small numbers of patients to-date with either recorded treatment switches or stops. Future work in the GLOW study will employ more robust methods to specifically explore patterns and effects of switching or stopping biologic therapy among the ISAR population.

10.0 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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13.0 List of Tables and Figures

14.0 Tables and Figures

Table 3: Patient disposition.

	n (%)
Total patients considered for inclusion, N=11798	
Age <18	274 (2.3%)
Missing biologic initiation date	1114 (9.4%)
Biologic initiated less than a year before dataset closure date (31-07-2025)	169 (1.4%)
Less than 1 year of follow-up	1882 (16.0%)
Missing age	2 (<0.1%)
Eligible after general exclusions	**8357 (70.8%)**
3-Domain Remission: No Exacerbation, No LTOCS Use, And Partly/Well Controlled, N=8357	
No follow up observations with remission information	2996 (35.9%)
First follow up observation not at 12 months	1871 (22.4%)
Fewer than two follow up observations	1666 (19.9%)
Not in remission at 12 months	1092 (13.1%)
Switched or stopped biologic in first 12 months	19 (0.2%)
Included	**713 (8.5%)**
3-Domain Remission: No Exacerbation, No LTOCS Use, And No Lung Function Impairment, N=8357	
No follow up observations with remission information	2983 (35.7%)
First follow up observation not at 12 months	1682 (20.1%)
Fewer than two follow up observations	1677 (20.1%)
Not in remission at 12 months	1403 (16.8%)
Switched or stopped biologic in first 12 months	21 (0.3%)
Included	**591 (7.1%)**
4-Domain Remission: No Exacerbation, No LTOCS Use, Partly/Well Controlled, And No Lung Function Impairment, N=8357	
No follow up observations with remission information	3802 (45.5%)
First follow up observation not at 12 months	1684 (20.2%)
Fewer than two follow up observations	1475 (17.6%)
Not in remission at 12 months	1033 (12.4%)
Switched or stopped biologic in first 12 months	11 (0.1%)
Included	**352 (4.2%)**

Table 4: Pre-biologic patient demographic and clinical characteristics for eligible patients with information on any remission definition.

Characteristic	N	Measure/category	Result
Age At Biologic Initiation (Years)	952	median (Q1, Q3)	56.6 (48.3, 65.9)
		<50: n (%)	280 (29.4%)
		50 – <60: n (%)	280 (29.4%)
		60 – <70: n (%)	256 (26.9%)
		≥70: n (%)	136 (14.3%)
Sex	952	Female: n (%)	560 (58.8%)
Geographic Setting*	952	Denmark: n (%)	310 (32.6%)
		Italy: n (%)	263 (27.6%)
		USA-NJH: n (%)	101 (10.6%)
		Spain: n (%)	67 (7.0%)
		UK: n (%)	33 (3.5%)
		Canada: n (%)	30 (3.2%)
		Belgium: n (%)	26 (2.7%)
		Colombia: n (%)	23 (2.4%)
		Japan: n (%)	20 (2.1%)
		Other: n (%)	79 (8.3%)
Biologic Initiation Date	952	median (range)	2020-02-29 (2008-07-21, 2023-02-22)
Biologic Class	952	Anti-IgE: n (%)	198 (20.8%)
		Anti-IL4Ralpha: n (%)	194 (20.4%)
		Anti-IL5: n (%)	390 (41.0%)
		Anti-IL5R: n (%)	168 (17.6%)
		Anti-TSLP: n (%)	2 (0.2%)
Ethnicity	830	Caucasian: n (%)	714 (86.0%)
		African: n (%)	4 (0.5%)
		South East Asian: n (%)	27 (3.3%)
		North East Asian: n (%)	31 (3.7%)
		Mixed: n (%)	21 (2.5%)
		Other: n (%)	33 (4.0%)
Smoking Status	945	Never smoker: n (%)	623 (65.9%)
		Ex-smoker: n (%)	305 (32.3%)
		Current smoker: n (%)	17 (1.8%)
BMI (kg/m^2)	940	median (Q1, Q3)	26.2 (23.1, 29.9)
Obese (BMI ≥30 kg/m^2)	940	Yes: n (%)	228 (24.3%)
Exacerbations In Past Year	735	median (Q1, Q3)	2.0 (1.0, 4.0)
LTOCS Use In Past Year	738	Yes: n (%)	125 (16.9%)
Most Recent Asthma Control In Past Year (GINA 2020)	522	Uncontrolled: n (%)	315 (60.3%)
		Partly controlled: n (%)	112 (21.5%)
		Well controlled: n (%)	95 (18.2%)
Most Recent Percent Predicted FEV1 In Past Year (%)	628	median (Q1, Q3)	78.5 (66.7, 94.9)
		<80%: n (%)	328 (52.2%)
Most Recent FEV1/FVC Ratio In Past Year	692	median (Q1, Q3)	0.7 (0.6, 0.8)
		<0.7: n (%)	350 (50.6%)
Age At Asthma Onset (Years)	672	median (Q1, Q3)	35.0 (20.0, 50.0)
		<12: n (%)	101 (15.0%)
		12 – 40: n (%)	314 (46.7%)
		>40: n (%)	257 (38.2%)

Characteristic	N	Measure/category	Result
Asthma Duration (Years)	672	median (Q1, Q3)	17.8 (8.2, 33.6)
		<10: n (%)	207 (30.8%)
		10 – <25: n (%)	211 (31.4%)
		≥25: n (%)	254 (37.8%)
Highest Blood Eosinophil Count (cells/µL)	674	median (Q1, Q3)	600.0 (300.0, 937.5)
		<300: n (%)	143 (21.2%)
		300 – <600: n (%)	188 (27.9%)
		600 – <1000: n (%)	189 (28.0%)
		≥1000: n (%)	154 (22.8%)
Latest Serum Total IgE Concentration (IU/mL)	637	median (Q1, Q3)	169.0 (67.0, 377.0)
Latest FENO Concentration (ppb)	597	median (Q1, Q3)	36.0 (18.0, 68.0)
		<20: n (%)	163 (27.3%)
		20 – <40: n (%)	170 (28.5%)
		≥40: n (%)	264 (44.2%)
Allergen Test Results	890	Positive: n (%)	425 (47.8%)
Eosinophilic Asthma Gradient	815	Grade 0: Unlikely/Noneosinophilic: n (%)	3 (0.4%)
		Grade 1: Least likely: n (%)	23 (2.8%)
		Grade 2: Likely: n (%)	31 (3.8%)
		Grade 3: Most likely: n (%)	758 (93.0%)
ICS dose (BDP-equivalent mcg/day)	749	median (Q1, Q3)	1500.0 (800.0, 2000.0)
		High ≥1000: n (%)	549 (73.3%)
		Medium >500 – <1000: n (%)	130 (17.4%)
		Low ≤500: n (%)	70 (9.3%)
	943	Yes: n (%)	435 (46.1%)
LTRA Use	874	Yes: n (%)	459 (52.5%)
Theophylline	874	Yes: n (%)	29 (3.3%)
Macrolide	874	Yes: n (%)	58 (6.6%)
Allergic Rhinitis	846	Ever: n (%)	512 (60.5%)
CRS (+/-NP)	907	Ever: n (%)	620 (68.4%)
CRSwNP	938	Ever: n (%)	440 (46.9%)
Eczema/Atopic Dermatitis	939	Ever: n (%)	166 (17.7%)
History Of Osteoporosis	750	Yes: n (%)	72 (9.6%)
History Of Anxiety And/Or Depression	884	Yes: n (%)	103 (11.7%)

*Other: Brazil, Bulgaria, Greece, Ireland-Tallaght, Kuwait, Mexico, Norway, Poland, Portugal, Saudi Arabia, Singapore, South Korea, Taiwan, UAE, USA-Michigan

Table 5: Pre-biologic patient demographic and clinical characteristics for eligible patients with information by remission definition.

Characteristic	Measure/category	3-Domain Remission: No Exacerbation, No LTOCS Use, And Partly/Well Controlled N	3-Domain Remission: No Exacerbation, No LTOCS Use, And Partly/Well Controlled Result	3-Domain Remission: No Exacerbation, No LTOCS Use, And No Lung Function Impairment N	3-Domain Remission: No Exacerbation, No LTOCS Use, And No Lung Function Impairment Result	4-Domain Remission: No Exacerbation, No LTOCS Use, Partly/Well Controlled, And No Lung Function Impairment N	4-Domain Remission: No Exacerbation, No LTOCS Use, Partly/Well Controlled, And No Lung Function Impairment Result
Age At Biologic Initiation (Years)	median (Q1, Q3)	713	57.9 (49.7, 66.3)	591	55.6 (47.7, 64.9)	352	56.9 (49.7, 65.4)
	<50: n (%)		187 (26.2%)		186 (31.5%)		93 (26.4%)
	50 – <60: n (%)		216 (30.3%)		185 (31.3%)		121 (34.4%)
	60 – <70: n (%)		196 (27.5%)		150 (25.4%)		90 (25.6%)
	≥70: n (%)		114 (16.0%)		70 (11.8%)		48 (13.6%)
Sex	Female: n (%)	713	413 (57.9%)	591	351 (59.4%)	352	204 (58.0%)
Geographic Setting*	Denmark: n (%)	713	245 (34.4%)	591	210 (35.5%)	352	145 (41.2%)
	Italy: n (%)		245 (34.4%)		112 (19.0%)		94 (26.7%)
	USA-NJH: n (%)		19 (2.7%)		92 (15.6%)		10 (2.8%)
	Spain: n (%)		53 (7.4%)		50 (8.5%)		36 (10.2%)
	UK: n (%)		25 (3.5%)		19 (3.2%)		11 (3.1%)
	Canada: n (%)		24 (3.4%)		15 (2.5%)		9 (2.6%)
	Belgium: n (%)		0 (0.0%)		26 (4.4%)		0 (0.0%)
	Colombia: n (%)		19 (2.7%)		12 (2.0%)		8 (2.3%)
	Japan: n (%)		20 (2.8%)		9 (1.5%)		9 (2.6%)
	Other: n (%)		63 (8.8%)		46 (7.8%)		30 (8.5%)
Biologic Initiation Date	median (range)	713	2020-05-28 (2009-08-31, 2023-02-22)	591	2020-02-12 (2008-07-21, 2023-02-22)	352	2020-08-03 (2009-08-31, 2023-02-22)
Biologic Class	Anti-IgE: n (%)	713	126 (17.7%)	591	132 (22.3%)	352	60 (17.0%)
	Anti-IL4Ralpha: n (%)		159 (22.3%)		123 (20.8%)		88 (25.0%)
	Anti-IL5: n (%)		294 (41.2%)		251 (42.5%)		155 (44.0%)
	Anti-IL5R: n (%)		132 (18.5%)		85 (14.4%)		49 (13.9%)
	Anti-TSLP: n (%)		2 (0.3%)		0 (0.0%)		0 (0.0%)
Ethnicity	Caucasian: n (%)	643	545 (84.8%)	503	444 (88.3%)	316	275 (87.0%)
	African: n (%)		2 (0.3%)		2 (0.4%)		0 (0.0%)
	South East Asian: n (%)		23 (3.6%)		11 (2.2%)		7 (2.2%)
	North East Asian: n (%)		28 (4.4%)		14 (2.8%)		11 (3.5%)
	Mixed: n (%)		16 (2.5%)		17 (3.4%)		12 (3.8%)
	Other: n (%)		29 (4.5%)		15 (3.0%)		11 (3.5%)
Smoking Status	Never smoker: n (%)	707	466 (65.9%)	586	391 (66.7%)	348	234 (67.2%)

Characteristic	Measure/category	3-Domain Remission: No Exacerbation, No LTOCS Use, And Partly/Well Controlled N	3-Domain Remission: No Exacerbation, No LTOCS Use, And Partly/Well Controlled Result	3-Domain Remission: No Exacerbation, No LTOCS Use, And No Lung Function Impairment N	3-Domain Remission: No Exacerbation, No LTOCS Use, And No Lung Function Impairment Result	4-Domain Remission: No Exacerbation, No LTOCS Use, Partly/Well Controlled, And No Lung Function Impairment N	4-Domain Remission: No Exacerbation, No LTOCS Use, Partly/Well Controlled, And No Lung Function Impairment Result
	Ex-smoker: n (%)		230 (32.5%)		184 (31.4%)		109 (31.3%)
	Current smoker: n (%)		11 (1.6%)		11 (1.9%)		5 (1.4%)
BMI (kg/m^2)	median (Q1, Q3)	701	25.8 (22.9, 29.3)	591	26.5 (23.1, 30.0)	352	25.7 (22.8, 28.7)
Obese (BMI ≥30 kg/m^2)	Yes: n (%)	701	144 (20.5%)	591	150 (25.4%)	352	66 (18.8%)
Exacerbations In Past Year	median (Q1, Q3)	554	2.0 (1.0, 4.0)	459	2.0 (1.0, 4.0)	278	2.0 (1.0, 4.0)
LTOCS Use In Past Year	Yes: n (%)	565	101 (17.9%)	457	76 (16.6%)	284	52 (18.3%)
Most Recent Asthma Control In Past Year (GINA 2020)	Uncontrolled: n (%)	416	231 (55.5%)	314	209 (66.6%)	208	125 (60.1%)
	Partly controlled: n (%)		99 (23.8%)		65 (20.7%)		52 (25.0%)
	Well controlled: n (%)		86 (20.7%)		40 (12.7%)		31 (14.9%)
Most Recent Percent Predicted FEV1 In Past Year (%)	median (Q1, Q3)	455	76.5 (64.4, 92.6)	412	86.0 (74.1, 99.5)	239	86.4 (74.8, 99.4)
	<80%: n (%)		260 (57.1%)		155 (37.6%)		87 (36.4%)
Most Recent FEV1/FVC Ratio In Past Year	median (Q1, Q3)	488	0.7 (0.6, 0.7)	459	0.7 (0.7, 0.8)	255	0.7 (0.6, 0.8)
	<0.7: n (%)		289 (59.2%)		185 (40.3%)		124 (48.6%)
Age At Asthma Onset (Years)	median (Q1, Q3)	557	35.0 (20.0, 50.0)	380	35.5 (19.8, 50.0)	265	36.0 (20.0, 50.0)
	<12: n (%)		81 (14.5%)		52 (13.7%)		32 (12.1%)
	12 – 40: n (%)		256 (46.0%)		177 (46.6%)		119 (44.9%)
	>40: n (%)		220 (39.5%)		151 (39.7%)		114 (43.0%)
Asthma Duration (Years)	median (Q1, Q3)	557	18.4 (8.7, 34.5)	380	16.7 (7.3, 31.0)	265	16.8 (7.9, 32.4)
	<10: n (%)		164 (29.4%)		135 (35.5%)		92 (34.7%)
	10 – <25: n (%)		180 (32.3%)		113 (29.7%)		82 (30.9%)
	≥25: n (%)		213 (38.2%)		132 (34.7%)		91 (34.3%)

Characteristic	Measure/category	3-Domain Remission: No Exacerbation, No LTOCS Use, And Partly/Well Controlled N	3-Domain Remission: No Exacerbation, No LTOCS Use, And Partly/Well Controlled Result	3-Domain Remission: No Exacerbation, No LTOCS Use, And No Lung Function Impairment N	3-Domain Remission: No Exacerbation, No LTOCS Use, And No Lung Function Impairment Result	4-Domain Remission: No Exacerbation, No LTOCS Use, Partly/Well Controlled, And No Lung Function Impairment N	4-Domain Remission: No Exacerbation, No LTOCS Use, Partly/Well Controlled, And No Lung Function Impairment Result
Highest Blood Eosinophil Count (cells/µL)	median (Q1, Q3)	500	600.0 (332.2, 980.0)	422	600.0 (300.0, 907.5)	248	648.5 (340.0, 962.5)
	<300: n (%)		99 (19.8%)		95 (22.5%)		51 (20.6%)
	300 – <600: n (%)		134 (26.8%)		115 (27.3%)		61 (24.6%)
	600 – <1000: n (%)		144 (28.8%)		122 (28.9%)		77 (31.0%)
	≥1000: n (%)		123 (24.6%)		90 (21.3%)		59 (23.8%)
Latest Serum Total IgE Concentration (IU/mL)	median (Q1, Q3)	464	177.5 (71.0, 393.2)	416	156.5 (64.1, 362.2)	243	162.0 (67.5, 378.5)
Latest FENO Concentration (ppb)	median (Q1, Q3)	438	37.0 (18.6, 72.5)	394	36.0 (18.0, 69.8)	235	37.7 (18.5, 76.0)
	<20: n (%)		116 (26.5%)		109 (27.7%)		62 (26.4%)
	20 – <40: n (%)		121 (27.6%)		111 (28.2%)		62 (26.4%)
	≥40: n (%)		201 (45.9%)		174 (44.2%)		111 (47.2%)
Allergen Test Results	Positive: n (%)	701	311 (44.4%)	536	264 (49.3%)	347	150 (43.2%)
Eosinophilic Asthma Gradient	Grade 0: Unlikely/Noneosinophilic: n (%)	619	3 (0.5%)	503	2 (0.4%)	307	2 (0.7%)
	Grade 1: Least likely: n (%)		18 (2.9%)		13 (2.6%)		8 (2.6%)
	Grade 2: Likely: n (%)		19 (3.1%)		21 (4.2%)		9 (2.9%)
	Grade 3: Most likely: n (%)		579 (93.5%)		467 (92.8%)		288 (93.8%)
ICS dose (BDP-equivalent mcg/day)	median (Q1, Q3)	556	1600.0 (800.0, 2000.0)	458	1200.0 (800.0, 2000.0)	265	1500.0 (800.0, 2000.0)
	High ≥1000: n (%)		413 (74.3%)		327 (71.4%)		191 (72.1%)
	Medium >500 – <1000: n (%)		104 (18.7%)		79 (17.2%)		53 (20.0%)
	Low ≤500: n (%)		39 (7.0%)		52 (11.4%)		21 (7.9%)
	Yes: n (%)	704	351 (49.9%)	588	241 (41.0%)	349	157 (45.0%)
LTRA Use	Yes: n (%)	650	332 (51.1%)	541	296 (54.7%)	317	169 (53.3%)
Theophylline	Yes: n (%)	650	26 (4.0%)	541	15 (2.8%)	317	12 (3.8%)
Macrolide	Yes: n (%)	650	39 (6.0%)	541	39 (7.2%)	317	20 (6.3%)
Allergic Rhinitis	Ever: n (%)	619	369 (59.6%)	544	336 (61.8%)	317	193 (60.9%)
CRS (+/-NP)	Ever: n (%)	678	473 (69.8%)	565	381 (67.4%)	336	234 (69.6%)

Characteristic	Measure/category	3-Domain Remission: No Exacerbation, No LTOCS Use, And Partly/Well Controlled		3-Domain Remission: No Exacerbation, No LTOCS Use, And No Lung Function Impairment		4-Domain Remission: No Exacerbation, No LTOCS Use, Partly/Well Controlled, And No Lung Function Impairment	
		N	Result	N	Result	N	Result
CRSwNP	Ever: n (%)	701	352 (50.2%)	584	267 (45.7%)	347	179 (51.6%)
Eczema/Atopic Dermatitis	Ever: n (%)	701	115 (16.4%)	584	111 (19.0%)	346	60 (17.3%)
History Of Osteoporosis	Yes: n (%)	554	54 (9.7%)	459	42 (9.2%)	263	24 (9.1%)
History Of Anxiety And/Or Depression	Yes: n (%)	661	60 (9.1%)	550	71 (12.9%)	327	28 (8.6%)

*Other: Brazil, Bulgaria, Greece, Ireland-Tallaght, Kuwait, Mexico, Norway, Poland, Portugal, Saudi Arabia, Singapore, South Korea, Taiwan, UAE, USA-Michigan

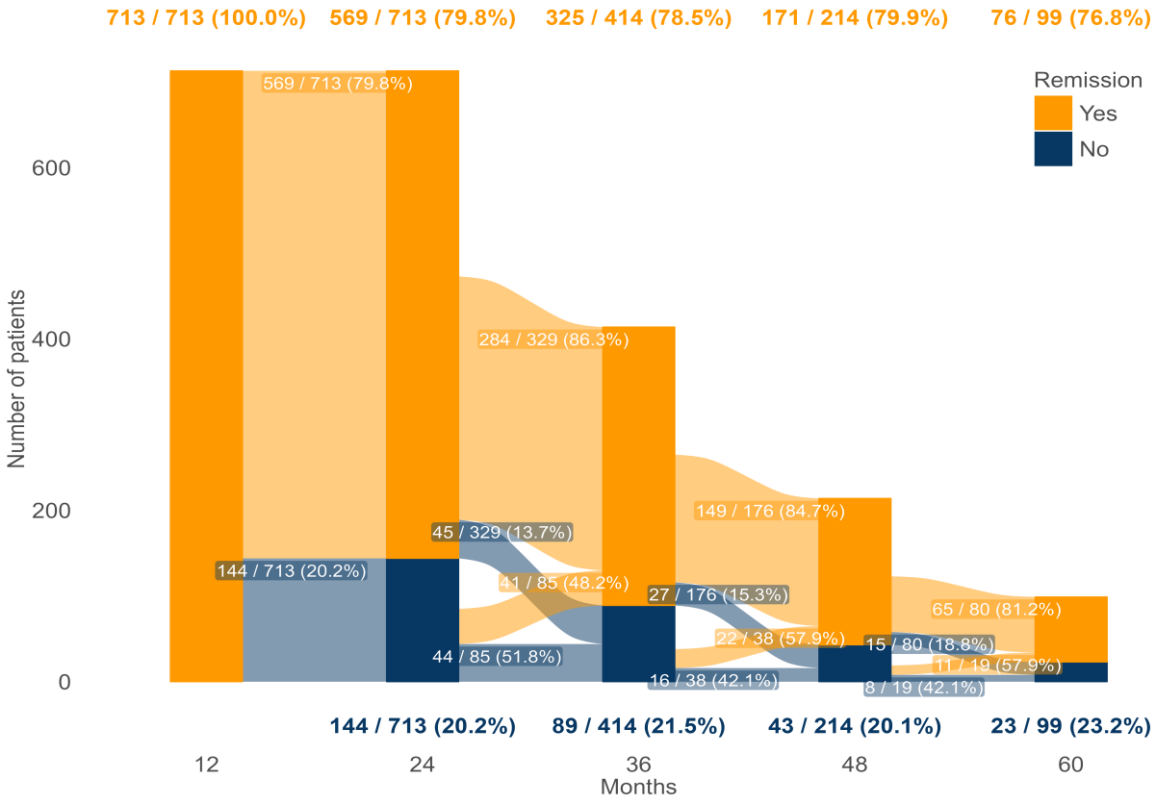


Figure 2: Number of patients with available information by remission status at each follow-up since initial remission at 12 months, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma. Numbers in orange show prevalence of remission and numbers in blue show prevalence of relapse. Numbers in white show the movement of patients between categories over time.

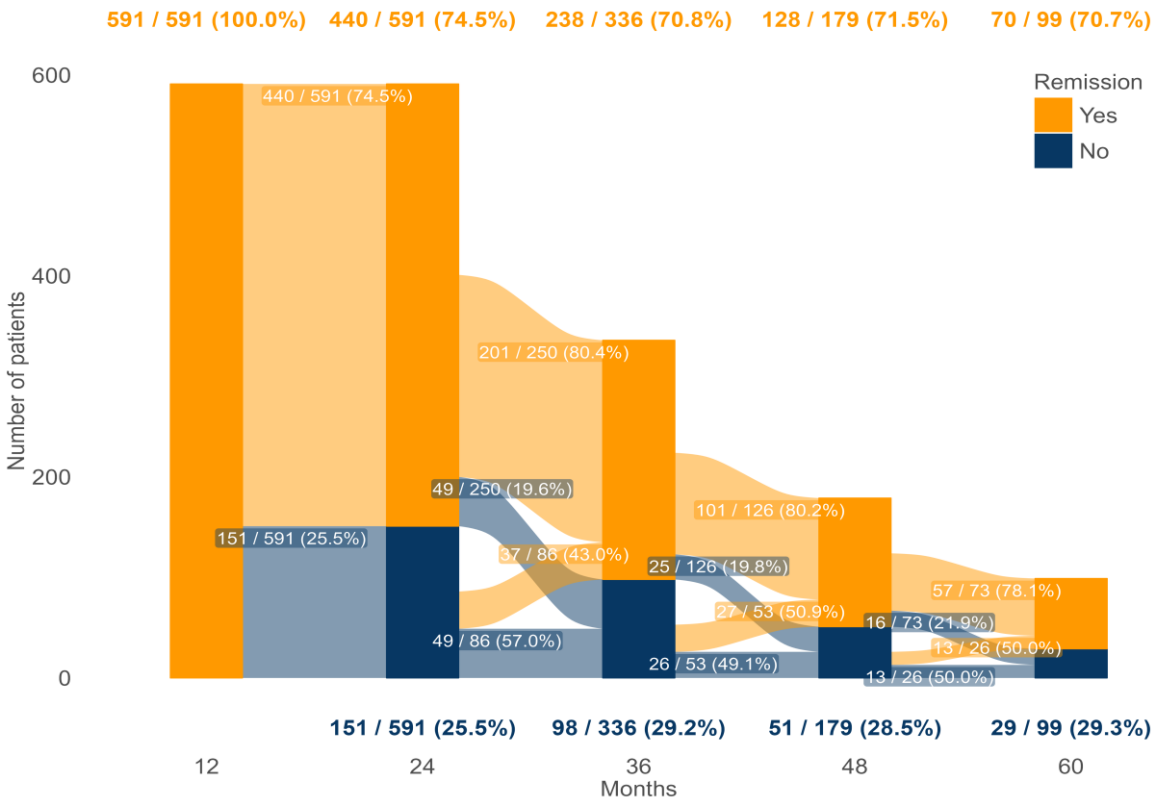


Figure 3: Number of patients with available information by remission status at each follow-up since initial remission at 12 months, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and FEV1 percent predicted ≥80%. Numbers in orange show prevalence of remission and numbers in blue show prevalence of relapse. Numbers in white show the movement of patients between categories over time.

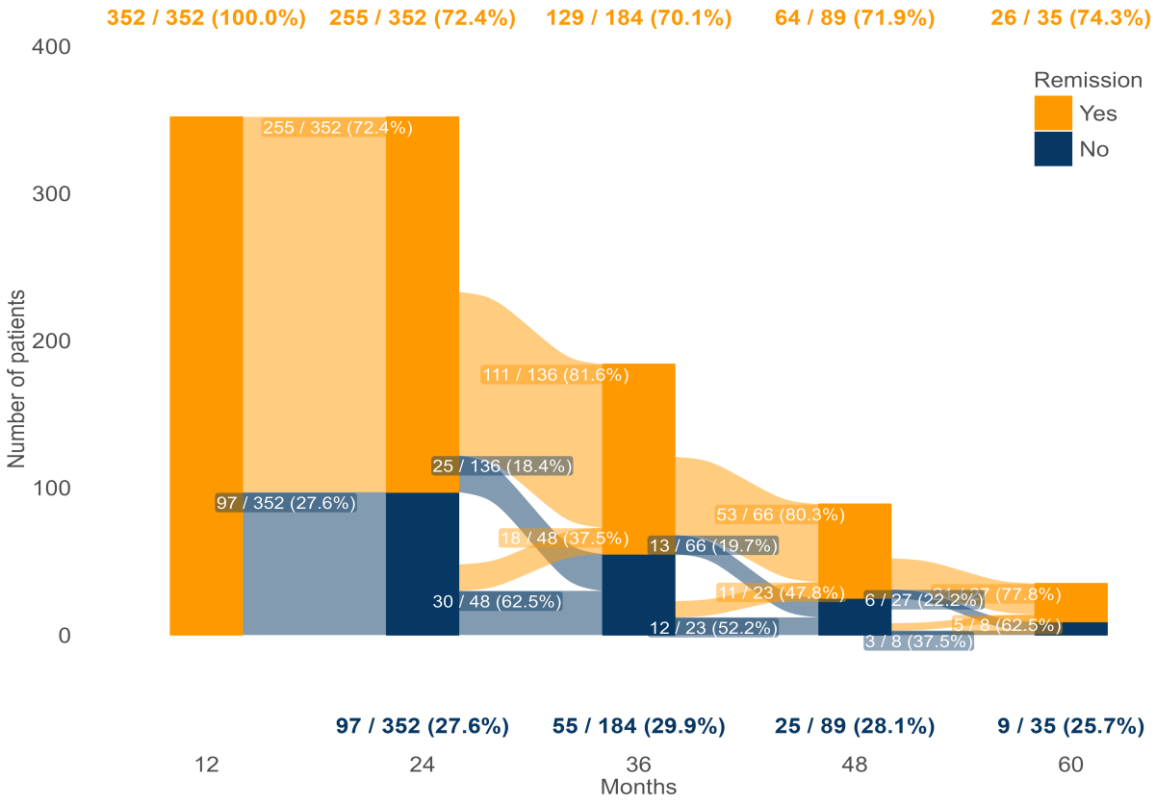


Figure 4: Number of patients with available information by remission status at each follow-up since initial remission at 12 months, using four-domain remission defined as no exacerbations in the past year, no LTOCS use, FEV1 percent predicted ≥80%, and well or partly controlled asthma. Numbers in orange show prevalence of remission and numbers in blue show prevalence of relapse. Numbers in white show the movement of patients between categories over time.

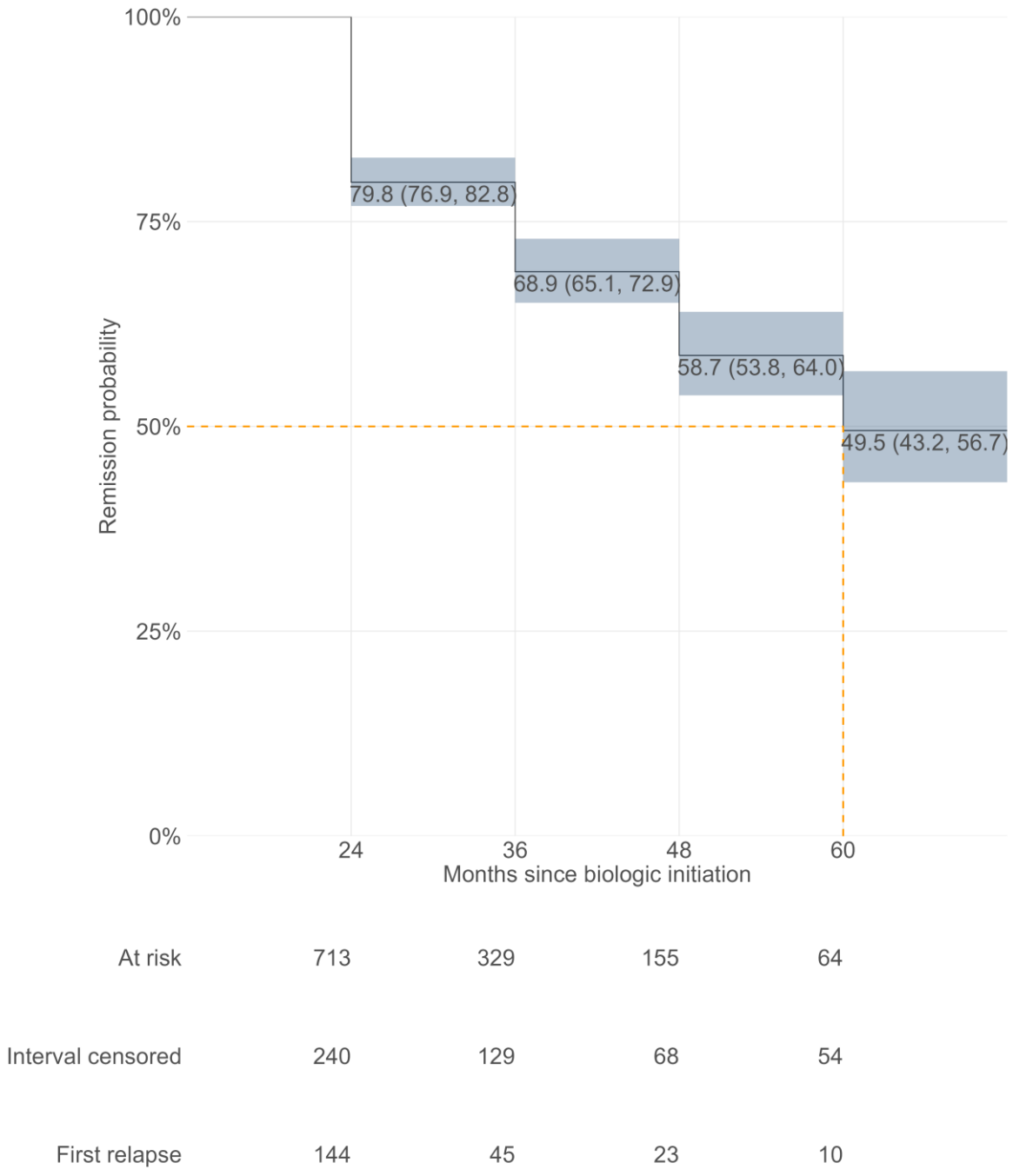


Figure 5: Sustained remission probability among patients in remission at 12 months, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma. Blue boxes represent estimated 95% confidence intervals, and orange lines indicate median time until first relapse.

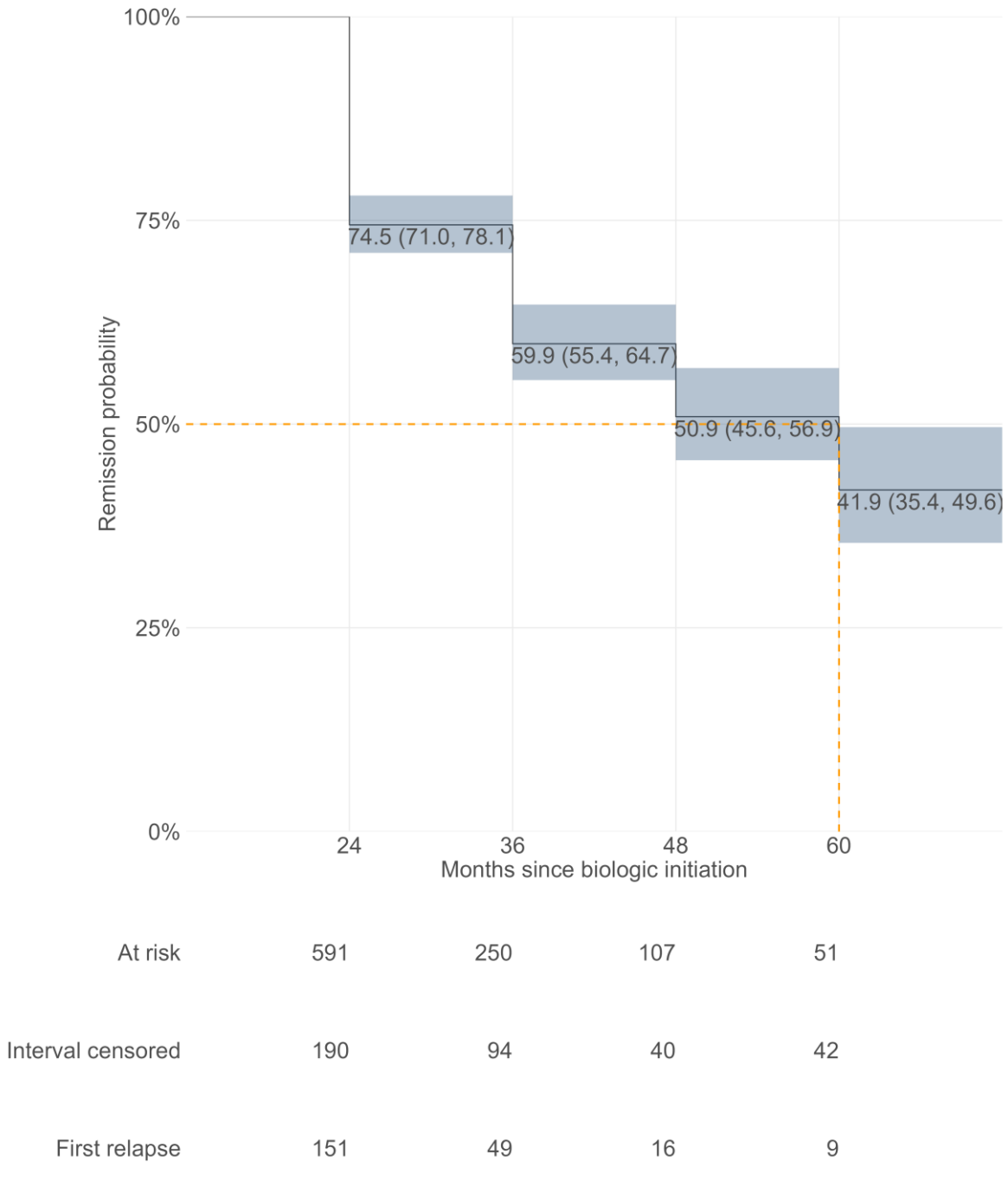
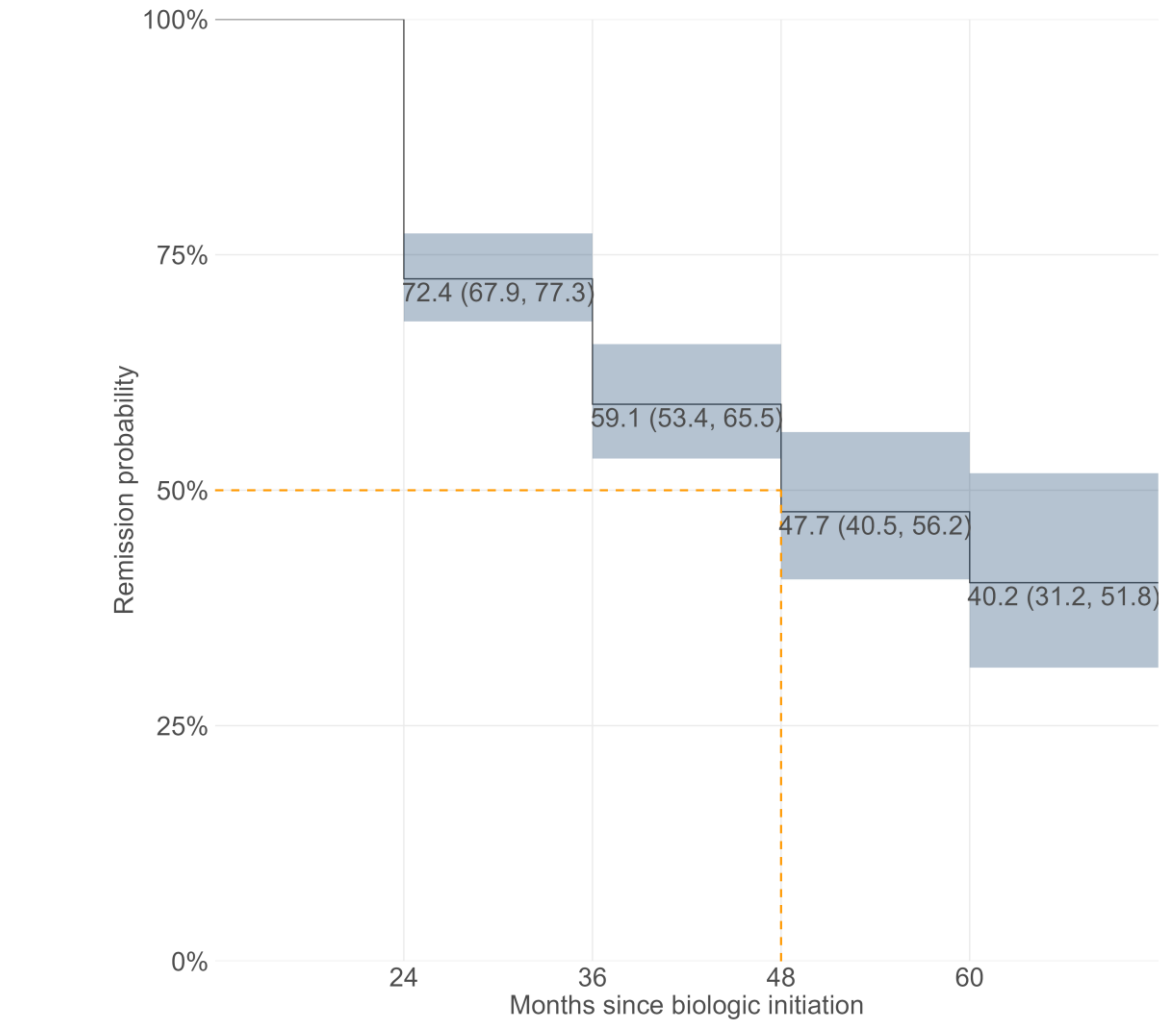


Figure 6: Sustained remission probability among patients in remission at 12 months, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and FEV1 percent predicted ≥80%. Blue boxes represent estimated 95% confidence intervals, and orange lines indicate median time until first relapse.



At risk	352	136	57	19
Interval censored	119	54	27	16
First relapse	97	25	11	3

Figure 7: Sustained remission probability among patients in remission at 12 months, using four-domain remission defined as no exacerbations in the past year, no LTOCS use, FEV1 percent predicted ≥80%, and well or partly controlled asthma. Blue boxes represent estimated 95% confidence intervals, and orange lines indicate median time until first relapse.

Table 6: Numbers of first relapses and sustained remission probability by period of follow-up among those in remission at 12 months by remission definition.

Follow-up	At Risk	Interval Censored	Cumulative Censored	First Relapses	Cumulative First Relapses	Remission probability
3-Domain Remission: No Exacerbation, No LTOCS Use, And Partly/Well Controlled						
12 months	713	0	0	0	0	100.0 (100.0, 100.0)
24 months	713	240	240	144	144	79.8 (76.9, 82.8)
36 months	329	129	369	45	189	68.9 (65.1, 72.9)
48 months	155	68	437	23	212	58.7 (53.8, 64.0)
60 months	64	54	491	10	222	49.5 (43.2, 56.7)
3-Domain Remission: No Exacerbation, No LTOCS Use, And No Lung Function Impairment						
12 months	591	0	0	0	0	100.0 (100.0, 100.0)
24 months	591	190	190	151	151	74.5 (71.0, 78.1)
36 months	250	94	284	49	200	59.9 (55.4, 64.7)
48 months	107	40	324	16	216	50.9 (45.6, 56.9)
60 months	51	42	366	9	225	41.9 (35.4, 49.6)
4-Domain Remission: No Exacerbation, No LTOCS Use, Partly/Well Controlled, And No Lung Function Impairment						
12 months	352	0	0	0	0	100.0 (100.0, 100.0)
24 months	352	119	119	97	97	72.4 (67.9, 77.3)
36 months	136	54	173	25	122	59.1 (53.4, 65.5)
48 months	57	27	200	11	133	47.7 (40.5, 56.2)
60 months	19	16	216	3	136	40.2 (31.2, 51.8)

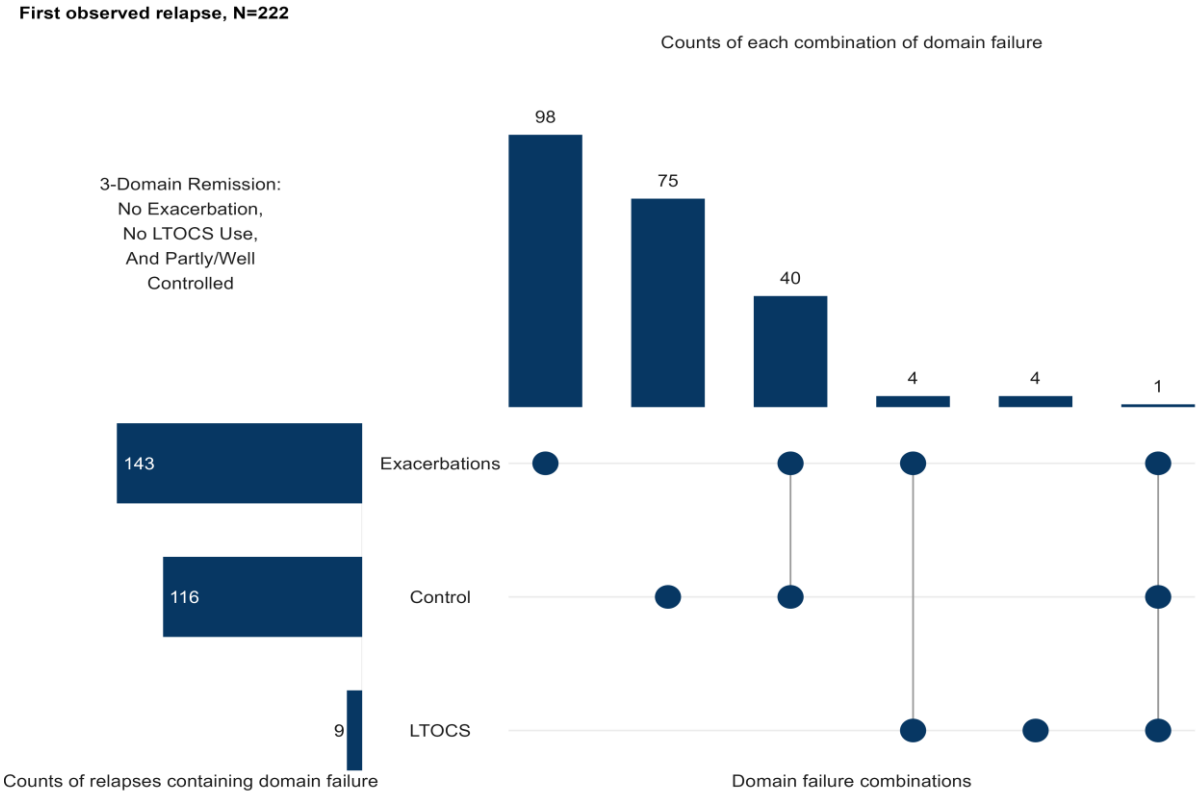


Figure 8: Patterns of domain failures contributing to first observed relapse among patients in remission at 12 months, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma.

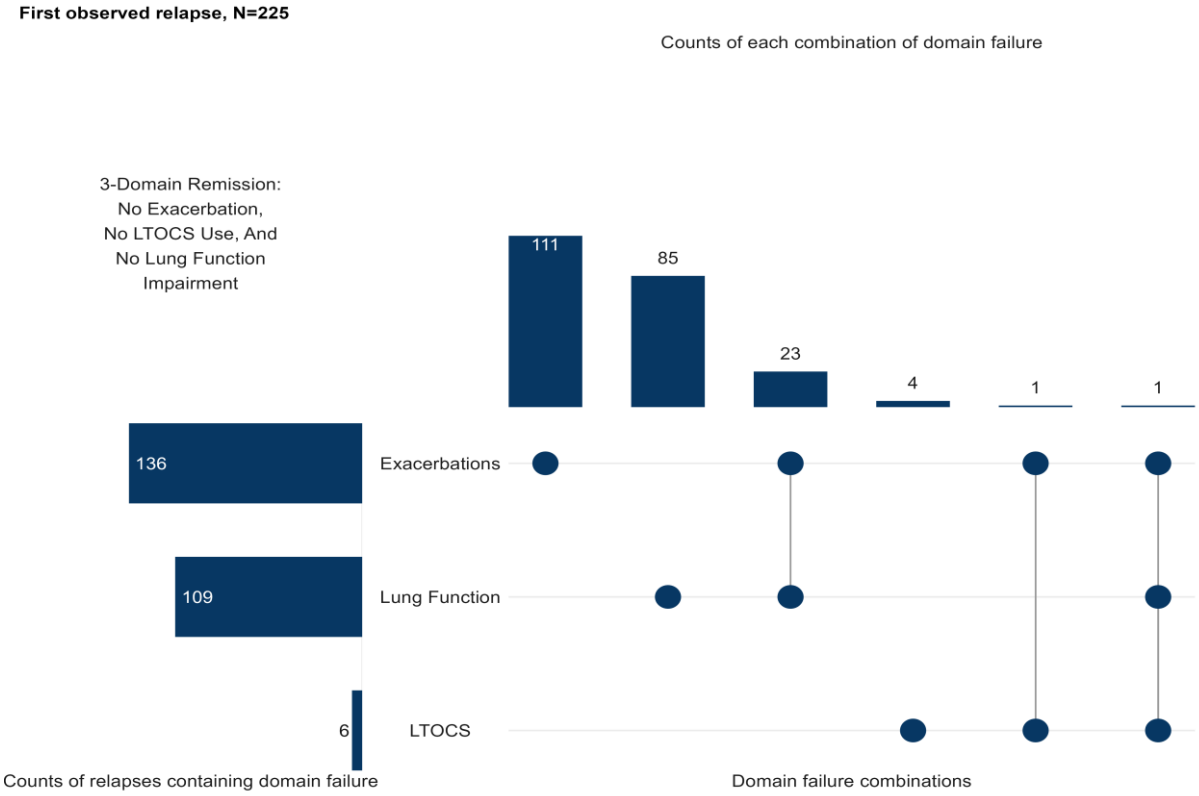


Figure 9: Patterns of domain failures contributing to first observed relapse among patients in remission at 12 months, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and FEV1 percent predicted ≥80%.

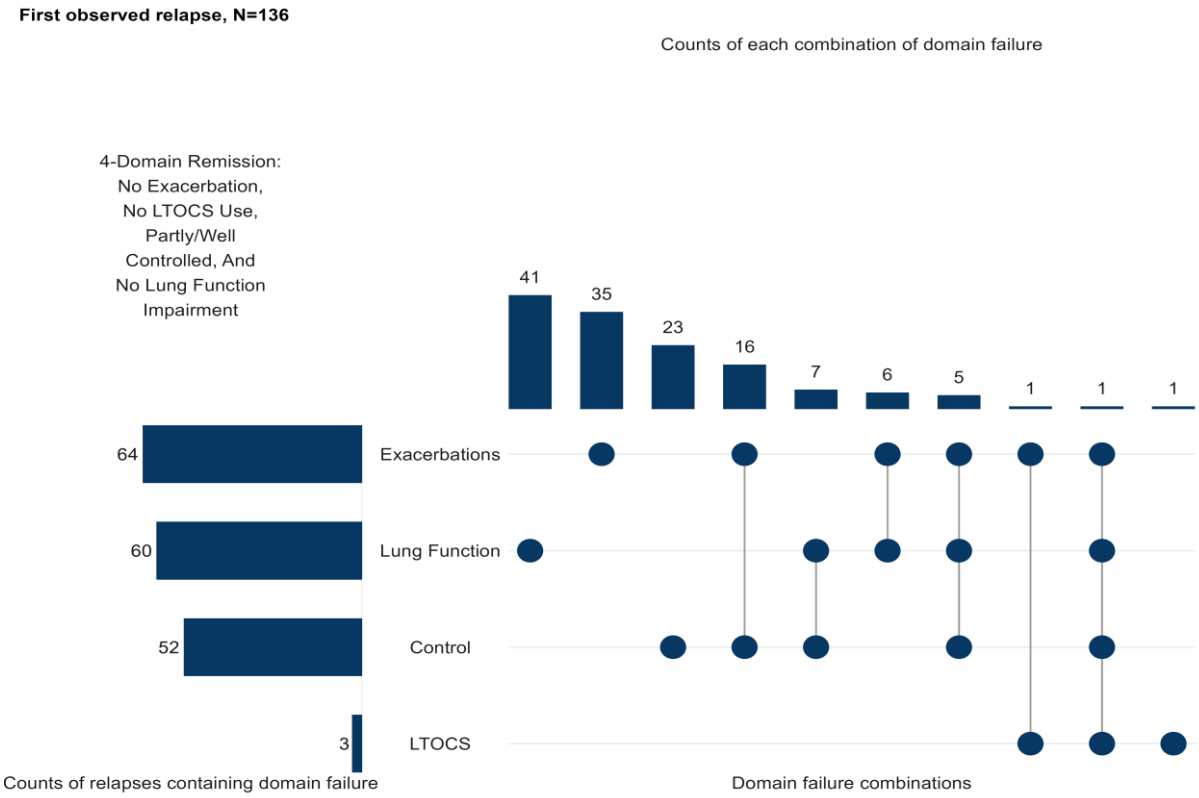


Figure 10: Patterns of domain failures contributing to first observed relapse among patients in remission at 12 months, using four-domain remission defined as no exacerbations in the past year, no LTOCS use, FEV1 percent predicted ≥80%, and well or partly controlled asthma.

Table 7: Distribution of domain measurements contributing to first observed relapse among patients in remission at 12 months by remission definition.

Domain	Measured	N	Median (Q1, Q3)	Range
3-Domain Remission: No Exacerbation, No LTOCS Use, And Partly/Well Controlled				
Number of exacerbations*	At relapse	143	1.0 (1.0, 1.0)	(1.0, 6.0)
Control: ACQ	At 12 months	61	0.7 (0.3, 1.0)	(0.0, 1.3)
	At relapse	73	2.0 (1.7, 2.7)	(1.5, 5.7)
	Difference	54	1.3 (0.8, 1.8)	(0.2, 5.2)
Control: ACT	At 12 months	54	20.5 (18.2, 23.8)	(16.0, 25.0)
	At relapse	41	14.0 (11.0, 15.0)	(5.0, 15.0)
	Difference	36	8.5 (6.0, 10.2)	(1.0, 17.0)
3-Domain Remission: No Exacerbation, No LTOCS Use, And No Lung Function Impairment				
Number of exacerbations*	At relapse	136	1.0 (1.0, 2.0)	(1.0, 6.0)
FEV1 percent predicted	At 12 months	109	85.5 (82.8, 90.9)	(80.1, 136.7)
	At relapse	109	75.3 (71.5, 78.0)	(41.9, 79.7)
	Difference	109	-11.6 (-16.8, -7.0)	(-65.5, -1.0)
4-Domain Remission: No Exacerbation, No LTOCS Use, Partly/Well Controlled, And No Lung Function Impairment				
Number of exacerbations*	At relapse	64	1.0 (1.0, 2.0)	(1.0, 3.0)
Control: ACQ	At 12 months	30	0.7 (0.3, 1.0)	(0.0, 1.3)
	At relapse	31	2.2 (1.9, 2.7)	(1.5, 5.7)
	Difference	27	1.5 (1.0, 1.9)	(0.2, 5.2)
Control: ACT	At 12 months	24	21.5 (18.8, 25.0)	(16.0, 25.0)
	At relapse	17	14.0 (12.0, 15.0)	(5.0, 15.0)
	Difference	13	10.0 (6.0, 11.0)	(1.0, 13.0)
FEV1 percent predicted	At 12 months	60	84.8 (82.8, 87.5)	(80.1, 136.7)
	At relapse	60	75.4 (71.1, 77.6)	(41.9, 79.7)
	Difference	60	-11.2 (-17.0, -6.5)	(-65.5, -1.0)

*Exacerbations in some settings recorded as 1+, 2+, etc.. These were converted to numeric values for analysis, so counts should be interpreted as "at least"

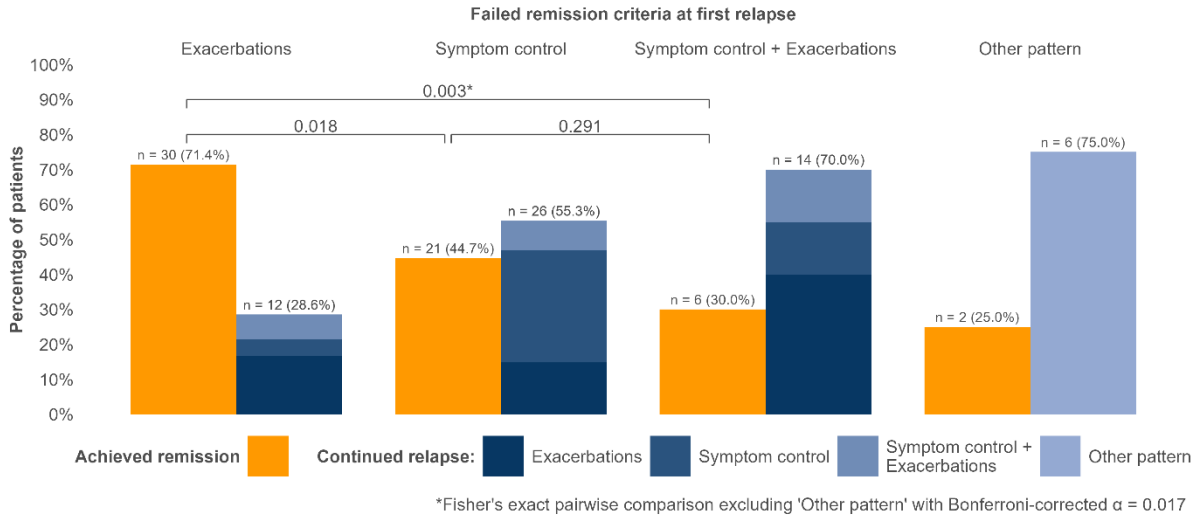


Figure 11: Status at following year by domain pattern attributed to first relapse, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma. Percentage of patients who achieved remission versus continued relapse by domain pattern attributed to first relapse, excluding "Other pattern" (Chi-squared(df = 2) = 11.24, p-value = 0.004).

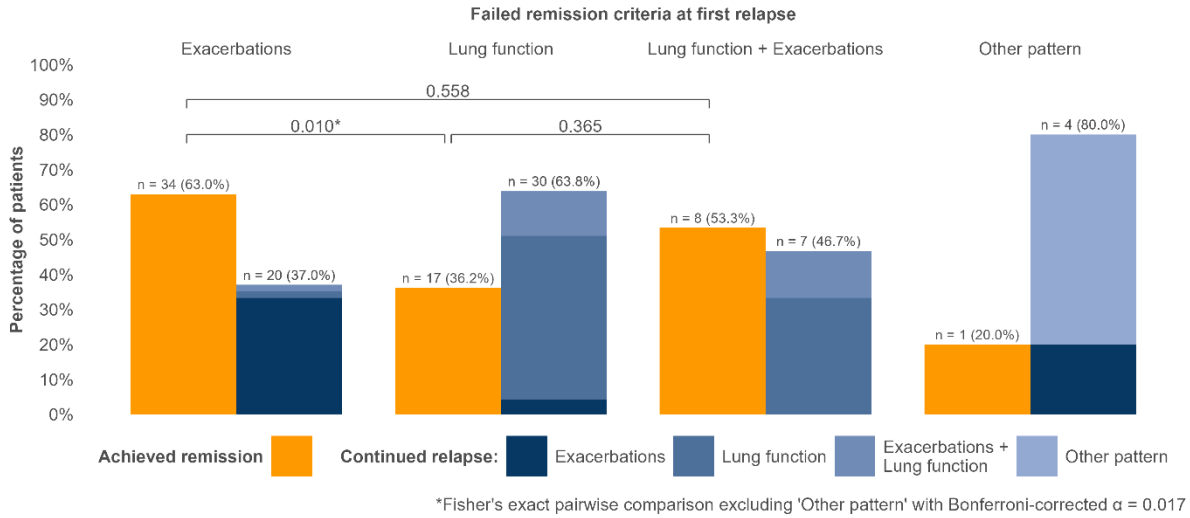


Figure 12: Status at following year by domain pattern attributed to first relapse, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and FEV1 percent predicted ≥80%. Percentage of patients who achieved remission versus continued relapse by domain pattern attributed to first relapse, excluding "Other pattern" (Chi-squared(df = 2) = 7.26, p-value = 0.027).

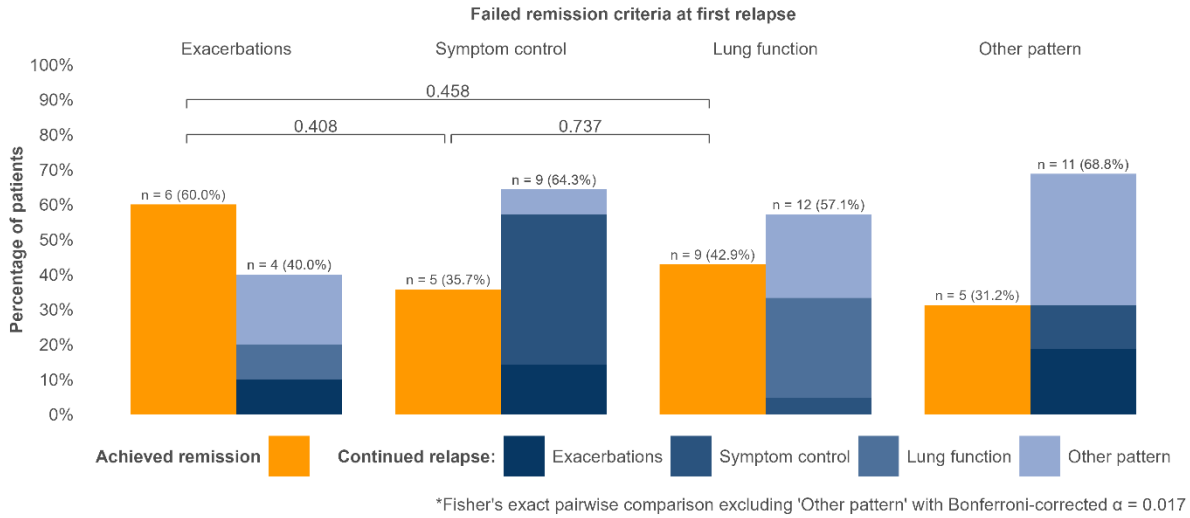


Figure 13: Status at following year by domain pattern attributed to first relapse, using four-domain remission defined as no exacerbations in the past year, no LTOCS use, FEV1 percent predicted ≥80%, and well or partly controlled asthma. Percentage of patients who achieved remission versus continued relapse by domain pattern attributed to first relapse, excluding "Other pattern" (Chi-squared(df = 2) = 1.43, p-value = 0.488).

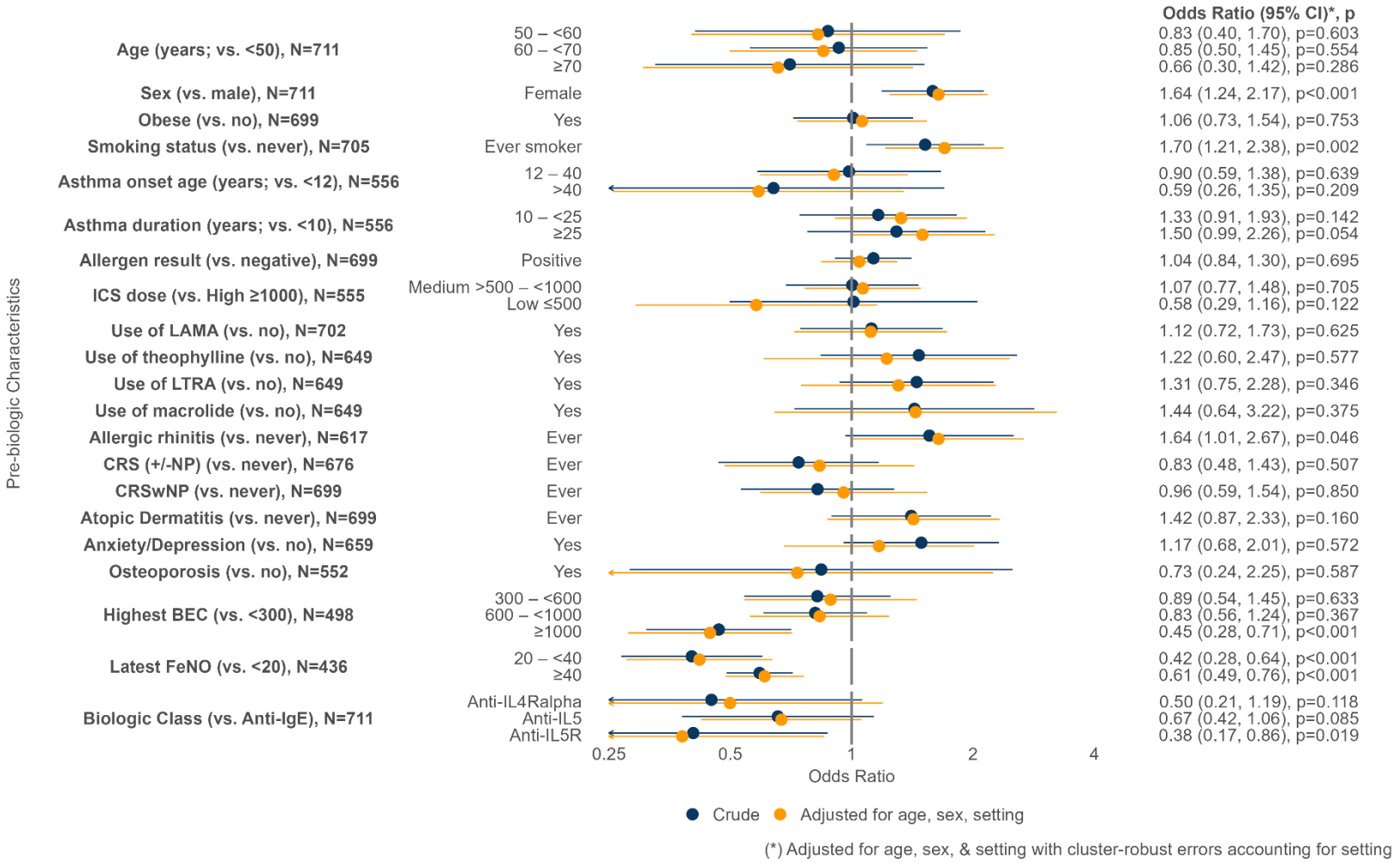


Figure 14: **Association of pre-biologic characteristics with severe asthma relapse at 24 months among patients in remission at 12 months, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma.**

Table 8: Association of pre-biologic characteristics with severe asthma relapse at 24 months among patients in remission at 12 months, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma.

Characteristic	Category	OR (95% CI)	p	aOR (95% CI)[a]	p	aOR (95% CI)[b]	p
Age (years; vs. <50), N=711	50 – <60	0.87 (0.41, 1.86)	0.726	0.83 (0.40, 1.70)	0.603	0.88 (0.43, 1.79)	0.716
	60 – <70	0.93 (0.56, 1.54)	0.776	0.85 (0.50, 1.45)	0.554	0.89 (0.52, 1.54)	0.679
	≥70	0.70 (0.33, 1.52)	0.368	0.66 (0.30, 1.42)	0.286	0.71 (0.33, 1.54)	0.388
Sex (vs. male), N=711	Female	1.59 (1.19, 2.13)	0.002	1.64 (1.24, 2.17)	<0.001	1.60 (1.20, 2.14)	0.001
Obese (vs. no), N=699	Yes	1.01 (0.72, 1.42)	0.962	1.06 (0.73, 1.54)	0.753	1.03 (0.68, 1.55)	0.897
Smoking status (vs. never), N=705	Ever smoker	1.52 (1.09, 2.13)	0.015	1.70 (1.21, 2.38)	0.002	1.74 (1.26, 2.39)	<0.001
Asthma onset age (years; vs. <12), N=556	12 – 40	0.98 (0.58, 1.66)	0.955	0.90 (0.59, 1.38)	0.639	0.97 (0.61, 1.54)	0.898
	>40	0.64 (0.24, 1.70)	0.370	0.59 (0.26, 1.35)	0.209	0.63 (0.25, 1.60)	0.332
Asthma duration (years; vs. <10), N=556	10 – <25	1.16 (0.74, 1.82)	0.508	1.33 (0.91, 1.93)	0.142	1.30 (0.92, 1.84)	0.143
	≥25	1.29 (0.78, 2.15)	0.324	1.50 (0.99, 2.26)	0.054	1.46 (1.00, 2.14)	0.050
Allergen result (vs. negative), N=699	Positive	1.13 (0.91, 1.41)	0.266	1.04 (0.84, 1.30)	0.695	0.90 (0.74, 1.09)	0.264
ICS dose (vs. High ≥1000), N=555	Medium >500 – <1000	1.00 (0.69, 1.47)	0.987	1.07 (0.77, 1.48)	0.705	1.02 (0.68, 1.53)	0.924
	Low ≤500	1.01 (0.50, 2.05)	0.976	0.58 (0.29, 1.16)	0.122	0.57 (0.29, 1.13)	0.106
Use of LAMA (vs. no), N=702	Yes	1.12 (0.75, 1.68)	0.586	1.12 (0.72, 1.73)	0.625	1.21 (0.81, 1.81)	0.360
Use of theophylline (vs. no), N=649	Yes	1.47 (0.84, 2.57)	0.181	1.22 (0.60, 2.47)	0.577	1.32 (0.61, 2.86)	0.475
Use of LTRA (vs. no), N=649	Yes	1.45 (0.93, 2.25)	0.098	1.31 (0.75, 2.28)	0.346	1.25 (0.71, 2.22)	0.438
Use of macrolide (vs. no), N=649	Yes	1.43 (0.72, 2.84)	0.305	1.44 (0.64, 3.22)	0.375	1.49 (0.64, 3.50)	0.355
Allergic rhinitis (vs. never), N=617	Ever	1.56 (0.96, 2.52)	0.070	1.64 (1.01, 2.67)	0.046	1.56 (0.96, 2.54)	0.071
CRS (+/-NP) (vs. never), N=676	Ever	0.74 (0.47, 1.17)	0.195	0.83 (0.48, 1.43)	0.507	0.91 (0.52, 1.59)	0.748
CRSwNP (vs. never), N=699	Ever	0.82 (0.53, 1.27)	0.382	0.96 (0.59, 1.54)	0.850	1.04 (0.64, 1.71)	0.865
Atopic Dermatitis (vs. never), N=699	Ever	1.41 (0.89, 2.22)	0.143	1.42 (0.87, 2.33)	0.160	1.46 (0.94, 2.26)	0.091
Anxiety/Depression (vs. no), N=659	Yes	1.49 (0.95, 2.32)	0.079	1.17 (0.68, 2.01)	0.572	1.15 (0.62, 2.11)	0.655
Osteoporosis (vs. no), N=552	Yes	0.84 (0.28, 2.51)	0.755	0.73 (0.24, 2.25)	0.587	0.75 (0.23, 2.47)	0.641
Highest BEC (vs. <300), N=498	300 – <600	0.82 (0.54, 1.25)	0.358	0.89 (0.54, 1.45)	0.633	1.10 (0.64, 1.88)	0.740
	600 – <1000	0.81 (0.60, 1.09)	0.168	0.83 (0.56, 1.24)	0.367	1.01 (0.65, 1.56)	0.970
	≥1000	0.47 (0.31, 0.71)	<0.001	0.45 (0.28, 0.71)	<0.001	0.56 (0.32, 0.97)	0.038
Latest FeNO (vs. <20), N=436	20 – <40	0.40 (0.27, 0.60)	<0.001	0.42 (0.28, 0.64)	<0.001	0.45 (0.30, 0.70)	<0.001
	≥40	0.59 (0.49, 0.71)	<0.001	0.61 (0.49, 0.76)	<0.001	0.67 (0.48, 0.93)	0.016
Biologic Class (vs. Anti-IgE), N=711	Anti-IL4Ralpha	0.45 (0.19, 1.06)	0.069	0.50 (0.21, 1.19)	0.118		
	Anti-IL5	0.66 (0.38, 1.13)	0.131	0.67 (0.42, 1.06)	0.085		
	Anti-IL5R	0.40 (0.19, 0.87)	0.021	0.38 (0.17, 0.86)	0.019		

OR = Odds Ratio; aOR = Adjusted Odds Ratio; CI = Confidence Interval

Characteristic	Category	OR (95% CI)	p	aOR (95% CI)[a]	p	aOR (95% CI)[b]	p

[a]Adjusted for age, sex, and setting

[b]Adjusted for age, sex, setting, and biologic class

Table 9: Clinical characteristics measured at 12 months post-biologic initiation for all eligible patients with information on three-domain clinical remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma.

Characteristic	Measure/category	N	Result
Percent Predicted FEV1 (%)	median (Q1, Q3)	416	86.7 (74.4, 100.2)
	<80%: n (%)		150 (36.1%)
	≥80%: n (%)		266 (63.9%)
Most Recent Blood Eosinophil Count (cells/mcL)	median (Q1, Q3)	348	100.0 (40.0, 362.5)
	<100: n (%)		142 (40.8%)
	≥100: n (%)		206 (59.2%)
Baseline to 12-month BEC relative change	median (Q1, Q3)	348	-78.5 (-94.9, -30.5)
	≤-75%: n (%)		186 (53.4%)
	>-75% – <0%: n (%)		106 (30.5%)
	≥0%: n (%)		56 (16.1%)
Most Recent FeNO Concentration (ppb)	median (Q1, Q3)	338	22.6 (14.0, 38.8)
	<20: n (%)		140 (41.4%)
	≥20: n (%)		198 (58.6%)
Baseline to 12-month FeNO relative change	median (Q1, Q3)	338	-32.5 (-62.4, 9.8)
	≤-34%: n (%)		165 (48.8%)
	>-34% – <0%: n (%)		65 (19.2%)
	≥0%: n (%)		108 (32.0%)
ICS dose (BDP-equivalent mcg/day)	median (Q1, Q3)	513	1200.0 (800.0, 2000.0)
	High ≥1000: n (%)		370 (72.1%)
	Medium >500 – <1000: n (%)		99 (19.3%)
	Low ≤500: n (%)		44 (8.6%)
Pre-biologic to 12-month ICS Dose Change	No change: n (%)	513	436 (85.0%)
	Decrease: n (%)		58 (11.3%)
	Increase: n (%)		19 (3.7%)
LAMA Use	No: n (%)	702	367 (52.3%)
	Yes: n (%)		335 (47.7%)
Pre-Biologic to 12-month LAMA Use Change	Continue LAMA: n (%)	702	319 (45.4%)
	Start LAMA: n (%)		16 (2.3%)
	Stop LAMA: n (%)		31 (4.4%)
	Continue off LAMA: n (%)		336 (47.9%)
Switch class or stop between 12 and 24 months	Continue: n (%)	588	564 (95.9%)
	Switch: n (%)		24 (4.1%)
	Stop: n (%)		0 (0.0%)

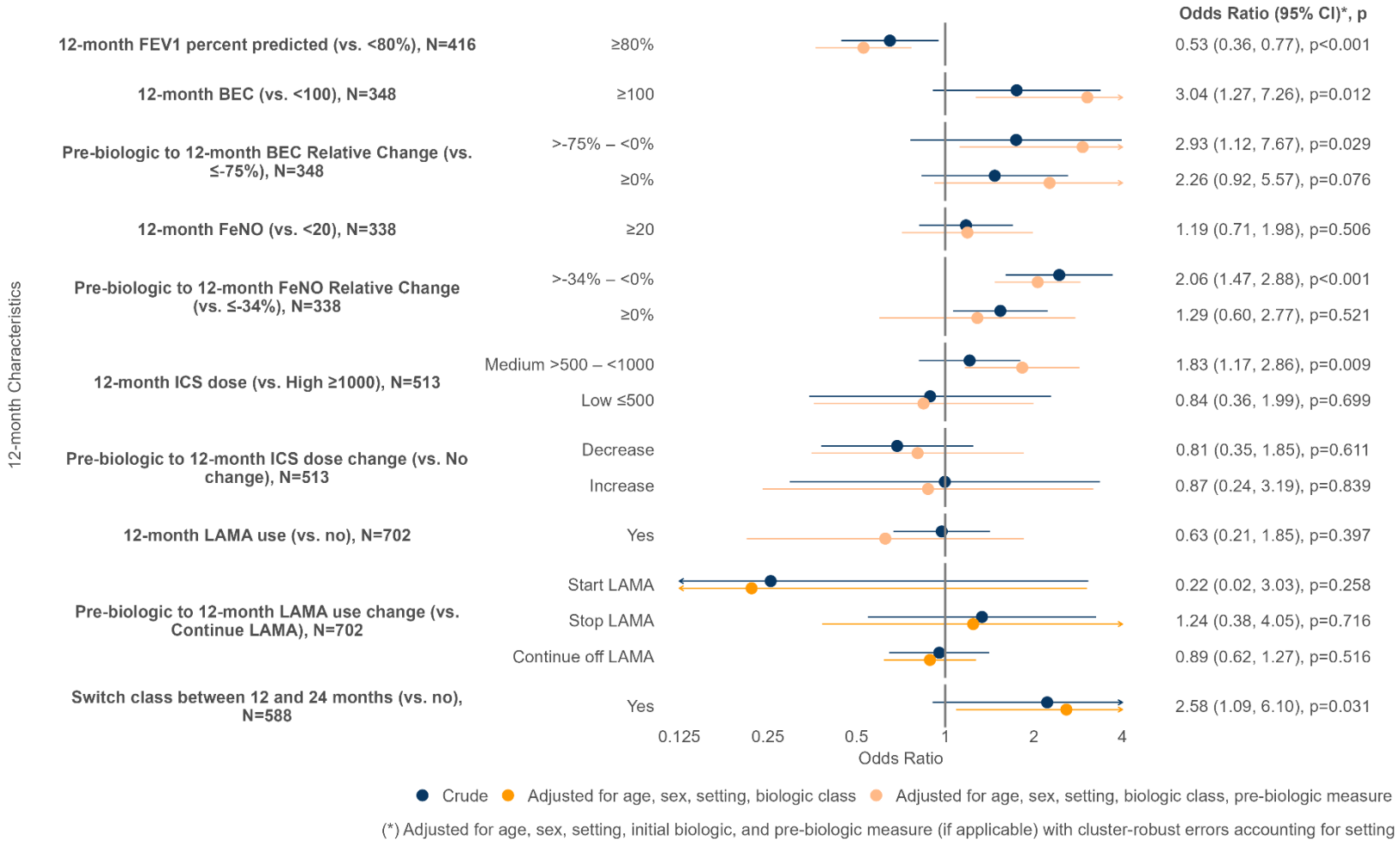


Figure 15: Association of 12-month clinical measures with severe asthma relapse at 24 months among patients in remission at 12 months, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma.

Table 10: Association of 12-month clinical measures with severe asthma relapse at 24 months among patients in remission at 12 months, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma.

Characteristic	Category	OR (95% CI)	p	aOR (95% CI)[a]	p	aOR (95% CI)[b]	p	aOR (95% CI)[c]	p	aOR (95% CI)[d]	p
12-month FEV1 percent predicted (vs. <80%), N=416	≥80%	0.65 (0.44, 0.95)	0.026	0.63 (0.42, 0.96)	0.031	0.68 (0.47, 0.99)	0.047	0.47 (0.30, 0.72)	<0.001	0.53 (0.36, 0.77)	<0.001
12-month BEC (vs. <100), N=348	≥100	1.75 (0.91, 3.37)	0.095	2.22 (1.26, 3.89)	0.005	2.63 (1.35, 5.11)	0.004	2.31 (1.24, 4.30)	0.008	3.04 (1.27, 7.26)	0.012
Pre-biologic to 12-month BEC Relative Change (vs. ≤-75%), N=348	>-75% – <0%	1.74 (0.76, 3.98)	0.188	2.07 (0.89, 4.80)	0.091	3.04 (1.21, 7.64)	0.018	1.95 (0.86, 4.42)	0.108	2.93 (1.12, 7.67)	0.029
	≥0%	1.47 (0.83, 2.61)	0.185	1.71 (0.86, 3.39)	0.128	2.54 (0.97, 6.64)	0.058	1.50 (0.81, 2.77)	0.199	2.26 (0.92, 5.57)	0.076
12-month FeNO (vs. <20), N=338	≥20	1.18 (0.82, 1.70)	0.385	1.06 (0.74, 1.52)	0.751	1.04 (0.69, 1.57)	0.834	1.26 (0.78, 2.03)	0.348	1.19 (0.71, 1.98)	0.506
Pre-biologic to 12-month FeNO Relative Change (vs. ≤-34%), N=338	>-34% – <0%	2.44 (1.60, 3.71)	<0.001	2.34 (1.60, 3.41)	<0.001	2.19 (1.49, 3.21)	<0.001	2.18 (1.55, 3.07)	<0.001	2.06 (1.47, 2.88)	<0.001
	≥0%	1.54 (1.06, 2.23)	0.022	1.51 (0.89, 2.54)	0.123	1.43 (0.71, 2.88)	0.316	1.33 (0.75, 2.35)	0.324	1.29 (0.60, 2.77)	0.521
12-month ICS dose (vs. High ≥1000), N=513	Medium >500 – <1000	1.21 (0.81, 1.80)	0.345	1.41 (0.94, 2.09)	0.094	1.39 (0.91, 2.13)	0.129	1.86 (1.21, 2.85)	0.005	1.83 (1.17, 2.86)	0.009
	Low ≤500	0.89 (0.35, 2.29)	0.807	0.65 (0.30, 1.39)	0.266	0.64 (0.28, 1.47)	0.295	0.85 (0.38, 1.89)	0.690	0.84 (0.36, 1.99)	0.699
Pre-biologic to 12-month ICS dose change (vs. No change), N=513	Decrease	0.69 (0.38, 1.24)	0.215	0.79 (0.35, 1.76)	0.564	0.84 (0.36, 1.95)	0.685	0.76 (0.34, 1.67)	0.488	0.81 (0.35, 1.85)	0.611
	Increase	1.00 (0.30, 3.36)	0.996	0.83 (0.19, 3.55)	0.801	0.80 (0.21, 3.06)	0.748	0.91 (0.22, 3.70)	0.891	0.87 (0.24, 3.19)	0.839

Characteristic	Category	OR (95% CI)	p	aOR (95% CI)[a]	p	aOR (95% CI)[b]	p	aOR (95% CI)[c]	p	aOR (95% CI)[d]	p
12-month LAMA use (vs. no), N=702	Yes	0.97 (0.67, 1.42)	0.889	1.00 (0.69, 1.47)	0.990	1.04 (0.73, 1.47)	0.842	0.71 (0.25, 2.07)	0.533	0.63 (0.21, 1.85)	0.397
Pre-biologic to 12-month LAMA use change (vs. Continue LAMA), N=702	Start LAMA	0.26 (0.02, 3.06)	0.282	0.27 (0.02, 3.36)	0.308	0.22 (0.02, 3.03)	0.258				
	Stop LAMA	1.33 (0.55, 3.25)	0.527	1.10 (0.34, 3.58)	0.875	1.24 (0.38, 4.05)	0.716				
	Continue off LAMA	0.95 (0.65, 1.41)	0.817	0.94 (0.63, 1.41)	0.778	0.89 (0.62, 1.27)	0.516				
Switch class between 12 and 24 months (vs. no), N=588	Yes	2.22 (0.91, 5.44)	0.081	2.94 (1.31, 6.59)	0.009	2.58 (1.09, 6.10)	0.031				

OR = Odds Ratio; aOR = Adjusted Odds Ratio; CI = Confidence Interval

[a]Adjusted for age, sex, and setting

[b]Adjusted for age, sex, setting, and biologic class

[c]Adjusted for age, sex, setting, and pre-biologic measure

[d]Adjusted for age, sex, setting, biologic class, and pre-biologic measure

Table 11: 12-month clinical characteristics for eligible patients with information on three-domain remission definition by initial biologic.

Characteristic	Measure/category	Anti-IgE N	Anti-IgE Result	Anti-Il4Ralpha N	Anti-Il4Ralpha Result	Anti-IL5 N	Anti-IL5 Result	Anti-IL5R N	Anti-IL5R Result
Percent Predicted FEV1 (%)	median (Q1, Q3)	69	84.2 (65.8, 104.8)	100	89.7 (80.0, 102.0)	181	85.8 (72.6, 97.2)	66	85.4 (74.6, 98.5)
	<80%: n (%)		28 (40.6%)		25 (25.0%)		71 (39.2%)		26 (39.4%)
	≥80%: n (%)		41 (59.4%)		75 (75.0%)		110 (60.8%)		40 (60.6%)
Most Recent Blood Eosinophil Count (cells/mcL)	median (Q1, Q3)	56	227.4 (155.2, 392.5)	75	530.0 (223.0, 925.0)	149	80.0 (40.0, 100.0)	68	0.0 (0.0, 60.0)
	<100: n (%)		7 (12.5%)		3 (4.0%)		80 (53.7%)		52 (76.5%)
	≥100: n (%)		49 (87.5%)		72 (96.0%)		69 (46.3%)		16 (23.5%)
Baseline to 12-month BEC Relative Change	median (Q1, Q3)		-32.0 (-57.1, 0.0)		-25.0 (-50.6, 39.0)		-89.9 (-95.0, -79.2)		-100.0 (-100.0, -88.9)
	≤-75%: n (%)	56	5 (8.9%)	75	9 (12.0%)	149	118 (79.2%)	68	54 (79.4%)
	>-75% – <0%: n (%)		34 (60.7%)		42 (56.0%)		20 (13.4%)		10 (14.7%)
	≥0%: n (%)		17 (30.4%)		24 (32.0%)		11 (7.4%)		4 (5.9%)
Most Recent FeNO Concentration (ppb)	median (Q1, Q3)	33	17.0 (10.0, 30.7)	107	18.0 (12.0, 26.0)	152	29.3 (16.0, 51.0)	46	27.8 (14.2, 62.0)
	<20: n (%)		19 (57.6%)		56 (52.3%)		48 (31.6%)		17 (37.0%)
	≥20: n (%)		14 (42.4%)		51 (47.7%)		104 (68.4%)		29 (63.0%)
Baseline to 12-month FeNO Relative Change	median (Q1, Q3)		-12.5 (-38.6, 24.0)		-60.2 (-76.4, -18.6)		-21.9 (-50.0, 20.9)		-27.4 (-54.9, 20.3)
	≤-34%: n (%)	33	11 (33.3%)	107	73 (68.2%)	152	60 (39.5%)	46	21 (45.7%)
	>-34% – <0%: n (%)		7 (21.2%)		12 (11.2%)		37 (24.3%)		9 (19.6%)
	≥0%: n (%)		15 (45.5%)		22 (20.6%)		55 (36.2%)		16 (34.8%)
ICS dose (BDP-equivalent mcg/day)	median (Q1, Q3)	92	1250.0 (800.0, 2000.0)	111	1496.0 (800.0, 1700.0)	197	1600.0 (800.0, 2000.0)	113	1000.0 (1000.0, 2000.0)
	High ≥1000: n (%)		64 (69.6%)		77 (69.4%)		142 (72.1%)		87 (77.0%)
	Medium >500 – <1000: n (%)		16 (17.4%)		25 (22.5%)		43 (21.8%)		15 (13.3%)
	Low ≤500: n (%)		12 (13.0%)		9 (8.1%)		12 (6.1%)		11 (9.7%)
Pre-biologic to 12-month ICS Dose Change	No change: n (%)	92	84 (91.3%)	111	85 (76.6%)	197	172 (87.3%)	113	95 (84.1%)
	Decrease: n (%)		3 (3.3%)		21 (18.9%)		19 (9.6%)		15 (13.3%)

Characteristic	Measure/category	Anti-IgE N	Anti-IgE Result	Anti-Il4Ralpha N	Anti-Il4Ralpha Result	Anti-IL5 N	Anti-IL5 Result	Anti-IL5R N	Anti-IL5R Result
	Increase: n (%)		5 (5.4%)		5 (4.5%)		6 (3.0%)		3 (2.7%)
LAMA Use	No: n (%)	125	66 (52.8%)	157	90 (57.3%)	288	149 (51.7%)	132	62 (47.0%)
	Yes: n (%)		59 (47.2%)		67 (42.7%)		139 (48.3%)		70 (53.0%)
Baseline to 12-month LAMA use change	Continue LAMA: n (%)	125	54 (43.2%)	157	64 (40.8%)	288	132 (45.8%)	132	69 (52.3%)
	Start LAMA: n (%)		5 (4.0%)		3 (1.9%)		7 (2.4%)		1 (0.8%)
	Stop LAMA: n (%)		4 (3.2%)		7 (4.5%)		10 (3.5%)		10 (7.6%)
	Continue off LAMA: n (%)		62 (49.6%)		83 (52.9%)		139 (48.3%)		52 (39.4%)
Switch class or stop between 12 and 24 months	Continue: n (%)	104	98 (94.2%)	133	129 (97.0%)	241	228 (94.6%)	110	109 (99.1%)
	Switch: n (%)		6 (5.8%)		4 (3.0%)		13 (5.4%)		1 (0.9%)
	Stop: n (%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)

Table 12: Association of 12-month clinical measures with severe asthma relapse at 24 months among patients initially on anti-IgE biologic and in remission at 12 months, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma.

Characteristic	Category	OR (95% CI)	p	aOR (95% CI)[a]	p	aOR (95% CI)[b]	p
12-month FEV1 percent predicted (vs. <80%), N=69	≥80%	0.43 (0.16, 1.19)	0.104	0.51 (0.08, 3.33)	0.484	0.23 (0.01, 6.09)	0.381
12-month BEC (vs. <100), N=56	≥100	2.65 (0.39, 18.17)	0.322	2.07 (0.04, 120.77)	0.727	2.38 (0.02, 230.30)	0.710
12-month FeNO (vs. <20), N=33	≥20	1.20 (0.38, 3.79)	0.751	9.84 (0.33, 291.25)	0.186	13.07 (0.33, 515.05)	0.170
12-month ICS dose (vs. High ≥1000), N=92	Medium >500 – <1000	0.47 (0.09, 2.47)	0.375	0.37 (0.02, 7.61)	0.521	0.60 (0.01, 24.57)	0.790
	Low ≤500	0.68 (0.23, 2.01)	0.488	0.78 (0.17, 3.67)	0.755	1.28 (0.14, 12.08)	0.829
12-month LAMA use (vs. no), N=125	Yes	0.58 (0.27, 1.24)	0.162	0.92 (0.27, 3.13)	0.900	0.36 (0.02, 5.82)	0.470
Switch class between 12 and 24 months (vs. no), N=104	Yes	2.16 (0.71, 6.57)	0.174	1.36 (0.24, 7.86)	0.729		

OR = Odds Ratio; aOR = Adjusted Odds Ratio; CI = Confidence Interval

[a]Adjusted for age, sex, and setting

[b]Adjusted for age, sex, setting, and pre-biologic measure

Table 13: Association of 12-month clinical measures with severe asthma relapse at 24 months among patients initially on anti-IL4Ralpha biologic and in remission at 12 months, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma.

Characteristic	Category	OR (95% CI)	p	aOR (95% CI)[a]	p	aOR (95% CI)[b]	p
12-month FEV1 percent predicted (vs. <80%), N=100	≥80%	4.12 (2.03, 8.39)	<0.001	4.25 (2.97, 6.08)	<0.001	4.35 (2.08, 9.06)	<0.001
12-month BEC (vs. <100), N=75	≥100	0.53 (0.04, 6.46)	0.616	0.63 (0.05, 7.54)	0.719	1.02 (0.14, 7.54)	0.986
12-month FeNO (vs. <20), N=107	≥20	1.65 (0.58, 4.67)	0.345	1.49 (0.39, 5.73)	0.560	1.40 (0.32, 6.15)	0.652
12-month ICS dose (vs. High ≥1000), N=111	Medium >500 – <1000	0.94 (0.45, 1.93)	0.862	1.06 (0.33, 3.43)	0.922	1.56 (0.49, 4.92)	0.449
	Low ≤500	1.41 (0.56, 3.56)	0.471	1.14 (0.33, 3.95)	0.837	1.52 (0.55, 4.22)	0.422
12-month LAMA use (vs. no), N=157	Yes	1.90 (0.84, 4.27)	0.121	2.53 (1.01, 6.33)	0.046	3.23 (1.40, 7.46)	0.006
Switch class between 12 and 24 months (vs. no), N=133	Yes	5.45 (0.46, 64.02)	0.177	2.51 (0.08, 74.86)	0.594		

OR = Odds Ratio; aOR = Adjusted Odds Ratio; CI = Confidence Interval

[a]Adjusted for age, sex, and setting

[b]Adjusted for age, sex, setting, and pre-biologic measure

Table 14: Association of 12-month clinical measures with severe asthma relapse at 24 months among patients initially on anti-IL5 biologic and in remission at 12 months, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma.

Characteristic	Category	OR (95% CI)	p	aOR (95% CI)[a]	p	aOR (95% CI)[b]	p
12-month FEV1 percent predicted (vs. <80%), N=181	≥80%	0.67 (0.48, 0.94)	0.020	0.66 (0.44, 1.00)	0.051	0.43 (0.24, 0.76)	0.004
12-month BEC (vs. <100), N=149	≥100	2.17 (0.89, 5.27)	0.088	3.71 (1.28, 10.75)	0.016	4.31 (1.16, 15.96)	0.029
12-month FeNO (vs. <20), N=152	≥20	1.06 (0.69, 1.63)	0.775	0.91 (0.49, 1.67)	0.755	0.98 (0.48, 1.98)	0.950
12-month ICS dose (vs. High ≥1000), N=197	Medium >500 – <1000	2.39 (1.26, 4.54)	0.008	2.86 (1.64, 5.00)	<0.001	3.31 (1.46, 7.50)	0.004
	Low ≤500	0.89 (0.28, 2.87)	0.849	0.49 (0.18, 1.34)	0.165	0.59 (0.17, 2.06)	0.409
12-month LAMA use (vs. no), N=288	Yes	1.05 (0.65, 1.69)	0.848	1.06 (0.65, 1.74)	0.809	0.18 (0.04, 0.73)	0.016
Switch class between 12 and 24 months (vs. no), N=241	Yes	1.47 (0.62, 3.46)	0.380	2.59 (1.16, 5.80)	0.021		

OR = Odds Ratio; aOR = Adjusted Odds Ratio; CI = Confidence Interval

[a]Adjusted for age, sex, and setting

[b]Adjusted for age, sex, setting, and pre-biologic measure

Table 15: Association of 12-month clinical measures with severe asthma relapse at 24 months among patients initially on anti-IL5R biologic and in remission at 12 months, using three-domain remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma.

Characteristic	Category	OR (95% CI)	p	aOR (95% CI)[a]	p	aOR (95% CI)[b]	p
12-month FEV1 percent predicted (vs. <80%), N=66	≥80%	0.48 (0.09, 2.39)	0.368	0.45 (0.04, 5.41)	0.528	0.42 (0.02, 7.80)	0.557
12-month BEC (vs. <100), N=68	≥100	2.17 (0.68, 6.91)	0.189	2.65 (0.86, 8.15)	0.089	2.98 (0.76, 11.77)	0.118
12-month FeNO (vs. <20), N=46	≥20	0.75 (0.32, 1.73)	0.496	0.25 (0.05, 1.32)	0.102	0.07 (0.02, 0.22)	<0.001
12-month ICS dose (vs. High ≥1000), N=113	Medium >500 – <1000	0.37 (0.13, 1.07)	0.068	0.33 (0.13, 0.84)	0.020	0.55 (0.34, 0.90)	0.017
	Low ≤500	0.52 (0.04, 7.68)	0.635	0.29 (0.02, 4.32)	0.370	0.46 (0.02, 9.91)	0.618
12-month LAMA use (vs. no), N=132	Yes	0.77 (0.41, 1.44)	0.409	0.58 (0.37, 0.90)	0.015	0.80 (0.08, 7.75)	0.846
Switch class between 12 and 24 months (vs. no), N=110	Yes	0.00 (0.00, 0.00)	<0.001	0.00 (0.00, 0.00)	<0.001		

OR = Odds Ratio; aOR = Adjusted Odds Ratio; CI = Confidence Interval

[a]Adjusted for age, sex, and setting

[b]Adjusted for age, sex, setting, and pre-biologic measure

Table 16: Frequency of biologic class switching or stopping at any point between patients in remission at 12 months with and without a recorded relapse by remission definition.

	Relapse	No Relapse	p*
3-Domain Remission: No Exacerbation, No LTOCS Use, And Partly/Well Controlled, N=713			
Switch class at any point, N	222	491	0.905
No: n (%)	207 (93.2%)	459 (93.5%)	
Yes: n (%)	15 (6.8%)	32 (6.5%)	
Stop biologic at any point, N	222	491	0.035
No: n (%)	220 (99.1%)	491 (100.0%)	
Yes: n (%)	2 (0.9%)	0 (0.0%)	
Switch or stop at any point, N	222	491	0.577
No: n (%)	205 (92.3%)	459 (93.5%)	
Yes: n (%)	17 (7.7%)	32 (6.5%)	
3-Domain Remission: No Exacerbation, No LTOCS Use, And No Lung Function Impairment, N=591			
Switch class at any point, N	225	366	0.243
No: n (%)	208 (92.4%)	347 (94.8%)	
Yes: n (%)	17 (7.6%)	19 (5.2%)	
Stop biologic at any point, N	225	366	0.071
No: n (%)	223 (99.1%)	366 (100.0%)	
Yes: n (%)	2 (0.9%)	0 (0.0%)	
Switch or stop at any point, N	225	366	0.117
No: n (%)	206 (91.6%)	347 (94.8%)	
Yes: n (%)	19 (8.4%)	19 (5.2%)	
4-Domain Remission: No Exacerbation, No LTOCS Use, Partly/Well Controlled, And No Lung Function Impairment, N=352			
Switch class at any point, N	136	216	0.869
No: n (%)	129 (94.9%)	204 (94.4%)	
Yes: n (%)	7 (5.1%)	12 (5.6%)	
Stop biologic at any point, N	136	216	0.207
No: n (%)	135 (99.3%)	216 (100.0%)	
Yes: n (%)	1 (0.7%)	0 (0.0%)	
Switch or stop at any point, N	136	216	0.897
No: n (%)	128 (94.1%)	204 (94.4%)	
Yes: n (%)	8 (5.9%)	12 (5.6%)	

*Pearson's Chi-squared test