Study Report

Assessing the impact of remission at 12-months post-initiation of biologic therapy on long-term clinical outcomes of patients with severe asthma (SPOTLIGHT)

An assessment of the long-term impact of remission

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TITLE	**Assessing the impact of remission at 12-months post-initiation of biologic therapy on long-term clinical outcomes of patients with severe asthma (SPOTLIGHT)**
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Study aims and objectives	**Aim:** To assess the long-term impact of remission at 12-months post-initiation of biologic therapy on clinical outcomes of asthma among patients with severe asthma. **Objective 1:** To describe the patterns of remission and the patient characteristics of various patterns of remission. **Objective 2:** To investigate the effect of remission on long-term clinical outcomes of asthma between those that graduate to remission compared to those that do not.
Countries of study	Argentina*, Brazil, Belgium, Bulgaria, Canada, Colombia, Denmark, Estonia, Greece, India*, Ireland, Italy, Japan, Kuwait, Mexico, Norway, Poland, Portugal, Saudi Arabia, Singapore, South Korea, Spain, Taiwan, UAE, UK, USA *Data available in ISAR were considered for the study but no patient met the inclusion criteria.
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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
IL4	Interleukin 4
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
OCS	Oral corticosteroids
OPRI	Observational and Pragmatic Research Institute
OR	Odds ratio
Q1, Q3	1st quartile, 3rd quartile
REG	Respiratory Effectiveness Group
RR	Rate ratio
SD	Standard deviation
SMD	Standardised mean difference
T2	Type 2 inflammation
TSLP	Thymic stromal lymphopoietin

1.0 Executive Summary

This study has investigated the stability of remission over up to 5 years of follow-up in adult patients with severe asthma treated with a biologic therapy in the international and real-word ISAR setting. We found that the remission status achieved in the first year following biologic initiation was relatively stable over time, i.e. losing remission or achieving remission in further years of follow-up were uncommon profiles. Consequently, the remission status in the first year of follow-up was a strong correlate of longer-term clinical outcomes of asthma.

To our knowledge, our study is the first attempt to investigate the effect of early remission on long-term clinical outcomes of asthma in the context of treatment with biologic therapies. It was made possible by the large number of patients enrolled in ISAR and the continuous collection of longitudinal data since ISAR inception in 2017, leading to growing numbers of patients enrolled in the registry with available data on key clinical outcomes over several years of follow-up after biologic initiation. Exploring a range of multi-domain remission criteria, we found that, in patients who met remission criteria in the first year following biologic initiation, approximately 60% sustained remission over 3 years, 50% over 4 years, and 40% over 5 years. These proportions were the highest when lung function was omitted from the remission criteria, and the lowest when optimization of lung function as defined by FEV_1 percent of predicted of at least 80% was a criterion. The level of symptom control criterion (well or partly controlled vs. well controlled asthma only) and using a relaxed criterion for lung function (allowing stabilization instead of imposing optimization as defined above) also led to slight variations in the estimated proportions of patients with sustained remission. The set of estimates were however largely consistent. Remaining in remission from year to year was interestingly more likely in patients who were in remission in the first year following biologic initiation than in patients who were not, indicating that the remission status in the first year has an effect on long-term clinical outcomes of asthma.

Meeting remission criteria in the first year following biologic therapy initiation was associated with better key clinical outcomes of asthma in further years of follow-up. Varying across the remission definitions used, patients in remission in the first year following biologic initiation, and compared to those who were not, had 3 to 4 times less exacerbations, 2 to 5 times higher odds of having better asthma symptom control, 10 to 20 percentage point higher FEV_1 percent of predicted value, and 8 to >30 times lower odds of using LTOCS in follow-up years. This indicates that the remission status in the first year following biologic initiation is key when trying to predict the long-term asthma outcomes in patients with severe asthma, irrespective of the remission definition. Of strong interest, the remission status in the first year following biologic initiation informed on the long-term clinical outcomes of asthma over and above differences in

baseline patient characteristics that correlate with remission status in the first year following biologic initiation. This indicates that early remission might be a key predictor of a successful biologic therapy initiation in the long run, and that failing meeting remission criteria in the first year following biologic initiation is a poor outcome that might predict limited chance of reaching remission thereafter. In other words, the remission status in the first year following biologic initiation is a marker of the long-term success of the therapy, implying that lack of early response to the therapy is a marker of difficulties for the patients and their physicians to find alternatives for better outcomes.

In adult patients with severe asthma who initiated biologic therapy, achieving remission in the first year of follow-up was strongly associated with better asthma-related outcomes in further years of follow-up. This warrants a close monitoring of asthma remission criteria early after biologic initiation, as meeting these criteria correlates with longer-term outcomes of asthma.

2.0 Background

Disease remission has been described as the state of low to no disease activity for an extended period of time in cancer and chronic inflammatory diseases, such as rheumatoid arthritis (Felson et al., 2011). Remission can be induced by therapy or achieved spontaneously. In adult severe asthma, with the arrival and increased use of targeted therapy via monoclonal antibodies, the possibility and aim of complete or partial remission has surfaced as well. According to the European Respiratory Society and the American Thoracic Society task force severe asthma is defined as asthma that requires high-dose inhaled corticosteroids plus a second controller and/or oral corticosteroids (OCS) to remain controlled or asthma that continues to be uncontrolled despite therapy (Chung et al., 2014).

As a first step, there have been multiple efforts to define remission in severe asthma. Although a universal consensus on the definition of remission has not been reached, clinical, inflammatory, partial and complete remission are types of definitions that have been recently explored. For this project, we have focused on clinical remission with therapy. Menzies-Gow et al. (2020), Upham et al. (2021) and Canonica et al. (2023) conducted modified Delphi surveys to define clinical remission. Upham et al. provided a 'super response' definition that involved improvement in three or more of the four clinical domains of asthma (exacerbations, asthma control, lung function, long-term oral corticosteroid use) over 12 months. Menzies-Gow et al. proposed a framework for clinical remission with treatment as (1) absence of significant symptoms by validated instrument, (2) lung function optimization/stabilization, (3) patient/provider agreement regarding remission, and (4) no use of systemic corticosteroids for 12 months or more. Canonica et al.'s modified Delphi presented a criterion for on-treatment, complete (the absence of the need for oral corticosteroids, symptoms, exacerbations or attacks, and pulmonary function stability) and partial (the absence of the need for oral corticosteroids, and two of three criteria: the absence of symptoms, exacerbations or attacks, and pulmonary stability) clinical remission. Therefore, current, expert-driven definition of remission has been a composite of multiple domains, involving a criterion that requires achievement of three or more of the clinical domains of asthma at one-year post-initiation of a biologic, four being the most common (Shackleford et al., 2025). With such a range of definitions, the proportion of patients with severe asthma that are obtaining remission in the real-world ranged from 12% to 47% (Menzies-Gow et al., 2022; Pavord et al., 2023; Oishi et al., 2023; McDowel et al., 2023; Perez-de-Llano et al., 2024; Hansen, et al., 2024; Hansen et al., 2025; Shackleford et al., 2025).

Thus far, real-world cohort studies of severe asthma have evaluated the prevalence of remission using various definitions mentioned above at multiple time points post-initiation, with

12-month post-initiation being the most common (Shackleford et al., 2025). However, the effect of early remission on longer-term clinical outcomes is not clear. In rheumatoid arthritis where biologics have been used for over 30 years, tapering of biologic drugs and even cessation of therapy is considered after remission (Schett et al., 2016). Therefore, it is important to understand how clinical outcomes of asthma behaves upon remission so that clinical management plans and/or goals of severe asthma post-remission can be informed and updated.

The aim of this study was to first investigate the remission-relapse patterns that patients enrolled in the International Severe Asthma Registry (ISAR) experience after up to five years of achieving remission as clinical remission can be lost over time. We will have also compared the asthma outcome between patients that reached remission at one-year post-initiation to those that did not. This will inform clinicians' and patients' long-term expectations once a patient arrives at remission at one-year and which aspects of the disease pathology and burden should be carefully monitored and managed.

3.0 Study Aims and Objectives

3.1 Study Aim

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

3.2 Study Objectives

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

Objective 2: To investigate the effect of remission on long-term clinical outcomes of asthma between those that graduate to remission at 12-months post-initiation of biologic therapy compared to those that do not.

4.0 Materials and Methods

4.1 Data Source

ISAR is an international collaborative initiative to gather pseudonymous (de-identified), longitudinal, observational data for patients with severe asthma. Eligible participants are patients aged 18 years or more who visit a participating secondary care centre, have a diagnosis of severe asthma, and are willing to contribute with their data. In ISAR, severe asthma is defined as asthma requiring treatment with GINA 2018 Treatment Step 4 (medium- or high-dose ICS-LABA therapy) but that remains uncontrolled, OR asthma requiring treatment with GINA 2018 Step 5 (with or without add-on LAMA, long-term OCS [LTOCS] or biologic therapy).

As of 25 March 2025, ISAR held standardized patient-level data for 21,600 patients from 26 countries[1], 11,798 of whom had initiated biologics. Data relevant to severe asthma research were collected at each visit or extracted from medical records. This includes details on asthma phenotype and endotype, asthma-related outcomes, treatment regimens, and data on comorbidities.

4.2 Study Design

For objective 1, remission status was assessed at each year following biologic initiation, up to 5 years of follow-up and evolution of remission status over time since biologic initiation was described.

For objective 2, individual clinical outcomes of asthma at Year 2, Year 3, Year 4 and Year 5 were compared between patients who had reached remission in Year 1 and those who had not.

For this study, we will have used the remission definition used by Perez-de-Llano et al. (2024): 0 exacerbations/year and no long-term oral corticosteroid (LTOCS) plus either or both partly/well controlled asthma or predicted percent predicted forced expiratory volume in one second (ppFEV1) ≥80% at twelve-months after biologic initiation. Any other definitions were explored beyond protocol.

[1] Argentina, Belgium, Brazil, Bulgaria, Canada, Colombia, Denmark, Estonia, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Norway, Poland, Portugal, Saudi Arabia, Singapore, South Korea, Spain, Taiwan, UAE, UK, USA.

4.3 Inclusion and exclusion criteria

To be eligible for the project, patients had to meet all the following criteria:

- Biologic therapy initiated (anti-IgE, anti-IL5/5R, anti-IL4Ralpha, or anti-TSLP);
- Age 18 years or older at the time of biologic initiation;
- Available biologic initiation date;
- Biologic initiated less than a year before dataset closure date (31-07-2025);
- At least 1 year of follow-up;
- Available data for at least one of the 3-domain remission definitions at Year 2 of follow-up;
- Available data for at least one clinical outcome at Year 2 of follow-up;
- Available data for age at biologic initiation and sex.

4.4 Patient disposition

A description of the number of biologic initiator patients considered for and included in the study is provided in Table 1. Numbers by geographical settings contributing to ISAR are available in Appendix 1: Patient disposition by geographical setting.

Table 1. Patient disposition.

	N	(%)
Total patients considered for inclusion	11,798	-
Sequential exclusions		
Age <18	274	(2.3)
Missing biologic initiation date	1,114	(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	1,882	(16.0)
Missing data for both 3-domain remission definitions at 1st year of follow-up	4,046	(34.3)
Missing data for all 4 domains in the 2nd year of follow-up	935	(7.9)
Missing age	6	(0.1)
Missing sex	1	(<0.1)
Eligible	3,371	(28.6)

5.0 Study Variables

5.1 Baseline (pre-biologic) patient characteristics

Patient characteristic variables that have been used for the study are described in Table 2. They have served to describe the study population, and as variables of interest and/or adjustment and/or stratification variables in Objectives 1 and 2.

Table 2. Patient characteristic variables.

Label	Type	Value	Construct/comments
Demographic characteristics			
Biologic initiation date	Date	-	First biologic initiated
Age at biologic initiation (years)	Numerical	-	
Sex	Nominal	Female, male	
Ethnicity	Nominal	Caucasian, North-East Asian, South-East Asian, African, Mixed, Other	
Country	Nominal	Argentina, Brazil, Belgium, Bulgaria, Canada, Colombia, Denmark, Estonia, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Norway, Poland, Portugal, Saudi Arabia, Singapore, South Korea, Spain, Taiwan, UAE, UK, USA	
Geographical setting	Nominal	Same as country, except for countries where the data collection system is different for the two contributing sites: Ireland-Beaumont Ireland-Tallaght USA-Michigan USA-NJH	
Body mass index (BMI) at biologic initiation (kg/m^2)	Numerical	-	Weight in kg/(height in m)^2
Smoking status at biologic initiation	Ordinal	Current smoker, ex-smoker, never smoker	
Asthma-related key clinical characteristics			
Number of asthma exacerbations in the year preceding biologic initiation	Discrete	-	A time window of 11 months minimum was required. When exacerbation dates were not available and the covered time window was more than 12 months (and no more than 24 months), the counts were annualized and rounded to the closest integer. Exacerbations were defined as requiring a course of OCS of at least 3 days.
Long-term OCS use in the year preceding biologic initiation	Binary	Yes, no	LTOCS is defined as using OCS daily (or every other day) for at least 3 months in the year preceding biologic initiation.

Label	Type	Value	Construct/comments
Long-term OCS daily dose during in the year preceding biologic initiation (mg/day)	Numerical	-	Prednisone-equivalent dosages over the period of use (most recent dosage if dosages changed over the year).
Asthma symptom control at biologic initiation	Ordinal	Well controlled Partly controlled Uncontrolled	Assessment in the year preceding biologic initiation, and closest to biologic initiation. In ISAR, GINA 2020 classification is collected by most participating ISAR centres. 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
FEV_1 at biologic initiation (mL)	Numerical		Assessment in the year preceding biologic initiation and closest to biologic initiation. Priority was given to post-bronchodilator measures if both pre- and post-bronchodilator measures were available.
FEV_1 percent predicted at biologic initiation (%)	Numerical	-	Assessment in the year preceding biologic initiation and closest to biologic initiation. Priority was given to post-bronchodilator measures if both pre- and post-bronchodilator measures were available. Reference equations: GLI 2022 race-neutral equations (Bowerman et al., 2023)
FEV_1/FVC ratio at biologic initiation	Numerical	-	Assessment in the year preceding biologic initiation and closest to biologic initiation. Priority was given to post-bronchodilator measures if both pre- and post-bronchodilator measures were available.
Biomarkers and other clinical features			
Age of asthma onset (years)	Numerical	-	Attained age in complete years at which asthma was diagnosed or symptoms began
Asthma duration at biologic initiation (years)	Numerical	-	Time since asthma onset (i.e., age at biologic initiation minus age at asthma onset)
Blood eosinophil count at biologic initiation (cells/mcL)	Numerical	-	Highest measure recorded up to index date
Blood total IgE count at biologic initiation (IU/mL)	Numerical	-	Latest measure recorded up to index date
FeNO concentration at biologic initiation (ppb)	Numerical	-	Latest measure recorded up to index date

Label	Type	Value	Construct/comments
Allergy test results	Binary	Positive, negative	From skin prick test or serum test for dust mite, grass mix, cat hair, mould mix, dog hair, aspergillus, weed mix, trees, food mix, animal mix, or other environmental allergens. Positive indicates that at least one test was positive; Negative indicates that at least one test was conducted and that no positive test was reported.
Eosinophilic gradient	Ordinal	Grade 0: unlikely/non-eosinophilic Grade 1: least likely Grade 2: likely Grade 3: most likely	Likelihood of eosinophilic asthma based on a composite of patient characteristics and prescriptions (Heaney et al., 2021)
Adds-on ICS/LABA asthma-related medications			
Biologic class	Nominal	Anti-IL5/5R Anti-IgE Anti-IL4Ralpha Anti-TSLP	First biologic initiated
Long-acting muscarinic antagonist (LAMA) in the year preceding biologic initiation	Binary	Yes, no	-
Leukotriene receptor antagonist (LTRA) in the year preceding biologic initiation	Binary	Yes, no	-
Theophylline in the year preceding biologic initiation	Binary	Yes, no	-
Macrolide antibiotic in the year preceding biologic initiation	Binary	Yes, no	-
Potentially T2-related comorbidities			
Allergic rhinitis	Binary	Ever, never	-
Chronic rhinosinusitis	Binary	Ever, never	-
Nasal polyps	Binary	Ever, never	-
Eczema/atopic dermatitis	Binary	Ever, never	-
History of potentially OCS-related comorbidities at biologic initiation			
Osteoporosis	Binary	Yes, no	
Anxiety/depression	Binary	Yes, no	

5.2 Clinical outcomes of asthma variables

Variables for clinical outcomes of asthma were computed at each Year of follow-up as described in Table 3. These variables were used as outcome variables for Objective 2, as well as for computing remission status variables as described in **Error! Reference source not found.**.

Table 3. Variables for clinical outcomes of asthma at follow-up

Label	Type	Value	Construct/comments
Exacerbation counts	Numerical	-	Requires at least 11 months of follow-up in each time window; i.e., at least from biologic initiation to 11 months of data for Year 1, at least 12 to 23 months of data post-biologics for Year 2, etc. When centres did not provide exacerbations dates and only provided counts within time windows, exacerbations reported up to 1 month after the time window of interest were assigned to the year prior. E.g., if 2 exacerbations were reported between initiation date and the follow-up visit at 13 months, these 2 exacerbations were assigned to Year 1. No annualized rates were computed.
Long-term OCS use	Binary	Yes, no	Requires at least at least from biologic initiation to 11 months of data for Year 1, at least 12 to 23 months of data post-biologics for Year 2, etc. When patients stopped using long-term OCS at least 1 month before the end of the year of interest, they were considered as not users.
Long-term OCS daily dose during (mg/day)	Numerical	-	Requires at least 11 months of follow-up in each time window; i.e., at least at least from biologic initiation to 11 months of data for Year 1, at least 12 to 23 months of data post-biologics for Year 2, etc. When patients stopped using long-term OCS at least 1 month before the end of the year of interest, they were considered as not users. Prednisone-equivalent dosages over the period of use (most recent dosage if dosages changed over the year).
Asthma symptom control	Ordinal	Well controlled Partly controlled Uncontrolled	Assessment closest to the end of year of interest after biologic initiation and allowing ≤6 months before and <6 months after end of year of interest; i.e., for Year 1, assessments between ≥6 months and <18 months after biologic initiation were eligible; for Year 2, assessments ≥18 months after and <30 months after biologic initiation were eligible; etc. In ISAR, GINA 2020 classification is collected by most participating ISAR centres. 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

Label	Type	Value	Construct/comments
FEV_1 (mL)	Numerical		Assessment closest to the end of year of interest after biologic initiation and allowing ≤6 months before and <6 months after end of year of interest; i.e., for Year 1, assessments between ≥6 months and <18 months after biologic initiation were eligible; for Year 2, assessments ≥18 months after and <30 months after biologic initiation were eligible; etc. Priority was given to post-bronchodilator measures if both pre- and post-bronchodilator measures were available.
FEV_1 percent predicted (%)	Numerical	-	Assessment closest to the end of year of interest after biologic initiation and allowing ≤6 months before and <6 months end of year of interest; i.e., for Year 1, assessments between ≥6 months and <18 months after biologic initiation were eligible; for Year 2, assessments ≥18 months after and <30 months after biologic initiation were eligible; etc. Priority was given to post-bronchodilator measures if both pre- and post-bronchodilator measures were available. Reference equations: GLI 2022 race-neutral equations (Bowerman et al., 2023)

5.3 Remission status variables

Based on variables described above in Table 3, remission status was computed at each Year of follow-up for different remission definitions as described below. All definitions included criteria for at least exacerbations and LTOCS:

- Four-domain definition:
  - No exacerbations, AND
  - No LTOCS use, AND
  - Partly/well controlled, AND
  - Percent predicted FEV_1 ≥80%.

- Three-domain definition (with control):
  - No exacerbations, AND
  - No LTOCS use, AND
  - Partly/well controlled.

- Three-domain definition (with lung function):
  - No exacerbations, AND
  - No LTOCS use, AND
  - Percent predicted FEV_1 ≥80%.

As sensitivity analyses, all combinations of remission were considered that included as part of the remission definition:

- For LTOCS: ≤5mg/day, prednisolone-equivalent, vs. no LTOCS use
- For symptom control: well controlled only, vs partly/well controlled
- Lung function stabilization: stabilization of FEV_1, i.e. not greater than 10% or 100mL of FEV1 decline compared to previous year assessment (Nolasco et al., 2024).

These modified criteria led to an additional 13 remission definitions. The sensitivity analyses were conducted beyond protocol and were performed for Objective 1 only.

6.0 Statistical Analysis

6.1 Objective 1

The evolution of remission status over time since biologic initiation was described through river plots, where vertical nodes correspond to the remission status at each year of follow-up. The proportion of patients that remain in the same remission status or that changed remission status was described for each year transition up to five years of follow-up, stratifying for the remission status at Year 1.

For patients who changed from remission to no remission, the number of domains and the identity of domains that failed reaching the remission criteria were described.

We further summarized remission patterns by categorizing patients with at least 3 years of follow-up data who had reached remission in the first year of follow-up into three groups (limiting this analysis to data over three years of follow-up):

- Sustained remission: remission maintained up to 3 years of follow-up;
- Unsustained remission: remission lost in the 2nd and 3rd years of follow-up;
- Semi-sustained remission: remission maintained in the 2nd year of follow-up but lost in the 3rd year of follow-up, or lost in the 2nd year of follow-up and regained in the 3rd year of follow-up.

Baseline patient characteristics were described for each remission pattern as proportions for categorical variables and as means (standard deviations) or medians (Q1-Q3) for continuous variables. Pearson's chi-squared tests, Student's t-tests, and Kruskal-Wallis tests were conducted, respectively, to compare patient characteristics between the groups.

6.2 Objective 2

Baseline patient characteristics were described separately for patients who had reached remission in Year 1 and for those who had not, and compared using standardised mean differences (SMD).

Descriptive analysis

The distribution of clinical outcomes at each further year of follow-up (up to five years post-biologic initiation) were described and compared between patients who had reached remission in Year 1 and those who had not, as follows:

- Exacerbations (categorical): none, 1, 2-3, 4+;
- LTOCS use (categorical): yes/no;

- Asthma control (categorical): uncontrolled, partly controlled, well controlled;
- Lung function:
    - Categorical: percent predicted FEV_1 ≥80%, percent predicted FEV_1 <80%;
    - Continuous: mean and standard deviation of percent predicted FEV_1.

Association analysis

Association between outcome and presence or absence of remission at Year 1 (explanatory variable) were modelled for each further year of follow-up (up to five years post-biologic initiation) using negative binomial regression for the count of exacerbations in the year, logistic regression for presence/absence of exacerbations, LTOCS use, partly/well controlled asthma, and percent predicted FEV_1 ≥80% outcomes, and linear regressions for percent predicted FEV_1 as continuous outcome. All association analyses were adjusted for age at biologic initiation, sex, and geographical setting (minimal adjustment). Analyses were repeated further adjusting for the pre-biologic measure of the outcome of interest (full adjustment).

Each regression was then repeated further adjusting for a set of covariates likely to be prognostic for remission (baseline values of percent predicted FEV_1, asthma control, exacerbation rate, LTOCS use, asthma duration, and diagnosis of anxiety/depression or obesity). Additional baseline patient characteristics with an SMD>0.1 between patients who were or were not in remission at Year 1 were also considered as adjustment factors. The effect of having remission at Year 1 was tested by repeating these regressions with and without remission status at Year 1 as an explanatory variable and comparing these using a likelihood ratio test for all nested models, except for linear models where the F-test was used. A significant likelihood ratio or F-test test indicated that remission at Year 1 had an effect on the outcomes over and above that due to differences in baseline characteristics. This approach was used rather than interpreting the coefficient for remission at Year 1 directly in the adjusted analyses due to its multicollinearity with some of the baseline characteristics.

6.3 Software

All analysis were conducted using R version 4.3.2 (2023-10-31).

6.4 Significance testing

Comparisons were two-sided and an α level of 0.05 was used to test for significance.

7.0 Results

7.1 Description of the study population

A total of 3,371 patients were eligible for at least one part of the analysis (see Table 1 for the patient disposition). Patient characteristics are described in Table 4. In this study population, biologic therapy was initiated between December 2007 and November 2023 and the most frequent initiated class was anti-IL5/5R (61.1%). Patients were from 26 geographical settings across 24 countries, with Denmark (24.9%), Italy (20.5%) and USA-NJH (19.4%) encompassing the majority of patients. Patients were on average 54.2 years old at biologic initiation, 60.0% were females, and 63.9% were never smokers. The median of asthma exacerbations in the year preceding biologic initiation was 2 (interquartile range [IQR]: 1-4) and 31.0% of patients were LTOCS users. Furthermore, 69.3% of patients had uncontrolled asthma symptoms and 62.8% had percent predicted FEV_1 below 80%.

Table 4. Baseline patient characteristics: biologic initiation, and pre-biologic demographic and clinical characteristics.

Characteristics	N	Measure/category	Result
Biologic initiation date	3,371	median (range)	Sep 2019 (Dec 2007-Nov 2023)
Biologic class	3,371	Anti-IL5/5R: n (%)	2,060 (61.11)
		Anti-IgE: n (%)	790 (23.44)
		Anti-IL4Ralpha: n (%)	509 (15.10)
		Anti-TSLP: n (%)	12 (0.36)
Geographical setting	3,371	Denmark: n (%)	839 (24.89)
		Italy: n (%)	690 (20.47)
		USA-NJH: n (%)	653 (19.37)
		UK: n (%)	275 (8.16)
		Spain: n (%)	183 (5.43)
		Belgium: n (%)	105 (3.11)
		Canada: n (%)	98 (2.91)
		Colombia: n (%)	80 (2.37)
		Poland: n (%)	83 (2.46)
		Japan: n (%)	62 (1.84)
		Others*: n (%)	303 (8.99)
Age at biologic initiation (years)	3,371	mean (SD)	54.2 (14.2)
Sex	3,371	Female: n (%)	2,021 (59.95)
Ethnicity	2,842	Caucasian: n (%)	2,336 (82.20)
		South-East Asian: n (%)	125 (4.40)
		North-East Asian: n (%)	97 (3.41)
		African: n (%)	48 (1.69)
		Mixed: n (%)	96 (3.38)
		Other: n (%)	140 (4.93)
Smoking status	3,337	Never smoker: n (%)	2,131 (63.86)
		Ex-smoker: n (%)	1,103 (33.05)
		Current smoker: n (%)	103 (3.09)
BMI (kg/m^2)	3,331	mean (SD)	27.9 (6.1)
		30+ (obesity): n (%)	1,021 (30.65)

Characteristics	N	Measure/category	Result
Number of asthma exacerbation in past year	2,242	median (Q1-Q3)	2 (1-4)
LTOCS use in past year	2,622	Yes: n (%)	814 (31.05)
Most recent asthma control in past year (GINA 2020)	1,602	Uncontrolled: n (%) Partly controlled: n (%) Well controlled: n (%)	1,110 (69.29) 276 (17.23) 216 (13.48)
Most recent percent predicted FEV_1 in past year (%)	2,312	mean (SD) <80%: n (%)	73.6 (21.8) 1,451 (62.76)
Most recent FEV_1/FVC ratio in past year	2,488	mean (SD) <0.70: n (%)	0.67 (0.13) 1,385 (55.67)
Age at asthma onset (years)	2,171	mean (SD) <12: n (%)	31.6 (19.1) 428 (19.71)
Asthma duration (years)	2,171	mean (SD) 10+: n (%)	23.0 (16.8) 1,553 (71.53)
Highest blood eosinophil count (cells/mcL)	2,330	median (Q1-Q3)	500 (300-870)
Latest serum total IgE concentration (IU/mL)	2,214	median (Q1-Q3)	166 (61- 402)
Latest FeNO concentration (ppb)	2,015	median (Q1-Q3)	33 (17-64)
Allergen test results	3,011	Positive: n (%)	1,494 (49.62)
Eosinophilic asthma gradient	2,813	Grade 0 - Unlikely/Non-eosinophilic: n (%) Grade 1 - Least likely: n (%) Grade 2 - Likely: n (%) Grade 3 - Most likely: n (%)	7 (0.25) 68 (2.42) 85 (3.02) 2,653 (94.31)
Add-on background therapy to ICS/LABA	3,084 3,084 3,083 3,083	LAMA: n (%) LTRA: n (%) Theophylline: n (%) Macrolide: n (%)	1,619 (52.50) 1,609 (52.17) 159 (5.16) 332 (10.77)
Allergic rhinitis	2,921	Ever: n (%)	1,678 (57.45)
Chronic rhinosinusitis	3,055	Ever: n (%)	1,939 (63.47)
Nasal polyposis	3,328	Ever: n (%)	1,277 (38.37)
Eczema/atopic dermatitis	3,330	Ever: n (%)	562 (16.88)
History of osteoporosis	2,660	Yes: n (%)	287 (10.79)
History of anxiety and/or depression	3,083	Yes: n (%)	477 (15.47)

*Brazil, Bulgaria, Estonia, Greece, Ireland-Beaumont, Ireland-Tallaght, Kuwait, Mexico, Norway, Portugal, Saudi Arabia, Singapore, South Korea, Taiwan, UAE, USA-Michigan.

7.2 Objective 1

Of the total of 3,371 patients eligible for at least one analysis of the overall project, 928 patients were excluded from the Objective 1 analyses because they were lacking sufficient data to assess remission status at Year 2. Patient characteristics are described in Table 5. In this study population, biologic therapy was initiated between December 2007 and April 2023 and the most frequent initiated class was anti-IL5/5R (61.8%). Patients were from 25 geographical settings across 23 countries, with Denmark (29.1%), Italy (20.5%) and USA-NJH (16.9%) encompassing the majority of patients. Patients were on average 54.8 years old at biologic initiation, 59.8% were females, and 63.5% were never smokers. The median of asthma exacerbations in the year preceding biologic initiation was 2 (IQR: 1-4) and 31.4% of patients were LTOCS users. Furthermore, 68.8% of patients had uncontrolled asthma symptoms and 63.2% had percent predicted FEV_1 below 80%.

Table 5. Baseline patient characteristics: biologic initiation, and pre-biologic demographic and clinical characteristics (patients eligible for Objective 1 analyses).

Characteristics	N	Measure/category	Result
Biologic initiation date	2,443	median (range)	Aug 2019 (Dec 2007-Apr 2023)
Biologic class	2,443	Anti-IL5/5R: n (%)	1,509 (61.77)
		Anti-IgE: n (%)	576 (23.58)
		Anti-IL4Ralpha: n (%)	354 (14.49)
		Anti-TSLP: n (%)	4 (0.16)
Geographical setting	2,443	Denmark: n (%)	710 (29.06)
		Italy: n (%)	502 (20.55)
		USA-NJH: n (%)	412 (16.86)
		UK: n (%)	185 (7.57)
		Spain: n (%)	125 (5.12)
		Belgium: n (%)	80 (3.27)
		Canada: n (%)	76 (3.11)
		Colombia: n (%)	64 (2.62)
		Poland: n (%)	60 (2.46)
		Japan: n (%)	52 (2.13)
		Others*: n (%)	177 (7.25)
Age at biologic initiation (years)	2,443	mean (SD)	54.8 (13.8)
Sex	2,443	Female: n (%)	1,460 (59.76)
Ethnicity	2,070	Caucasian: n (%)	1,722 (83.19)
		North-East Asian: n (%)	85 (4.11)
		South-East Asian: n (%)	74 (3.57)
		African: n (%)	33 (1.59)
		Mixed: n (%)	60 (2.90)
		Other: n (%)	96 (4.64)
Smoking status	2,419	Never smoker: n (%)	1,537 (63.54)
		Ex-smoker: n (%)	815 (33.69)
		Current smoker: n (%)	67 (2.77)
BMI (kg/m^2)	2,414	mean (SD)	27.7 (5.9)
		30+ (obesity): n (%)	669 (28.96)

Characteristics	N	Measure/category	Result
Number of asthma exacerbation in past year	1,699	median (Q1-Q3)	2 (1-4)
LTOCS use in past year	1,954	Yes: n (%)	614 (31.42)
Most recent asthma control in past year (GINA 2020)	1,213	Uncontrolled: n (%) Partly controlled: n (%) Well controlled: n (%)	835 (68.84) 205 (16.90) 173 (14.26)
Most recent percent predicted FEV_1 in past year (%)	1,717	mean (SD) <80%: n (%)	73.6 (21.7) 1,085 (63.19)
Most recent FEV_1/FVC ratio in past year	1,821	mean (SD) <0.70: n (%)	0.67 (0.13) 1,037 (56.95)
Age at asthma onset (years)	1,639	mean (SD) <12: n (%)	32.2 (19.1) 309 (18.85)
Asthma duration (years)	1,639	mean (SD) 10+: n (%)	22.9 (16.8) 1,177 (71.81)
Highest blood eosinophil count (cells/mcL)	1,663	median (Q1-Q3)	510 (300-890)
Latest serum total IgE concentration (IU/mL)	1,615	median (Q1-Q3)	163 (60- 394)
Latest FeNO concentration (ppb)	1,484	median (Q1-Q3)	33 (17-65)
Allergen test results	2,216	Positive: n (%)	1,092 (49.28)
Eosinophilic asthma gradient	2,053	Grade 0 - Unlikely/Non-eosinophilic: n (%) Grade 1 - Least likely: n (%) Grade 2 - Likely: n (%) Grade 3 - Most likely: n (%)	5 (0.24) 54 (2.63) 60 (2.92) 1,934 (94.20)
Add-on background therapy to ICS/LABA	2,235 2,235 2,234 2,234	LAMA: n (%) LTRA: n (%) Theophylline: n (%) Macrolide: n (%)	1,170 (52.35) 1,169 (52.30) 120 (5.37) 237 (10.61)
Allergic rhinitis	2,121	Ever: n (%)	1,244 (58.65)
Chronic rhinosinusitis	2,227	Ever: n (%)	1,459 (65.51)
Nasal polyposis	2,409	Ever: n (%)	948 (39.35)
Eczema/atopic dermatitis	2,414	Ever: n (%)	432 (17.90)
History of osteoporosis	1,889	Yes: n (%)	216 (11.43)
History of anxiety and/or depression	2,246	Yes: n (%)	322 (14.34)

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

The proportions of patients who were in remission at Year 1 to Year 5 were, respectively, 26.0% (363/1,396), 29.2% (408/1,396), 31.9% (240/753), 33.3% (129/387), and 30.6% (59/193) for the four-domain remission definition; 40.1% (732/1,824), 46.4% (845/1,824), 49.8% (529/1,062), 53.4% (311/582), and 51.5% (155/301) for the three-domain with asthma control; and 30.4% (612/2,015), 33.8% (681/2,015), 34.9% (405/1,161), 35.6% (237/666), and 32.6% (124/380) for the three-domain with lung function. Numbers for additional remission definitions are available in Appendix 2:.

The evolution of remission status over time since biologic initiation stratified by remission status at Year 1 is shown for each main remission definition in Figure 1 (four-domain remission), Figure 2 (three-domain with control), and Figure 3 (three-domain with lung function). Corresponding numbers for these main remission definitions as well as for the additional remission definitions are tabulated in Appendix 2:. Remission status appeared stable over time, with globally larger proportions of patients remaining in the same remission status from one year to the next than of patients changing remission status, irrespective of the remission definition used.

In this population, 209/2,429 patients (8.56%) switched or stopped biologics in Year 1. Of these, 54 (25.84%) stopped their biologics. Among switchers, the most common switches were within the anti-IL5/5R biologic class (38.46%), followed by switches from anti-IgE to anti-IL5/5R (19.87%) and from anti-IL5/5R to anti-IL4Ralpha (16.03%). In each further year of follow-up, approximately 10% switched or stopped, with only around 1% who stopped. In patients who were in remission at Year 1, restricting the analyses to patients who had maintained the same biologic up to the year of remission assessment had limited impact on the proportions of patients who were in remission at further years of follow-up. For the four-domain remission, these were 75% (243/325), 70% (114/162), 74% (55/74), and 74% (20/27) at Years 2 to 5, respectively. For the three-domain remission with control, they were 81% (543/668), 78% (284/362), 80% (142/177), and 76% (62/82), and for the three-domain with lung function, they were 76% (410/540), 71% (205/287), 76% (112/147), and 74% (59/80) at Years 2 to 5, respectively. In patients not in remission in Year 1, the proportions were also similar to those shown in Figures 2 to 3 (data not shown).

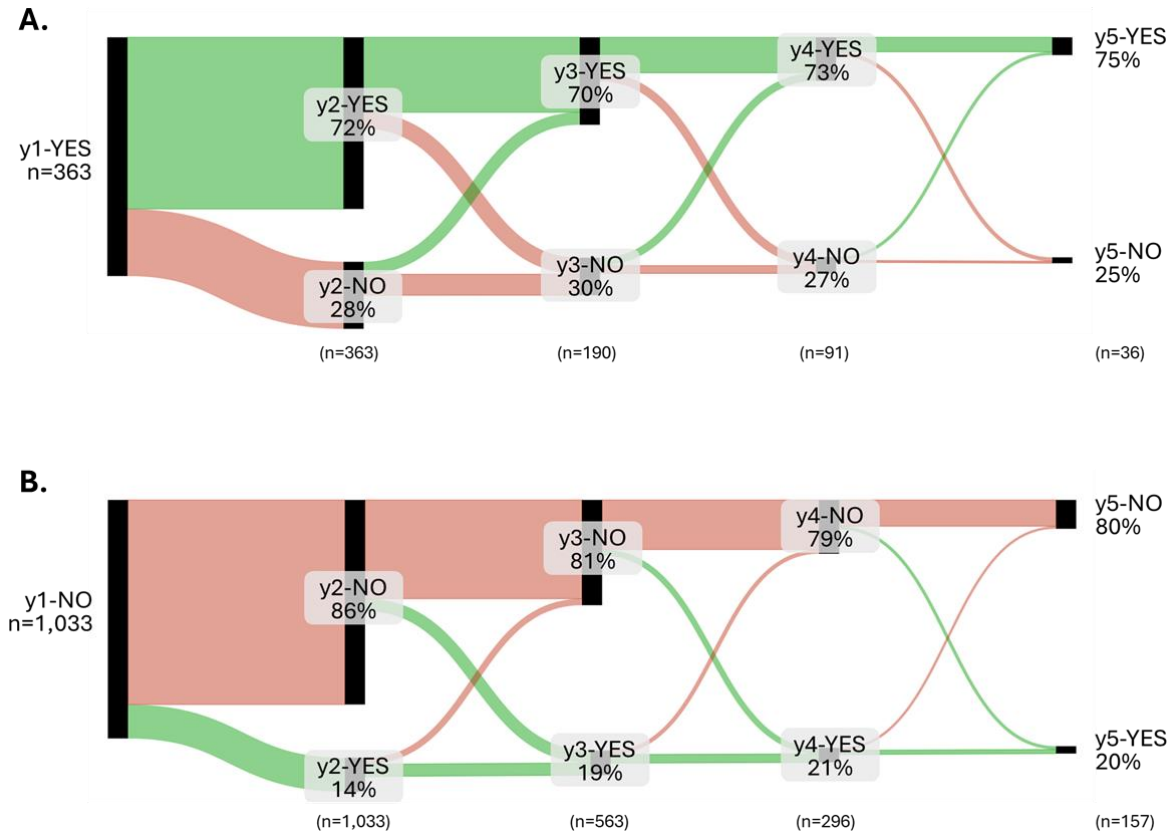

Figure 1. Evolution of remission status over time since biologic initiation, in A. patients who met remission criteria at Year 1, and B. patients who had not met remission criteria at Year 1. Four-domain remission defined as no exacerbations in the past year, no LTOCS use, well or partly controlled asthma, and percent predicted FEV_1 ≥80%.

y1-5: timepoints since biologic initiation (years); YES: remission criteria met; NO: at least one remission criterion not met. Green streams correspond to reaching or remaining in remission; red streams correspond to not reaching or remaining not in remission.

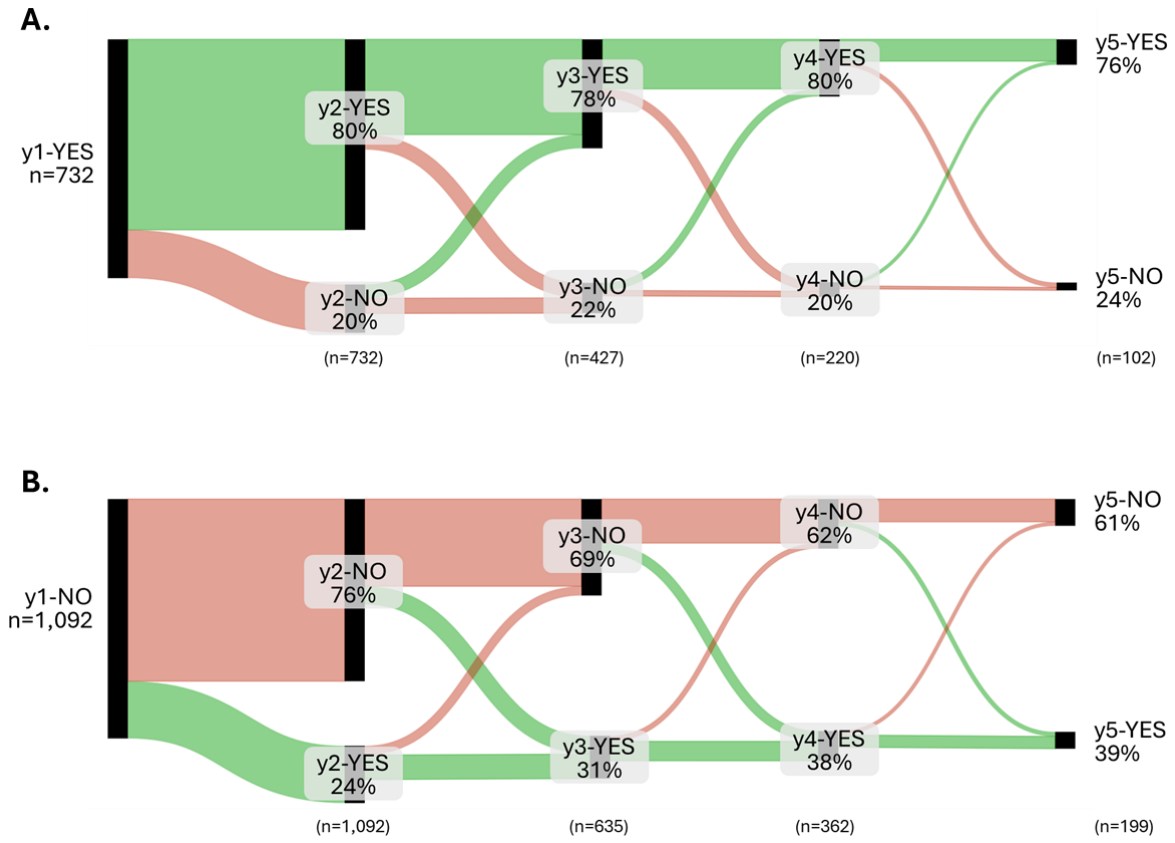

Figure 2. Evolution of remission status over time since biologic initiation, in A. patients who met remission criteria at Year 1, and B. patients who had not met remission criteria at Year 1. Three-domain remission defined as no exacerbations in the past year, no LTOCS use, and well or partly controlled asthma.

y1-5: timepoints since biologic initiation (years); YES: remission criteria met; NO: at least one remission criterion not met. Green streams correspond to reaching or remaining in remission; red streams correspond to not reaching or remaining not in remission.

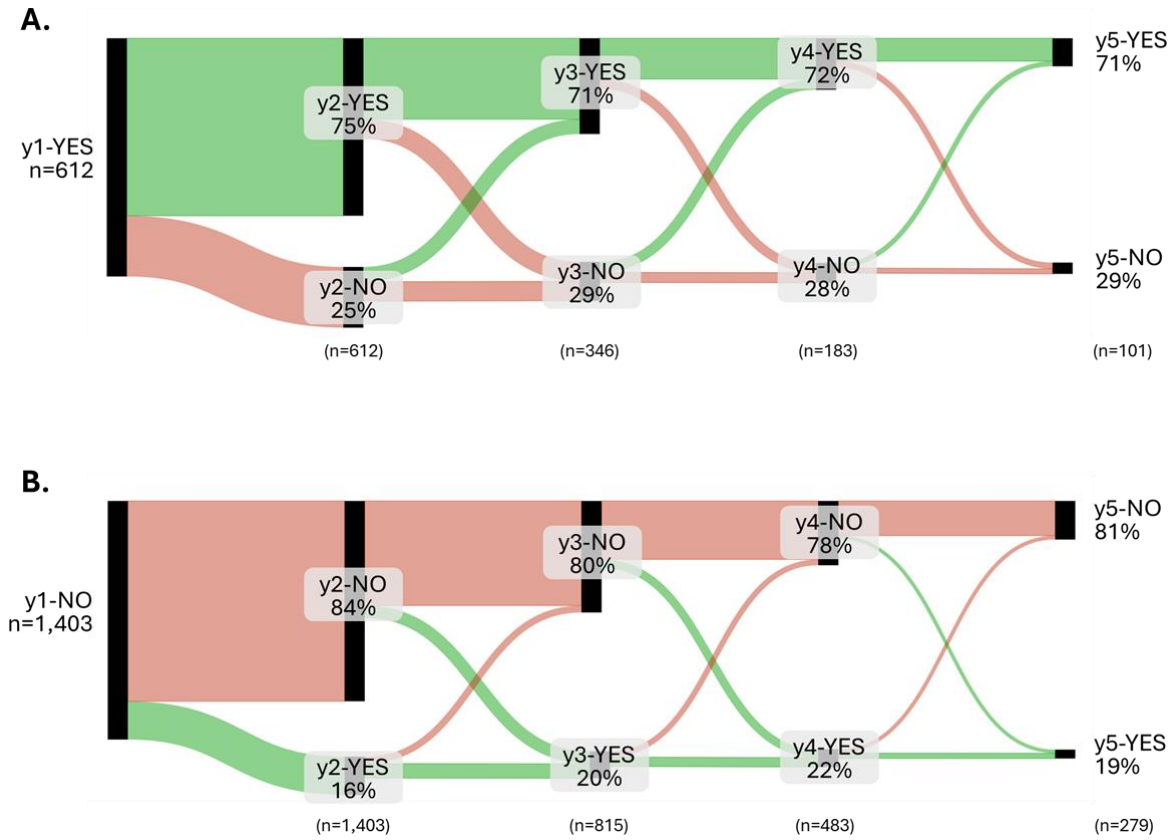

Figure 3. Evolution of remission status over time since biologic initiation, in A. patients who met remission criteria at Year 1, and B. patients who had not met remission criteria at Year 1. Three-domain remission defined as no exacerbations in the past year, no LTOCS use, and percent predicted FEV_1 ≥80%.
y1-5: timepoints since biologic initiation (years); YES: remission criteria met; NO: at least one remission criterion not met. Green streams correspond to reaching or remaining in remission; red streams correspond to not reaching or remaining not in remission.

The proportions of patients that remained in the same remission status or that changed remission status from year to year are shown in Table 6 up to five years of follow-up, stratified for the remission status at Year 1. These numbers are derived from the river plots above and provide detailed numbers on changing or maintaining remission status from year to year. Maintaining remission from year to year in patients who were in remission at Year 1 was observed for above 70% of patients, with little variation across time since biologic initiation and across remission definitions. For patients who were not in remission at Year 1, the proportions of patients who later reached and maintained remission over the following year were slightly lower although still generally above 60% and above 70% for the remission definition that did not include the lung function criterion. Changing from no remission to remission over years was observed in 37% to 62% of patients depending on the timepoint and the remission definition in patients who were in remission at Year 1. In patients who were not in remission at Year 1, these proportions were lower (9% to 24%), with the highest proportions observed for the remission definition that did not include the lung function criterion.

Proportions for additional remission definitions are available in

Appendix 3:. Similar trends as described above for the three main remission definitions were observed.

Table 6. Remission status transitions over time since biologic initiation, stratified by remission status at Year 1.

Remission transitions	Patients in remission at Year 1				Patients not in remission at Year 1			
	Year 1 to 2	Year 2 to 3	Year 3 to 4	Year 4 to 5	Year 1 to 2	Year 2 to 3	Year 3 to 4	Year 4 to 5
Four-domain remission: no exacerbations, no LTOCS use, well or partly controlled, and percent predicted FEV_1 ≥80%								
Patients in remission in the previous year, N	363	139	67	28	0	81	55	29
Maintained remission: n (%)	261 (71.90)	114 (82.01)	54 (80.60)	22 (78.57)	N/A	53 (65.43)	37 (67.27)	18 (62.07)
Changed from remission to no remission: n (%)	102 (28.10)	25 (17.99)	13 (19.40)	6 (21.43)	N/A	28 (34.57)	18 (32.73)	11 (37.93)
Patients not in remission in the previous year, N	0	51	24	8	1,033	482	241	128
Remained below remission criteria: n (%)	N/A	32 (62.75)	12 (50.00)	3 (37.50)	886 (85.77)	428 (88.80)	215 (89.21)	114 (89.06)
Changed from no remission to remission: n (%)	N/A	19 (37.25)	12 (50.00)	5 (62.50)	147 (14.23)	54 (11.20)	26 (10.79)	14 (10.94)
Three-domain remission: no exacerbations, no LTOCS use, and well or partly controlled								
Patients in remission in the previous year, N	732	338	180	82	0	154	114	74
Maintained remission: n (%)	584 (79.78)	292 (86.39)	152 (84.44)	67 (81.71)	N/A	112 (72.73)	89 (78.07)	56 (75.68)
Changed from remission to no remission: n (%)	148 (20.22)	46 (13.61)	28 (15.56)	15 (18.29)	N/A	42 (27.27)	25 (21.93)	18 (24.32)
Patients not in remission in the previous year, N	0	89	40	20	1,092	481	248	125
Remained below remission criteria: n (%)	N/A	47 (52.81)	17 (42.50)	9 (45.00)	831 (76.10)	398 (82.74)	201 (81.05)	104 (83.20)
Changed from no remission to remission: n (%)	N/A	42 (47.19)	23 (57.50)	11 (55.00)	261 (23.90)	83 (17.26)	47 (18.95)	21 (16.80)
Three-domain remission: no exacerbations, no LTOCS use, and percent predicted FEV_1 ≥80%								
Patients in remission in the previous year, N	612	258	130	75	0	126	89	54
Maintained remission: n (%)	456 (74.51)	208 (80.62)	105 (80.77)	59 (78.67)	N/A	85 (67.46)	55 (61.80)	31 (57.41)
Changed from remission to no remission: n (%)	156 (25.49)	50 (19.38)	25 (19.23)	16 (21.33)	N/A	41 (32.54)	34 (38.20)	23 (42.59)
Patients not in remission in the previous year, N	0	88	53	26	1,403	689	394	225
Remained below remission criteria: n (%)	N/A	50 (56.82)	26 (49.06)	13 (50.00)	1,178 (83.96)	615 (89.26)	344 (87.31)	204 (90.67)
Changed from no remission to remission: n (%)	N/A	38 (43.18)	27 (50.94)	13 (50.00)	225 (16.04)	74 (10.74)	50 (12.69)	21 (9.33)

N/A: not applicable.

In patients who were in remission at Year 1 and who had complete data over 3, 4 or 5 years of follow-up, the proportion who remained in remission over the observation period are shown in Table 7 by remission definition. They varied from 60-68% in Year 3, 51-61% in Year 4, and 44-54% in Year 5. Restricting the study populations to patients who had maintained the same biologic throughout the study period had little impact on the observed proportions. Numbers for additional remission definitions are available in

Appendix 4: and showed little variation from the proportions observed for the three main definitions.

Table 7. Proportions of patients that remained in remission over 3, 4, and 5 years, in patients who met remission criteria in the first year post-biologic initiation.

Study population	Over 3 years		Over 4 years		Over 5 years	
	Denominator	n (%)	Denominator	n (%)	Denominator	n (%)
Overall (intention-to-treat approach)	**Four-domain remission:** no exacerbations, no LTOCS use, well or partly controlled, and percent predicted FEV_1 ≥80%					
	190	114 (60.0)	91	46 (50.5)	36	16 (44.4)
	Three-domain remission: no exacerbations, no LTOCS use, and well or partly controlled					
	427	292 (68.4)	220	134 (60.9)	102	55 (53.9)
	Three-domain remission: no exacerbations, no LTOCS use, and percent predicted FEV1 ≥80%					
	346	208 (60.1)	183	94 (51.4)	101	44 (43.6)
Patients who maintained the same biologic throughout the study period	**Four-domain remission:** no exacerbations, no LTOCS use, well or partly controlled, and percent predicted FEV_1 ≥80%					
	162	98 (60.5)	74	40 (54.1)	27	13 (48.1)
	Three-domain remission: no exacerbations, no LTOCS use, and well or partly controlled					
	362	256 (70.7)	177	112 (63.3)	82	45 (54.9)
	Three-domain remission: no exacerbations, no LTOCS use, and percent predicted FEV1 ≥80%					
	287	176 (61.3)	147	78 (53.1)	80	35 (43.6)

For patients who changed from remission to no remission at any timepoint, the number of domains and the identity of domains that failed reaching the remission criteria were examined at each timepoint and by remission status at Year 1. The distributions were similar across timepoints and remission status at Year 1 (data not shown). The overall distributions are shown by remission definitions in Table 88. In most cases (75% to 89% depending on the remission definition), losing remission was due to one domain only. The domain in question was relatively balanced between exacerbations, asthma control, and lung function, but was rarely related to LTOCS (<2%). Failing two domains was seen in 10% to 21% of the patients (depending on the remission definition), while failing all domains considered in each remission definition was rare (<1%).

Table 8. Number and identity of domains contributing to losing remission in patients who were in remission in the previous year.

Number and identity of domains failing remission	n	(%)
Four-domain remission: no exacerbations, no LTOCS use, well or partly controlled, and ppFEV1 ≥80%		
Patients in remission in the previous year, N	*203*	
Failing 1 domain only	**153**	**(75.37)**
1+ exacerbations	48	(23.65)
Became uncontrolled	40	(19.70)
Percent predicted FEV_1 passed below 80%	63	(31.03)
Started/resumed LTOCS use	2	(0.99)
Failing 2 domains only	**42**	**(20.69)**
Exacerbations and asthma control	19	(9.36)
Exacerbations and lung function	9	(4.43)
Asthma control and lung function	12	(5.91)
Exacerbations and LTOCS	2	(0.99)
Asthma control and LTOCS	0	(0.00)
Lung function and LTOCS	0	(0.00)
Failing 3 domains only	**7**	**(3.45)**
Exacerbations, asthma control, and lung function	7	(3.45)
Exacerbations, LTOCS, and asthma control	0	(0.00)
Exacerbations, LTOCS, and lung function	0	(0.00)
LTOCS, asthma control, and lung function	0	(0.00)
Failing all 4 domains	**1**	**(0.49)**
Three-domain remission: no exacerbations, no LTOCS use, and well or partly controlled		
Patients in remission in the previous year, N	*322*	
Failing 1 domain only	**265**	**(82.30)**
1+ exacerbations	140	(43.48)
Became uncontrolled	120	(37.27)
Started/resumed LTOCS use	5	(1.55)
Failing 2 domains only	**55**	**(17.08)**
Exacerbations and asthma control	49	(15.22)
Exacerbations and LTOCS	6	(1.86)
Asthma control and LTOCS	0	(0.00)
Failing all 3 domains	**2**	**(0.62)**
Three-domain remission: no exacerbations, no LTOCS use, and ppFEV1 ≥80%		
Patients in remission in the previous year, N	*345*	
Failing 1 domain only	**307**	**(88.99)**
1+ exacerbations	161	(46.67)
Percent predicted FEV_1 passed below 80%	140	(40.58)
Started/resumed LTOCS use	6	(1.74)
Failing 2 domains only	**36**	**(10.43)**
Exacerbations and lung function	34	(9.86)
Exacerbations and LTOCS	2	(0.58)
Lung function and LTOCS	0	(0.00)
Failing all 3 domains	**2**	**(0.58)**

Patients remission at Year 1 were categorized into three remission patterns across three years of follow-up post-biologic initiation:

- Sustained remission: remission maintained up to 3 years of follow-up;
- Unsustained remission: remission lost in the 2nd and 3rd years of follow-up;
- Semi-sustained remission: remission maintained in the 2nd year of follow-up but lost in the 3rd year of follow-up, or lost in the 2nd year of follow-up and regained in the 3rd year of follow-up.

The proportion of patients in each remission pattern is shown by remission definitions in Table 9. The proportion of patients who sustained remission up to three years after biologic initiation was at least 60% (up to 38% when lung function was not considered), whereas patients who relapsed in the second year after biologic initiation and did not regain remission at Year 3 was comprised between 11% and 17% depending on the remission definition considered.

Table 9. Remission patterns over 3 years of follow-up in patients who were in remission at Year 1, by remission definitions.

Remission patterns	Four-domain remission[1]	Three-domain remission (with control)[2]	Three-domain remission (with lung function)[3]
Patients in remission at Year 1, N	*190*	*427*	*346*
Sustained remission: n (%)	114 (60.00)	292 (68.38)	208 (60.12)
Semi-sustained remission: n (%)	44 (23.16)	88 (20.61)	88 (25.43)
Unsustained remission: n (%)	32 (16.84)	47 (11.01)	50 (14.45)

1. No exacerbations, no LTOCS use, well or partly controlled, and ppFEV$_1$ ≥80%.
2. No exacerbations, no LTOCS use, and well or partly controlled
3. No exacerbations, no LTOCS use, and ppFEV$_1$ ≥80%.

Baseline patient characteristics within each remission pattern and by remission definitions are available in Table 10. The statistical power was overall limited, considering the small sample size for the semi-sustained and unsustained remission groups. Consistencies were observed for asthma duration, with shorter duration in the sustained remission group, as well as for asthma control, with better control pre-biologic in the sustained remission group. Percent predicted FEV1 was also consistently higher in the sustained remission group when the lung function criterion was included in the remission definition. On the other hand, anxiety and/or depression was more frequent in patients with unsustained remission when the asthma control criterion was included in the remission definition.

Table 10. Patient characteristics by remission patterns over three years post-biologic initiation.

Patient characteristics at biologic initiation	Sustained	Semi-sustained	p*	Unsustained	p*
Demographics					
Age (years), Mean (SD)					
4-domain	55.8 (10.7)	56.6 (14.7)	0.717	57.8 (13.1)	0.382
3-domain (+control)	57.2 (12.2)	59.0 (11.9)	0.219	56.9 (12.5)	0.871
3-domain (+lung)	54.1 (12.7)	54.2 (15.5)	0.961	57.4 (13.6)	0.104
Sex, Female: n (%)					
4-domain	62 (54.39)	30 (68.18)	0.115	20 (62.50)	0.414
3-domain (+control)	164 (56.16)	61 (69.32)	0.059	31 (65.96)	0.207
3-domain (+lung)	113 (54.33)	64 (72.73)	0.003	34 (68.00)	0.080
BMI (kg/m^2), Mean (SD)					
4-domain	25.6 (4.0)	26.8 (4.8)	0.095	25.8 (5.1)	0.771
3-domain (+control)	26.2 (4.9)	27.9 (5.7)	0.021	26.5 (4.9)	0.748
3-domain (+lung)	26.7 (4.8)	27.7 (5.5)	0.098	26.2 (5.4)	0.556
Obesity (BMI ≥30 kg/m^2), Yes: n (%)					
4-domain	14 (12.28)	13 (29.55)	0.010	32 (12.50)	0.973
3-domain (+control)	56 (19.38)	24 (27.27)	0.113	8 (17.78)	0.800
3-domain (+lung)	43 (20.67)	27 (30.68)	0.064	10 (20.00)	0.916
Tobacco use, Never smoker: n (%)					
4-domain	81 (71.05)	29 (69.05)	0.808	17 (53.12)	0.056
3-domain (+control)	194 (67.13)	63 (72.41)	0.353	26 (55.32)	0.114
3-domain (+lung)	132 (64.08)	61 (70.11)	0.319	35 (70.00)	0.430
Geographical setting					
4-domain			0.287		0.677
Denmark	55 (48.25)	18 (40.91)		20 (62.50)	
Italy	26 (22.81)	10 (22.73)		6 (18.75)	
USA-NJH	1 (0.88)	3 (6.82)		0 (0.00)	
Spain	12 (10.53)	4 (9.09)		2 (6.25)	
Others	20 (17.54)	9 (20.45)		4 (12.50)	
3-domain (+control)			0.279		0.377
Denmark	114 (39.04)	23 (26.14)		23 (48.94)	
Italy	94 (32.19)	35 (39.77)		13 (27.66)	
USA-NJH	4 (1.37)	2 (2.27)		2 (4.26)	
Spain	20 (6.85)	7 (7.95)		2 (4.26)	
Others	60 (20.55)	21 (23.86)		7 (14.89)	
3-domain (+lung)			0.025		0.016
Denmark	102 (49.04)	32 (36.36)		19 (38.00)	
Italy	31 (14.90)	10 (11.36)		5 (10.00)	
USA-NJH	21 (10.10)	21 (23.86)		13 (26.00)	
Spain	16 (7.69)	7 (7.95)		1 (2.00)	
Others	38 (18.27)	18 (20.45)		12 (24.00)	

Table 10 (cont'd)

Patient characteristics at biologic initiation	Sustained	Semi-sustained	p*	Unsustained	p*
Clinical characteristics					
Age at asthma onset (years), Mean (SD)					
4-domain	35.2 (17.9)	31.3 (20.3)	0.321	33.6 (17.1)	0.683
3-domain (+control)	35.9 (17.9)	32.5 (18.5)	0.180	30.0 (15.5)	0.057
3-domain (+lung)	34.8 (18.7)	30.2 (19.2)	0.142	32.2 (15.9)	0.498
Asthma duration (years), Mean (SD)					
4-domain	19.6 (15.1)	23.3 (17.6)	0.269	24.5 (15.5)	0.141
3-domain (+control)	21.0 (15.7)	25.9 (18.9)	0.031	27.0 (15.8)	0.029
3-domain (+lung)	18.0 (14.9)	24.3 (17.0)	0.014	25.5 (15.7)	0.016
Number of exacerbations in the past year, Median (Q1-Q3)					
4-domain	2 (1-5)	3 (2-4)	0.998	2 (1-4)	0.622
3-domain (+control)	2 (1-4)	2 (1-4)	0.635	2 (1-4)	0.951
3-domain (+lung)	2 (1-4)	2 (1-4)	0.622	2 (1-3)	0.160
LTOCS use in the past year, Yes: n (%)					
4-domain	19 (20.43)	4 (10.81)	0.195	4 (10.81)	0.514
3-domain (+control)	50 (20.66)	10 (13.89)	0.199	3 (7.89)	0.062
3-domain (+lung)	27 (16.07)	10 (15.38)	0.898	4 (10.00)	0.333
Asthma control, Uncontrolled: n (%)					
4-domain	27 (41.54)	19 (70.37)	0.012	12 (66.67)	0.059
3-domain (+control)	82 (46.07)	31 (62.00)	0.046	16 (69.57)	0.034
3-domain (+lung)	62 (55.86)	33 (76.74)	0.017	19 (76.00)	0.064
Percent predicted FEV1 (%), Mean (SD)					
4-domain	89.1 (19.9)	82.8 (22.0)	0.149	80.8 (16.7)	0.075
3-domain (+control)	77.0 (21.8)	77.6 (22.1)	0.853	75.2 (19.3)	0.659
3-domain (+lung)	89.4 (19.1)	82.3 (17.5)	0.013	79.4 (18.2)	0.004
Percent predicted FEV1 (%), ≥80%: n (%)					
4-domain	58 (76.32)	16 (50.00)	0.007	11 (47.83)	0.009
3-domain (+control)	86 (44.56)	23 (39.66)	0.509	10 (31.25)	0.159
3-domain (+lung)	106 (72.11)	31 (50.00)	0.002	18 (47.37)	0.004
FEV1/FVC ratio, Mean (SD)					
4-domain	0.71 (0.11)	0.68 (0.13)	0.227	0.67 (0.12)	0.141
3-domain (+control)	0.65 (0.13)	0.69 (0.12)	0.048	0.67 (0.11)	0.588
3-domain (+lung)	0.72 (0.10)	0.71 (0.12)	0.371	0.70 (0.11)	0.261
FEV1/FVC ratio, ≥0.70: n (%)					
4-domain	43 (53.09)	19 (59.38)	0.545	9 (39.13)	0.237
3-domain (+control)	77 (37.93)	31 (53.45)	0.034	11 (34.38)	0.699
3-domain (+lung)	103 (63.58)	45 (63.38)	0.977	22 (55.00)	0.317

Table 10 (cont'd)

Patient characteristics at biologic initiation	Sustained	Semi-sustained	p*	Unsustained	p*
Biomarkers					
Highest blood eosinophil count (cells/mcL), Median (Q1-Q3)					
4-domain	600 (340-980)	765 (377-1000)	0.561	600 (455-760)	0.485
3-domain (+control)	630 (362-1092)	600 (300-900)	0.284	570 (310-780)	0.138
3-domain (+lung)	645 (302-960)	500 (300-910)	0.405	600 (300-760)	0.135
Latest FeNO concentration (ppb), Median (Q1-Q3)					
4-domain	33 (18-89)	28 (11-73)	0.296	37 (14-48)	0.424
3-domain (+control)	34 (19-73)	28 (16-46)	0.137	37 (14-52)	0.557
3-domain (+lung)	31 (16-72)	29 (14-73)	0.386	38 (22-64)	0.694
Latest serum total IgE concentration (IU/mL), Median (Q1-Q3)					
4-domain	145 (70-434)	147 (90-336)	0.769	332 (75-723)	0.163
3-domain (+control)	166 (74-369)	194 (79-452)	0.780	230 (57-766)	0.458
3-domain (+lung)	156 (72-417)	147 (82-354)	0.687	120 (44-419)	0.366
Allergen test results, Postive: n (%)					
4-domain	54 (47.79)	11 (25.58)	0.012	14 (45.16)	0.795
3-domain (+control)	135 (46.55)	34 (39.08)	0.219	22 (47.83)	0.872
3-domain (+lung)	101 (52.06)	37 (45.68)	0.335	19 (47.50)	0.599
Comorbidities					
Allergic rhinitis, Yes: n (%)					
4-domain	58 (55.77)	26 (68.42)	0.175	19 (63.33)	0.460
3-domain (+control)	154 (61.85)	49 (62.03)	0.977	28 (70.00)	0.322
3-domain (+lung)	115 (59.59)	58 (70.73)	0.080	26 (56.52)	0.704
Chronic rhinosinusitis, Yes: n (%)					
4-domain	82 (74.55)	28 (70.00)	0.578	22 (70.97)	0.689
3-domain (+control)	204 (73.38)	60 (70.59)	0.613	29 (65.91)	0.303
3-domain (+lung)	141 (70.85)	54 (64.29)	0.275	34 (72.34)	0.840
Nasal polyposis, Yes: n (%)					
4-domain	63 (55.75)	19 (45.24)	0.244	18 (56.25)	0.960
3-domain (+control)	151 (52.98)	47 (54.02)	0.865	23 (50.00)	0.707
3-domain (+lung)	103 (50.00)	28 (32.56)	0.006	25 (50.00)	>0.999
Eczema/atopic dermatitis, Yes: n (%)					
4-domain	19 (16.96)	9 (21.43)	0.522	7 (21.88)	0.524
3-domain (+control)	54 (18.95)	12 (13.79)	0.271	11 (23.91)	0.431
3-domain (+lung)	45 (21.95)	18 (20.93)	0.847	10 (20.00)	0.764
Osteoporosis, Yes: n (%)					
4-domain	8 (10.26)	1 (3.23)	0.229	1 (5.26)	0.501
3-domain (+control)	25 (11.74)	5 (6.94)	0.252	2 (6.45)	0.381
3-domain (+lung)	13 (9.15)	6 (9.38)	0.960	1 (2.56)	0.172
Anxiety and/or depression, Yes: n (%)					
4-domain	8 (7.21)	1 (2.56)	0.294	7 (23.33)	0.011
3-domain (+control)	20 (7.27)	10 (11.76)	0.190	7 (6.28)	0.049
3-domain (+lung)	22 (11.06)	10 (12.50)	0.732	5 (10.42)	0.899

Table 10 (cont'd)

Patient characteristics at biologic initiation	Sustained	Semi-sustained	p*	Unsustained	p*
Therapies					
LAMA, Yes: n (%)					
4-domain	47 (45.63)	21 (52.50)	0.460	17 (58.62)	0.216
3-domain (+control)	144 (53.73)	48 (57.83)	0.512	23 (53.49)	0.976
3-domain (+lung)	77 (40.74)	37 (46.25)	0.403	24 (50.00)	0.247
LTRA, Yes: n (%)					
4-domain	56 (54.37)	23 (57.50)	0.735	17 (58.62)	0.684
3-domain (+control)	136 (50.75)	49 (59.04)	0.186	28 (65.12)	0.080
3-domain (+lung)	102 (53.97)	45 (56.25)	0.731	25 (52.08)	0.815
Theophylline, Yes: n (%)					
4-domain	3 (2.91)	3 (7.50)	0.219	2 (6.90)	0.321
3-domain (+control)	13 (4.85)	5 (60.2)	0.672	5 (11.63)	0.077
3-domain (+lung)	4 (2.12)	2 (2.50)	0.846	3 (6.25)	0.131
Macrolides, Yes: n (%)					
4-domain	5 (4.85)	2 (5.00)	0.971	4 (13.79)	0.092
3-domain (+control)	15 (5.60)	1 (1.20)	0.094	5 (11.63)	0.135
3-domain (+lung)	12 (6.35)	7 (8.75)	0.482	7 (14.58)	0.061
Biologic class initiated					
4-domain			0.532		0.677
Anti-IL5/5R	74 (64.91)	32 (72.73)		20 (62.50)	
Anti-IgE	21 (18.42)	5 (11.36)		6 (18.75)	
Anti-IL4Ralpha	19 (16.67)	7 (15.91)		6 (18.75)	
3-domain (+control)			0.650		0.497
Anti-IL5/5R	195 (66.78)	58 (65.91)		30 (63.83)	
Anti-IgE	49 (16.78)	18 (20.45)		11 (23.40)	
Anti-IL4Ralpha	48 (16.44)	12 (13.64)		6 (12.77)	
3-domain (+lung)			0.141		0.757
Anti-IL5/5R	131 (62.98)	54 (61.36)		32 (64.00)	
Anti-IgE	44 (21.15)	26 (29.55)		12 (24.00)	
Anti-IL4Ralpha	33 (15.87)	8 (9.09)		6 (12.00)	

*Comparing to the sustained remission group. Pearson's chi-squared tests were used to compare proportions, Student's t-tests were used to compare means, and Kruskal-Wallis tests were used to compare medians.

7.3 Objective 2

Remission criteria were met at Year 1 in 564/2,268 (24.9%) of patients for the four-domain definition, 1,020/2,645 (38.6%) of patients for the three-domain definition with asthma control, and 894/2,994 (29.9%) of patients for the three-domain definition with lung function.

Baseline patient characteristics are described in Table 1111 separately for patients who had reached remission in Year 1 and for those who had not, and compared using standardised mean differences (SMD). Differences between the two groups were notable (SMD>0.1) regarding BMI, tobacco smoking, age at asthma onset, asthma duration, exacerbation rates, LTOCS use, asthma control, and lung function. Patients who met remission at Year 1 had lower BMI, were less frequently smokers, were older at asthma onset and had shorter asthma duration, had lower exacerbation rates, were less frequently LTOCS users, and had better lung function than their counterparts. They also had higher blood eosinophil counts and higher FeNO concentrations. In terms of comorbidities, they more frequently had chronic rhinosinusitis, nasal polyposis, and less frequently had osteoporosis and anxiety and/or depression. They were less frequently LAMA, theophylline and macrolide users. Finally, the distribution of biologic class also varied between the two groups.

Table 11. Patient characteristics for patients in remission or not at Year 1 of follow-up.

Patient characteristics at biologic initiation	In remission	Not in remission	Absolute SMD
Demographics			
Age (years), Mean (SD)			
4-domain	54.9 (13.1)	55.1 (14.0)	0.015
3-domain (+control)	56.0 (13.4)	53.9 (14.2)	0.153
3-domain (+lung)	53 (13.8)	54.7 (14.2)	0.081
Sex, Female: n (%)			
4-domain	325 (57.62)	1,005 (58.98)	0.027
3-domain (+control)	583 (57.16)	995 (61.23)	0.083
3-domain (+lung)	528 (59.06)	1,245 (59.29)	0.005
BMI (kg/m^2), Mean (SD)			
4-domain	26.5 (4.9)	28.3 (6.2)	0.310
3-domain (+control)	26.7 (5.2)	28.5 (6.4)	0.306
3-domain (+lung)	27.2 (5.6)	28.3 (6.3)	0.174
Obesity (BMI ≥30 kg/m^2), Yes: n (%)			
4-domain	119 (21.14)	559 (32.82)	0.266
3-domain (+control)	221 (22.03)	556 (34.64)	0.283
3-domain (+lung)	238 (26.65)	684 (32.63)	0.131
Tobacco use, Never smoker: n (%)			
4-domain	380 (68.59)	1,044 (61.92)	0.140
3-domain (+control)	672 (66.67)	1,009 (62.83)	0.080
3-domain (+lung)	590 (66.97)	1,284 (61.67)	0.111
Clinical characteristics			
Age at asthma onset (years), Mean (SD)			
4-domain	34.3 (18.4)	30.9 (19.3)	0.182
3-domain (+control)	34.1 (18.9)	30.6 (19.2)	0.183
3-domain (+lung)	33.6 (18.4)	30.6 (19.3)	0.159
Asthma duration (years), Mean (SD)			
4-domain	20.6 (16.1)	24.3 (17.1)	0.225
3-domain (+control)	22.3 (17.0)	23.4 (16.7)	0.065
3-domain (+lung)	20.4 (15.9)	24.5 (17.1)	0.247
Number of exacerbations in the past year, Median (Q1-Q3)			
4-domain	2 (1-4)	2 (1-4)	0.094
3-domain (+control)	2 (1-4)	3 (1-5)	0.247
3-domain (+lung)	2 (1-3)	2 (1-4)	0.124
LTOCS use in the past year, Yes: n (%)			
4-domain	79 (18.20)	566 (40.54)	0.506
3-domain (+control)	139 (17.80)	587 (44.44)	0.601
3-domain (+lung)	106 (16.04)	627 (37.12)	0.492
Asthma control, Uncontrolled: n (%)			
4-domain	188 (58.02)	681 (74.34)	0.350
3-domain (+control)	319 (55.96)	667 (78.38)	0.492
3-domain (+lung)	285 (63.33)	708 (72.91)	0.207
Percent predicted FEV1 (%), Mean (SD)			
4-domain	86.6 (18.9)	70.8 (21.6)	0.778
3-domain (+control)	77.7 (21.2)	72.5 (22.3)	0.239
3-domain (+lung)	86.6 (18.5)	68.7 (20.9)	0.909
Percent predicted FEV1 (%), ≥80%: n (%)			
4-domain	242 (64.36)	384 (31.87)	0.688
3-domain (+control)	282 (43.52)	405 (36.52)	0.143
3-domain (+lung)	381 (63.61)	419 (27.26)	0.784
FEV1/FVC ratio, Mean (SD)			
4-domain	0.70 (0.11)	0.66 (0.13)	0.396
3-domain (+control)	0.67 (0.12)	0.67 (0.13)	0.036
3-domain (+lung)	0.72 (0.10)	0.65 (0.13)	0.580
FEV1/FVC ratio, ≥0.70: n (%)			
4-domain	216 (52.43)	500 (40.62)	0.238
3-domain (+control)	308 (43.44)	511 (44.20)	0.015
3-domain (+lung)	406 (59.71)	594 (37.45)	0.457

Table 11 (cont'd)

Patient characteristics at biologic initiation	In remission	Not in remission	Absolute SMD
Biomarkers			
Highest blood eosinophil count (cells/mcL), Median (Q1-Q3)			
4-domain	680 (352-1000)	500 (292-840)	0.165
3-domain (+control)	600 (320-982)	500 (300-820)	0.148
3-domain (+lung)	600 (300-950)	500 (300-800)	0.133
Latest FeNO concentration (ppb), Median (Q1-Q3)			
4-domain	37 (20-76)	30 (16-58)	0.261
3-domain (+control)	36 (19-70)	31 (16-61)	0.126
3-domain (+lung)	36 (19-70)	30 (16-58)	0.201
Latest serum total IgE concentration (IU/mL), Median (Q1-Q3)			
4-domain	179 (71-388)	156 (57-435)	0.007
3-domain (+control)	180 (71-399)	153 (55-434)	0.051
3-domain (+lung)	166 (68-371)	162 (59-427)	0.019
Allergen test results, Postive: n (%)			
4-domain	243 (44.18)	790 (48.59)	0.088
3-domain (+control)	453 (45.94)	740 (47.90)	0.039
3-domain (+lung)	393 (49.25)	941 (50.65)	0.028
Comorbidities			
Allergic rhinitis, Yes: n (%)			
4-domain	308 (61.60)	836 (58.54)	0.062
3-domain (+control)	535 (59.84)	787 (59.49)	0.007
3-domain (+lung)	496 (60.93)	1,004 (55.23)	0.116
Chronic rhinosinusitis, Yes: n (%)			
4-domain	369 (68.59)	929 (62.22)	0.134
3-domain (+control)	657 (67.45)	858 (62.49)	0.104
3-domain (+lung)	566 (66.28)	1,156 (61.33)	0.103
Nasal polyposis, Yes: n (%)			
4-domain	286 (51.44)	631 (37.69)	0.279
3-domain (+control)	483 (48.01)	598 (37.38)	0.216
3-domain (+lung)	401 (45.46)	712 (34.40)	0.227
Eczema/atopic dermatitis, Yes: n (%)			
4-domain	90 (16.25)	306 (18.25)	0.053
3-domain (+control)	161 (16.04)	292 (18.20)	0.058
3-domain (+lung)	153 (17.37)	352 (16.99)	0.010
Osteoporosis, Yes: n (%)			
4-domain	37 (8.58)	146 (11.78)	0.106
3-domain (+control)	76 (9.43)	135 (11.43)	0.066
3-domain (+lung)	57 (8.02)	202 (12.38)	0.144
Anxiety and/or depression, Yes: n (%)			
4-domain	47 (9.22)	210 (13.67)	0.140
3-domain (+control)	92 (9.85)	205 (14.12)	0.132
3-domain (+lung)	116 (14.16)	321 (16.68)	0.070

Table 11 (cont'd)

Patient characteristics at biologic initiation	In remission	Not in remission	Absolute SMD
Therapies			
LAMA, Yes: n (%)			
4-domain	256 (49.61)	895 (58.19)	0.173
3-domain (+control)	493 (52.84)	844 (57.41)	0.092
3-domain (+lung)	379 (46.16)	1,054 (55.07)	0.179
LTRA, Yes: n (%)			
4-domain	272 (52.71)	785 (51.04)	0.033
3-domain (+control)	484 (51.88)	749 (50.95)	0.018
3-domain (+lung)	444 (54.08)	989 (51.67)	0.048
Theophylline, Yes: n (%)			
4-domain	16 (3.10)	101 (6.57)	0.162
3-domain (+control)	33 (3.75)	107 (7.28)	0.155
3-domain (+lung)	20 (2.44)	114 (5.96)	0.176
Macrolides, Yes: n (%)			
4-domain	30 (5.81)	140 (9.11)	0.126
3-domain (+control)	56 (6.00)	146 (9.94)	0.146
3-domain (+lung)	61 (7.43)	239 (12.49)	0.170
Biologic class initiated			
4-domain			0.288
Anti-IL5/5R	337 (59.75)	1,093 (64.14)	
Anti-IgE	96 (17.02)	390 (22.89)	
Anti-IL4Ralpha	130 (23.05)	216 (12.68)	
Anti-TSLP	1 (0.18)	5 (0.29)	
3-domain (+control)			0.271
Anti-IL5/5R	602 (59.02)	1,077 (66.28)	
Anti-IgE	195 (19.12)	356 (21.91)	
Anti-IL4Ralpha	217 (21.27)	188 (11.57)	
Anti-TSLP	6 (0.59)	4 (0.25)	
3-domain (+lung)			0.260
Anti-IL5/5R	499 (55.82)	1312 (62.48)	
Anti-IgE	198 (22.15)	527 (25.10)	
Anti-IL4Ralpha	195 (21.81)	255 (12.14)	
Anti-TSLP	2 (0.22)	6 (0.29)	

SMD: Standardized mean difference.

Descriptive analysis

The distribution of clinical outcomes at each further year of follow-up (up to five years post-biologic initiation) in patients who had reached remission in Year 1 and those who had not are shown in Table 12 for the four-domain remission definition, in Table 13 for the three-domain definition with asthma control, and in Table 14 for the three-domain definition with lung function. Patients in remission at Year 1 consistently had better clinical outcomes at further years of follow-up compared to their counterparts, irrespective of the remission definition. For example, above 85% of patients in remission at Year 1 for the four-domain definition had no exacerbations in further years of follow-up (compared to less than 75% in patients not in remission at Year 1). Asthma was well controlled in 57% to 61% (compared to less than 41% in patients not in remission at Year 1), and above 98% remained LTOCS-free (compared to less than 85% in patients not in remission at Year 1). Lung function was also higher in patients in remission at Year 1, with their percent predicted FEV_1 being, on average, over 20 percentage points higher than that of their counterparts.

Table 12. Distribution of clinical outcomes by year of follow-up post-biologic initiation, by remission status at Year 1 (four-domain remission definition).

Clinical outcome and year of follow-up	Measure/category	In remission at Year 1 (N=564)		Not in remission at Year 1 (N=1,704)	
		N	Results	N	Results
Exacerbations					
Year 2	None: n(%)	490	440 (89.80)	1,308	828 (63.30)
	1: n(%)		39 (7.96)		240 (18.35)
	2-3: n(%)		11 (2.24)		175 (13.38)
	4+: n(%)		0 (0.00)		65 (4.97)
Year 3	None: n(%)	322	287 (89.13)	960	681 (70.94)
	1: n(%)		24 (7.45)		150 (15.62)
	2-3: n(%)		8 (2.48)		104 (10.83)
	4+: n(%)		3 (0.93)		25 (2.60)
Year 4	None: n(%)	186	172 (92.47)	674	512 (75.96)
	1: n(%)		11 (5.91)		86 (12.76)
	2-3: n(%)		3 (1.61)		53 (7.86)
	4+: n(%)		0 (0.0)		23 (3.41)
Year 5	None: n(%)	115	104 (90.43)	461	352 (76.36)
	1: n(%)		9 (7.83)		64 (13.88)
	2-3: n(%)		2 (1.74)		32 (6.94)
	4+: n(%)		0 (0.00)		13 (2.82)
LTOCS use (continued use from previous year and did not stop, or resumed use)					
Year 2	Yes: n (%)	501	4 (0.80)	1,486	296 (19.92)
Year 3	Yes: n (%)	337	5 (1.48)	1,110	210 (18.92)
Year 4	Yes: n (%)	207	3 (1.45)	807	139 (17.22)
Year 5	Yes: n (%)	129	3 (2.33)	575	99 (17.22)
Asthma control					
Year 2	Uncontrolled: n(%)	474	50 (10.55)	1,380	520 (37.68)
	Partly controlled: n(%)		85 (17.93)		347 (25.14)
	Well controlled: n(%)		339 (71.52)		513 (37.17)
Year 3	Uncontrolled: n(%)	321	38 (11.84)	981	361 (36.80)
	Partly controlled: n(%)		48 (14.95)		224 (22.83)
	Well controlled: n(%)		235 (73.21)		396 (40.37)
Year 4	Uncontrolled: n(%)	196	22 (11.22)	687	258 (37.55)
	Partly controlled: n(%)		35 (17.86)		138 (20.09)
	Well controlled: n(%)		139 (70.92)		291 (42.36)
Year 5	Uncontrolled: n(%)	131	19 (14.50)	494	192 (38.87)
	Partly controlled: n(%)		25 (19.08)		91 (18.42)
	Well controlled: n(%)		87 (66.41)		211 (42.71)
Percent predicted FEV_1					
Year 2	Mean (SD)	444	96.4 (16.3)	1,331	75.3 (22.1)
	≥80%		388 (87.39)		552 (41.47)
Year 3	Mean (SD)	303	97.8 (17.3)	940	76.6 (22.0)
	≥80%		262 (86.47)		411 (43.72)
Year 4	Mean (SD)	199	95.8 (16.0)	675	76.8 (22.2)
	≥80%		171 (85.93)		294 (43.56)
Year 5	Mean (SD)	121	94.4 (13.6)	505	76.0 (21.2)
	≥80%		105 (86.78)		212 (41.98)

Table 13. Distribution of clinical outcomes by year of follow-up post-biologic initiation, by remission status at Year 1 (three-domain remission definition with asthma control).

Clinical outcome and year of follow-up	Measure/category	In remission at Year 1 (N=1,020)		Not in remission at Year 1 (N=1,625)	
		N	Results	N	Results
Exacerbations					
Year 2	None: n(%)	875	770 (88.00)	1,214	697 (57.41)
	1: n(%)		83 (9.49)		237 (19.52)
	2-3: n(%)		22 (2.51)		193 (15.90)
	4+: n(%)		0 (0.00)		87 (7.17)
Year 3	None: n(%)	595	525 (88.24)	864	569 (65.86)
	1: n(%)		51 (8.57)		149 (17.25)
	2-3: n(%)		14 (2.35)		111 (12.85)
	4+: n(%)		5 (0.84)		35 (4.05)
Year 4	None: n(%)	369	332 (89.97)	607	433 (71.33)
	1: n(%)		31 (8.40)		82 (13.51)
	2-3: n(%)		6 (1.63)		64 (10.54)
	4+: n(%)		0 (0.00)		28 (4.61)
Year 5	None: n(%)	223	203 (91.03)	408	301 (73.77)
	1: n(%)		16 (7.17)		59 (14.46)
	2-3: n(%)		4 (1.79)		33 (8.09)
	4+: n(%)		0 (0.00)		15 (3.68)
LTOCS use (continued use from previous year and did not stop, or resumed use)					
Year 2	Yes: n (%)	896	8 (0.89)	1,414	328 (23.20)
Year 3	Yes: n (%)	620	9 (1.45)	1,026	228 (22.22)
Year 4	Yes: n (%)	400	5 (1.25)	746	156 (20.91)
Year 5	Yes: n (%)	246	5 (2.03)	528	108 (20.45)
Asthma control					
Year 2	Uncontrolled: n(%)	858	87 (10.14)	1,296	549 (42.36)
	Partly controlled: n(%)		176 (20.51)		318 (24.54)
	Well controlled: n(%)		595 (69.35)		429 (33.10)
Year 3	Uncontrolled: n(%)	580	73 (12.59)	924	373 (40.37)
	Partly controlled: n(%)		101 (17.41)		208 (22.51)
	Well controlled: n(%)		406 (70.00)		343 (37.12)
Year 4	Uncontrolled: n(%)	371	47 (12.67)	640	256 (40.00)
	Partly controlled: n(%)		68 (18.33)		129 (20.16)
	Well controlled: n(%)		256 (69.00)		255 (39.84)
Year 5	Uncontrolled: n(%)	247	34 (13.77)	455	190 (41.76)
	Partly controlled: n(%)		51 (20.65)		79 (17.36)
	Well controlled: n(%)		162 (65.59)		186 (40.88)
Percent predicted FEV_1					
Year 2	Mean (SD)	752	86.7 (21.0)	1,158	77.3 (23.1)
	≥80%		480 (63.83)		549 (47.41)
Year 3	Mean (SD)	527	87.9 (21.4)	818	78.2 (23.0)
	≥80%		344 (65.28)		391 (47.80)
Year 4	Mean (SD)	354	86.2 (20.4)	605	78.6 (23.0)
	≥80%		225 (63.56)		295 (48.76)
Year 5	Mean (SD)	231	83.8 (19.3)	441	78.0 (22.1)
	≥80%		139 (60.17)		208 (47.17)

Table 14. Distribution of clinical outcomes by year of follow-up post-biologic initiation, by remission status at Year 1 (three-domain remission definition with lung function).

Clinical outcome and year of follow-up	Measure/category	In remission at Year 1 (N=894)		Not in remission at Year 1 (N=2,100)	
		N	Results	N	Results
Exacerbations					
Year 2	None: n(%)	788	685 (86.93)	1,629	999 (61.33)
	1: n(%)		80 (10.15)		310 (19.03)
	2-3: n(%)		23 (2.92)		234 (14.36)
	4+: n(%)		0 (0.00)		86 (5.28)
Year 3	None: n(%)	536	462 (86.19)	1,260	873 (69.29)
	1: n(%)		55 (10.26)		202 (16.03)
	2-3: n(%)		16 (2.99)		142 (11.27)
	4+: n(%)		3 (0.56)		43 (3.41)
Year 4	None: n(%)	338	297 (87.87)	925	666 (72.00)
	1: n(%)		27 (7.99)		140 (15.14)
	2-3: n(%)		10 (2.96)		89 (9.62)
	4+: n(%)		4 (1.18)		30 (3.24)
Year 5	None: n(%)	228	202 (88.60)	676	498 (73.67)
	1: n(%)		21 (9.21)		104 (15.38)
	2-3: n(%)		5 (2.19)		53 (7.84)
	4+: n(%)		0 (0.00)		21 (3.11)
LTOCS use (continued use from previous year and did not stop, or resumed use)					
Year 2	Yes: n (%)	804	6 (0.75)	1,856	330 (17.78)
Year 3	Yes: n (%)	562	6 (1.07)	1,436	238 (16.57)
Year 4	Yes: n (%)	366	4 (1.09)	1,089	160 (14.69)
Year 5	Yes: n (%)	248	4 (1.61)	811	112 (13.81)
Asthma control					
Year 2	Uncontrolled: n(%)	625	125 (20.00)	1,402	515 (36.73)
	Partly controlled: n(%)		118 (18.88)		345 (24.61)
	Well controlled: n(%)		382 (61.12)		542 (38.66)
Year 3	Uncontrolled: n(%)	430	78 (18.14)	1,026	381 (37.13)
	Partly controlled: n(%)		74 (17.21)		237 (23.10)
	Well controlled: n(%)		278 (64.65)		408 (39.77)
Year 4	Uncontrolled: n(%)	271	52 (19.19)	746	293 (39.28)
	Partly controlled: n(%)		53 (19.56)		149 (19.97)
	Well controlled: n(%)		166 (61.25)		304 (40.75)
Year 5	Uncontrolled: n(%)	203	51 (25.12)	551	224 (40.65)
	Partly controlled: n(%)		36 (17.73)		104 (18.87)
	Well controlled: n(%)		116 (57.14)		223 (40.47)
Percent predicted FEV_1					
Year 2	Mean (SD)	685	95.6 (15.7)	1,588	72.8 (21..9)
	≥80%		593 (86.57)		571 (35.96)
Year 3	Mean (SD)	477	96.3 (17.0)	1,153	73.7 (22.1)
	≥80%		408 (85.53)		429 (37.21)
Year 4	Mean (SD)	327	95.7 (15.7)	848	73.0 (21.6)
	≥80%		280 (85.63)		307 (36.20)
Year 5	Mean (SD)	228	93.9 (15.0)	633	72.4 (21.5)
	≥80%		188 (82.46)		219 (34.60)

Association analysis

Association between outcome and presence or absence of remission at Year 1 (explanatory variable) were modelled for each further year of follow-up (up to five years post-biologic initiation) using negative binomial regression for the count of exacerbations in the year, logistic regression for presence/absence of exacerbations, LTOCS use, partly/well controlled asthma, and ppFEV$_1$ ≥80% outcomes, and linear regressions for ppFEV$_1$ as continuous outcome. All association analyses were minimally adjusted for age at biologic initiation, sex, and geographical setting, and further adjusted for the pre-biologic measure of the outcome of interest.

Patients in remission at Year 1 experienced less exacerbations in further years of follow-up, with rate ratios (RR) in the range of 2 to 5 depending on the time since biologic initiation and the remission definition (Figure 4). This translates in patients in remission at Year 1 having 2 to 5 times less exacerbations in following years than their counterparts. Adjusting for pre-biologic exacerbation rates had little impact on the results. The odds of having no exacerbations the following years were in the range of 2 to 5 times higher in patients who reached remission at Year 1 than in those who did not, and adjusting for pre-biologic exacerbation rates had little impact on the results for these analyses too (Figure 5). Minimally adjusted results were of similar range in this subset of the study population with available pre-biologic exacerbations rates compared to the population without this restriction (Appendix 5: Minimally adjusted association analysis results without restricting on study population with available pre-biologic measure of the outcome of interest

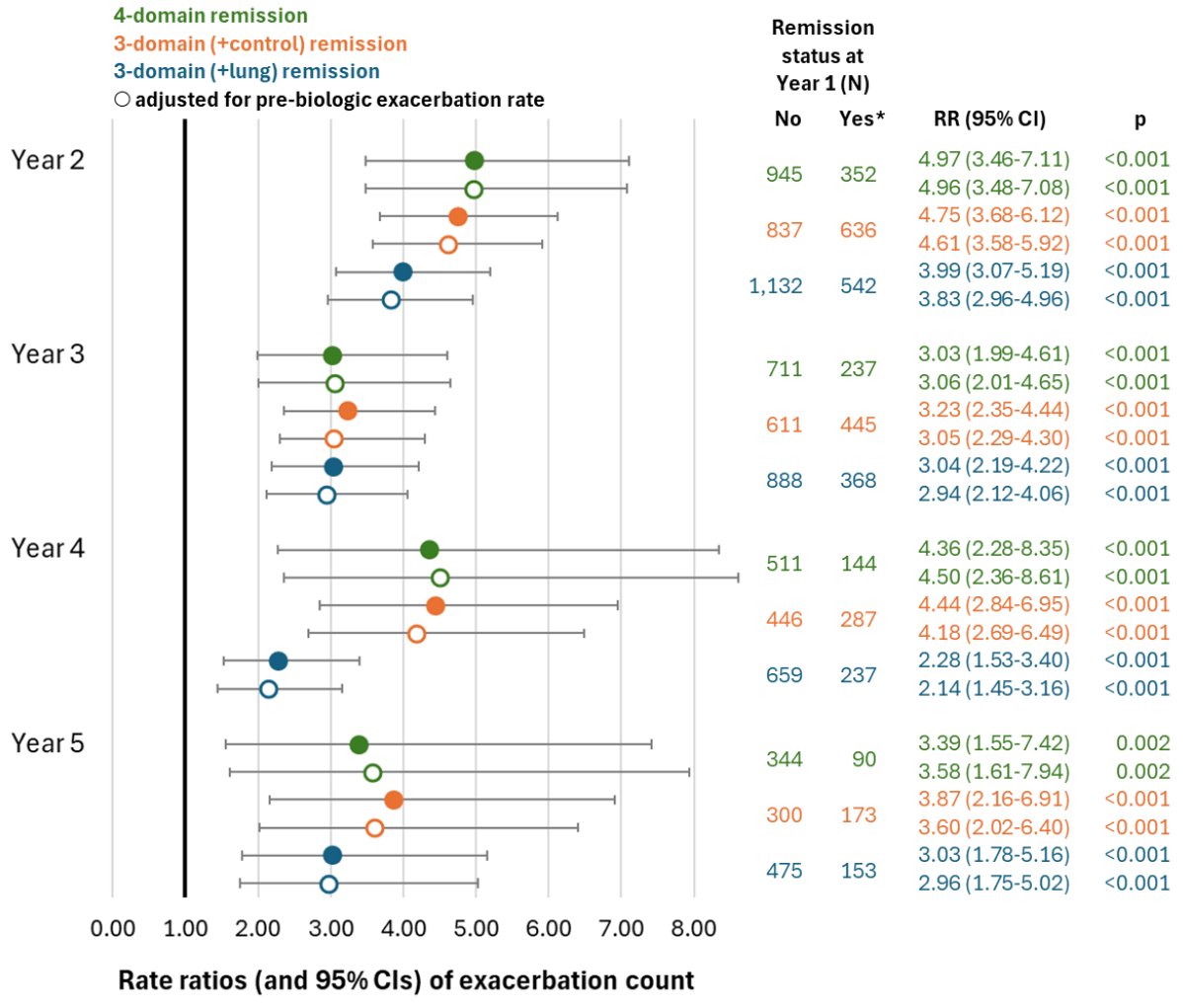

Figure 4. Association between remission status at Year 1 and exacerbation rates in further years of follow-up, adjusting for age, sex, and geographical setting, +/- pre-biologic exacerbation rates.

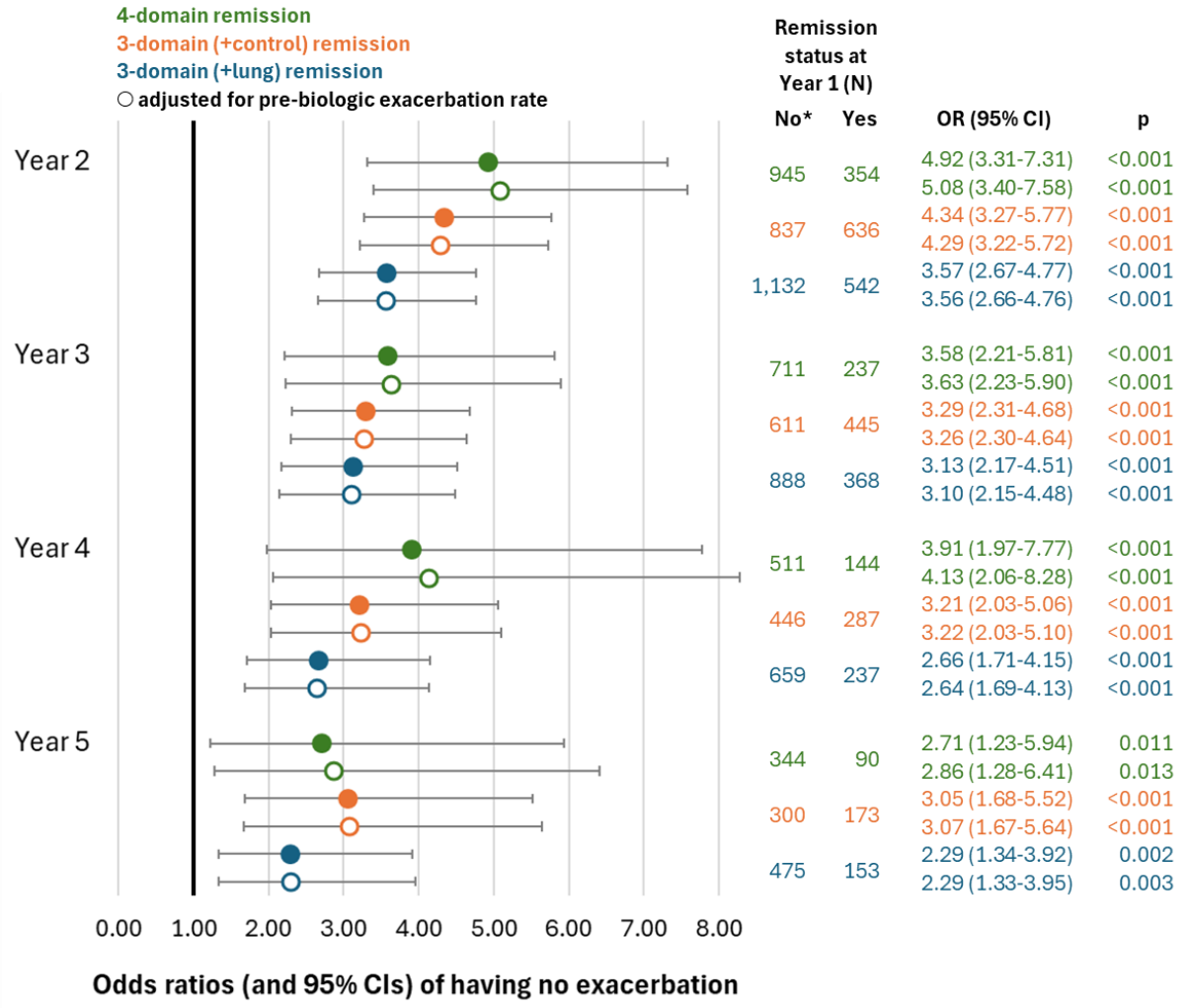

Figure 5. Association between remission status at Year 1 and occurrence (yes/no) of exacerbations in further years of follow-up, adjusting for age, sex, and geographical setting, +/- pre-biologic exacerbation rates.

Compared to patients who did not reach remission at Year 1, patients in remission at Year 1 had 2 to 4 times higher odds of having well controlled asthma in further years of follow-up (Figure 6). The ORs were higher when asthma control was part of the remission definition at Year 1 and tended to decrease with increasing time since biologic initiation. Adjusting for pre-biologic asthma control score slightly attenuated the associations. Trends were similar when the outcome was having well or partly asthma controlled (Appendix 6: Association between remission status at Year 1 and having well or partly controlled asthma in further years of follow-up, adjusting for age, sex, and geographical setting, +/- pre-biologic asthma control). Minimally adjusted results were of similar range in this subset of the study population with available pre-biologic asthma control assessment compared to the population without this restriction

(Appendix 5: Minimally adjusted association analysis results without restricting on study population with available pre-biologic measure of the outcome of interest

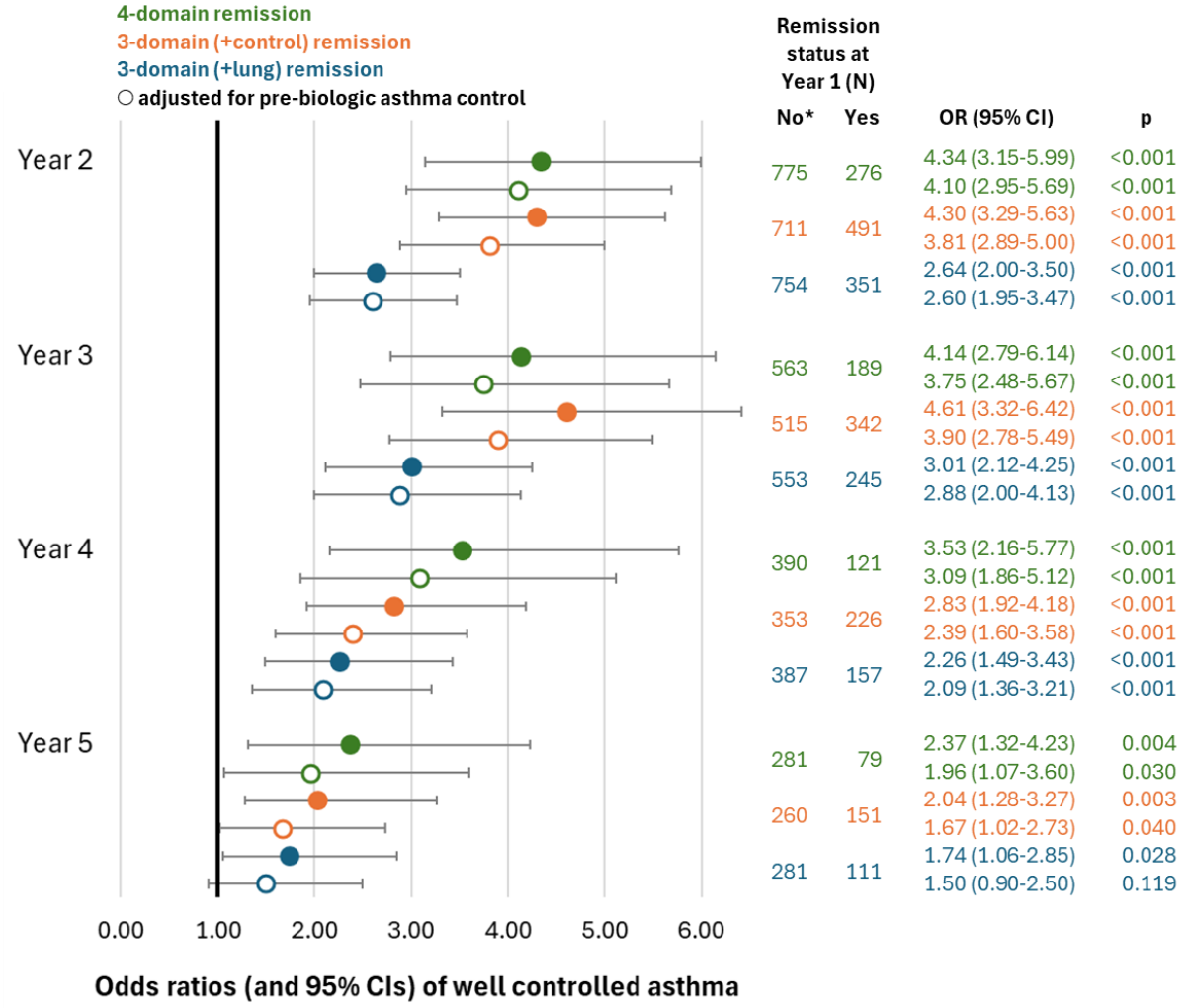

Figure 6. Association between remission status at Year 1 and having well controlled asthma in further years of follow-up, adjusting for age, sex, and geographical setting, +/- pre-biologic asthma control.

Patients who were in remission at Year 1 also had better lung function in further years of follow-up compared to patients who were not in remission at Year 1. When lung function was a component of the remission definition at Year 1 and adjusting for pre-biologic percent predicted FEV_1, patients in remission had approximately 7 to 11 percentage points higher percent predicted FEV_1 (Figure 7) and 5 to 6 times higher odds of having FEV_1 ≥80% of predicted at follow-up years (Figure 8). The estimates remained of same magnitude over time since biologic initiation. When lung function was not a criterion for reaching remission, percent predicted FEV_1 was still numerically higher in patients who were in remission at Year 1

compared to those who were not, although the differences between the two groups of patients were smaller than when lung function is part of the remission definition. Adjusting for pre-biologic percent predicted FEV_1 had a large impact on the results. Nevertheless, the estimates remained substantial, indicating that remission at Year 1 was independently associated with lung function in further years of follow-up.

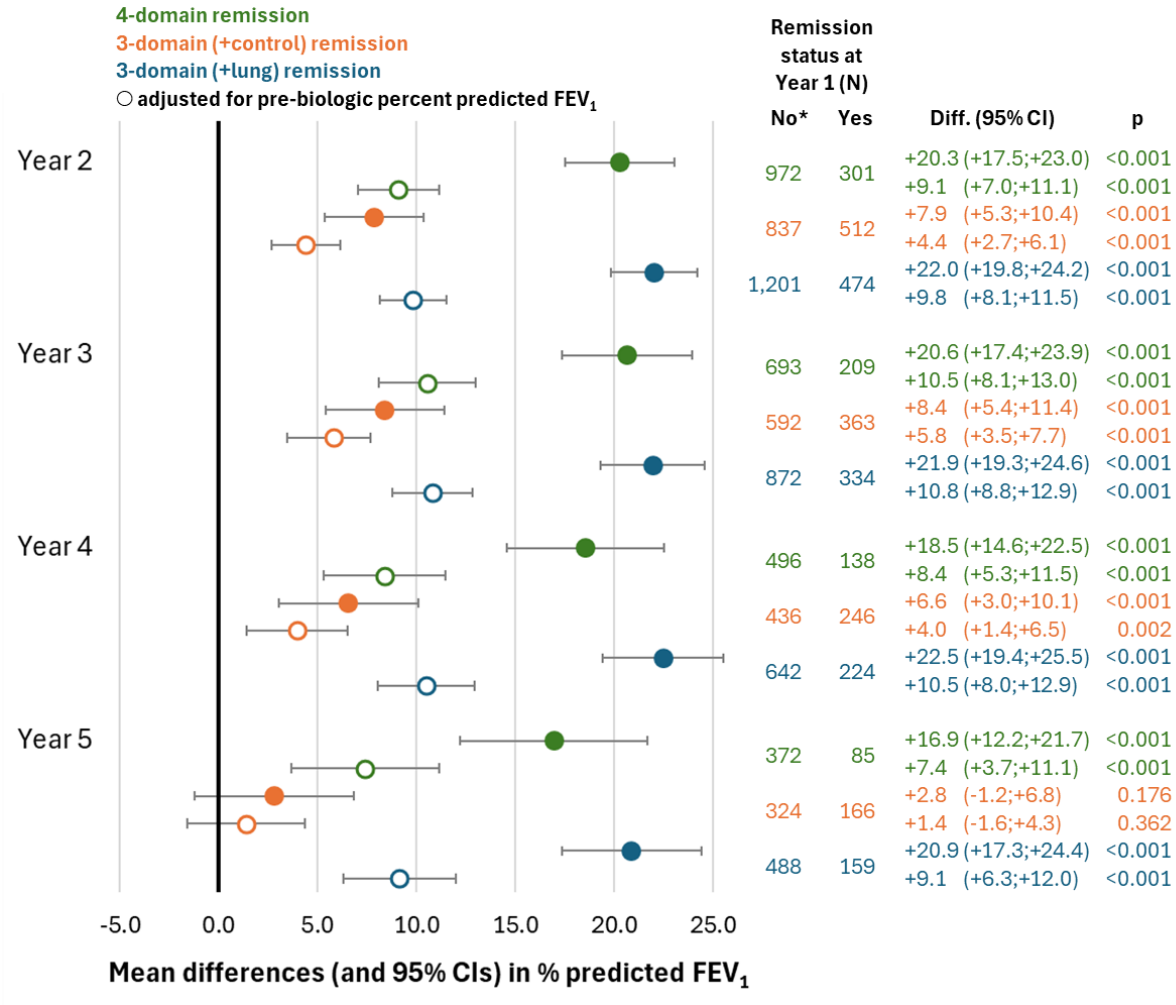

Figure 7. Association between remission status at Year 1 and percent predicted FEV_1 in further years of follow-up, adjusting for age, sex, and geographical setting, +/- pre-biologic percent predicted FEV_1.

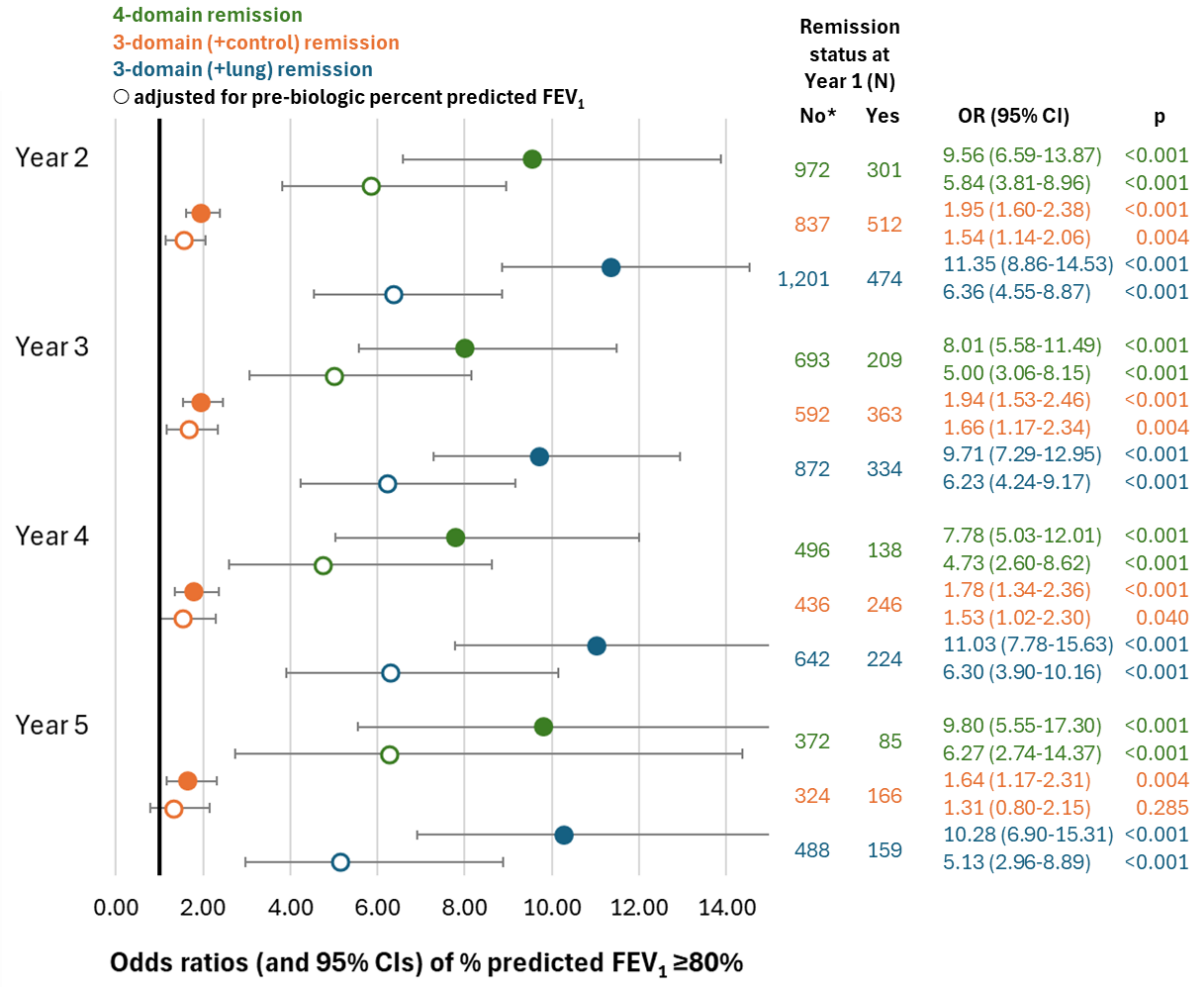

Figure 8. Association between remission status at Year 1 and having percent predicted FEV_1 ≥80% in further years of follow-up, adjusting for age, sex, and geographical setting, +/- pre-biologic percent predicted FEV_1.

Lastly, compared to patients who did not reach remission at Year 1, patients in remission at Year 1 had higher odds of not using LTOCS in further years of follow-up (Figure 9). The odds ratios (OR) were in globally above 5, with large statistical instability considering the low numbers of patients resuming or starting LTOCS after one year of follow-up (Table 12, Table 13, Table 14). Adjusting for pre-biologic LTOCS use attenuated the associations, although results remained significant. A trend towards lower ORs as time since biologic initiation increased was observed, indicating that patients not reaching remission in Year 1 still had opportunities to stop using LTOCS in further years of follow-up.

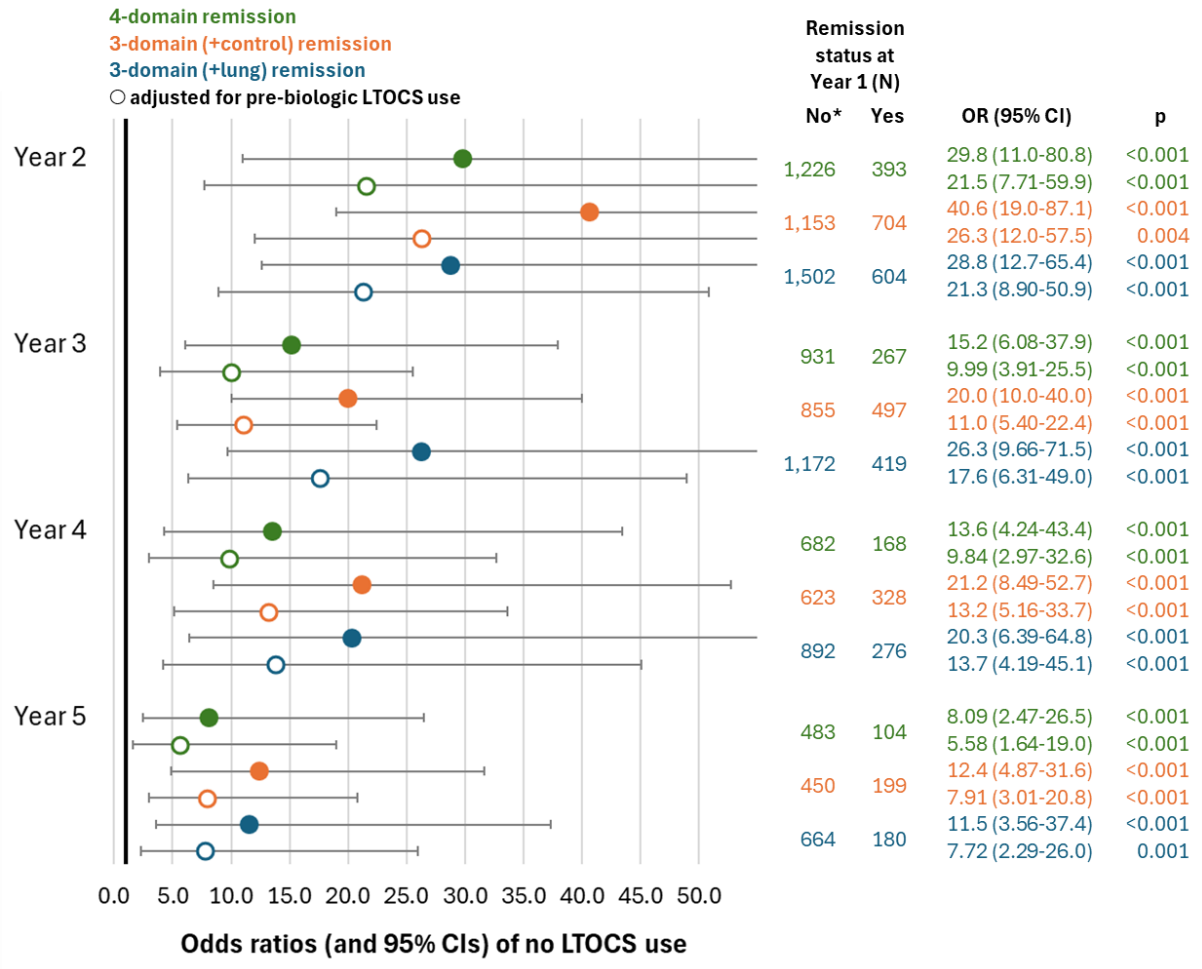

Figure 9. Association between remission status at Year 1 and LTOCS use in further years of follow-up, adjusting for age, sex, and geographical setting, +/- pre-biologic LTOCS use.

To investigate whether being in remission at Year 1 informs on longer-term clinical outcomes above and beyond that due to differences in baseline patient characteristics, models that included patient characteristics potentially associated with remission at Year 1 were compared with models that included these variables plus remission status at Year 1 (nested models). Baseline patient characteristics included in the models were: age, sex, geographical setting, smoking status, percent predicted FEV_1, FEV_1/FVC ratio, asthma control, exacerbation count, LTOCS use, asthma duration, obesity, anxiety/depression, nasal polyposis, blood eosinophil count, and FeNO concentration. Nested logistic and negative binomial models were compared through log-likelihood ratio tests and nested linear models were compared through F-tests. Resulting p-values are available in Table 15, for all clinical outcomes by years of follow-up and remission definition. P-values were <0.05 for most comparisons, indicating that globally

remission status at Year 1 had an effect on longer-term clinical outcomes independently of baseline patient characteristics.

Table 15. P-values* comparing models with baseline patient characteristics only as explanatory variables to models additionally including remission status at Year 1, by clinical outcomes, years post-biologic initiation, and remission definition.**

Explanatory variable	Outcomes	Year 2	Year 3	Year 4	Year 5
4-domain remission status at Year 1	Exacerbation rates	<0.001	0.038	0.009	0.240
	Absence of exacerbation	<0.001	0.002	<0.001	0.218
	Well/partly controlled asthma	<0.001	0.196	0.037	0.340
	Well controlled asthma	<0.001	0.002	0.238	0.075
	Continous percent predicted FEV_1	<0.001	<0.001	<0.001	0.007
	Percent predicted FEV_1 ≥80%	<0.001	0.007	<0.001	<0.001
	No LTOCS use (or stopping using)	<0.001	0.229	0.597	0.308
3-domain remission status (with asthma control) at Year 1	Exacerbation rates	<0.001	0.004	0.007	0.013
	Absence of exacerbation	<0.001	0.002	0.001	0.040
	Well/partly controlled asthma	<0.001	0.003	0.012	0.260
	Well controlled asthma	<0.001	<0.001	0.249	0.088
	Continous percent predicted FEV_1	0.005	0.010	0.004	0.026
	Percent predicted FEV_1 ≥80%	0.005	0.272	0.003	<0.001
	No LTOCS use (or stopping using)	<0.001	0.028	0.071	0.028
3-domain remission status (with lung function) at Year 1	Exacerbation rates	<0.001	0.002	<0.001	0.025
	Absence of exacerbation	<0.001	<0.001	<0.001	0.029
	Well/partly controlled asthma	0.001	0.077	0.048	0.447
	Well controlled asthma	0.019	0.008	0.074	0.026
	Continous percent predicted FEV_1	<0.001	<0.001	<0.001	<0.001
	Percent predicted FEV_1 ≥80%	<0.001	<0.001	<0.001	<0.001
	No LTOCS use (or stopping using)	<0.001	0.022	0.280	0.219

*F-tests for continuous percent predicted FEV_1 outcome, log-likelihood ratio tests for all other outcomes.
**Age, sex, geographical setting, smoking status, percent predicted FEV_1, FEV_1/FVC ratio, asthma control, exacerbation count, LTOCS use, asthma duration, obesity, anxiety/depression, nasal polyposis, blood eosinophil count, and FeNO concentration.

Biologic switching/stopping

In this study population, 28.98% (973/3,357) patients had switched or stopped biologics in the five-year period following biologic initiation. This was most common in patients who were not in remission at Year 1 (34.24%, 35.99%, and 34.34%, for the four-domain, the three-domain with control, and with lung, respectively) than in patients who met remission at Year 1 (17.29%, 17.54%, and 19.35%, respectively). Association analyses were repeated restricting the study population to patients who had maintained the same biologic throughout the study period (ie, for up to at least 2 to 5 years depending on the time point of interest). Results showed limited variations compared to the main results presented in Figures 4 to 9.

8.0 Summary and Discussion

This study has investigated the stability of remission over up to 5 years of follow-up in adult patients with severe asthma treated with a biologic therapy in the international and real-word ISAR setting. We found that the remission status achieved in the first year following biologic initiation was relatively stable over time, i.e. losing remission or changing to remission in further years of follow-up were uncommon profiles. Consequently, the remission status in the first year of follow-up was a strong correlate of longer-term clinical outcomes of asthma.

To our knowledge, our study is the first attempt to investigate the effect of early remission on long-term clinical outcomes of asthma in the context of treatment with biologic therapies. It was made possible by the large number of patients enrolled in ISAR and the continuous collection of longitudinal data since ISAR inception in 2017, leading to growing numbers of patients enrolled in the registry with available data on key clinical outcomes over several years of follow-up after biologic initiation. Exploring a range of multi-domain remission criteria, we found that, in patients who met remission criteria in the first year following biologic initiation, approximately 60% sustained remission over 3 years, 50% over 4 years, and 40% over 5 years. These proportions were the highest when lung function was omitted from the remission criteria, and the lowest when optimization of lung function as defined by FEV_1 percent of predicted of at least 80% was a criterion. The level of symptom control criterion (well or partly controlled vs. well controlled asthma only) and using a relaxed criterion for lung function (allowing stabilization instead of imposing optimization as defined above) also led to slight variations in the estimated proportions of patients with sustained remission. The set of estimates were however largely consistent. Remaining in remission from year to year was interestingly more likely in patients who were in remission in the first year following biologic initiation than in patients who were not, indicating that the remission status in the first year has an effect on long-term clinical outcomes of asthma.

Patient characteristics associated with sustaining remission over time were no different from those previously reported as associated with the likelihood of remission in the first year following biologic therapy initiation. Namely, better asthma symptom control, better lung function, shorter asthma duration, no tobacco smoking, lower BMI, and having no anxiety/depression history correlated with higher probabilities of remaining in remission in further years of follow-up (McDowell et al., 2023; Hansen et al. 2024; Perez-de-Llano et al., 2024; Hansen et al., 2025, Shackleford et al., 2025). These associations were replicated in the current study (Table 11). Here we also detected associations between higher likelihood of remission in the first year of follow-up and higher blood eosinophil counts, higher FeNO concentrations, lower exacerbation rates, and no use of LTOCS, LAMA, theophylline or

macrolides but these factors were not significantly associated with sustainability remission patterns, although this could be due to a lack of statistical power. In terms of potentially T2-related comorbidities, diagnoses of chronic rhinosinusitis with or without nasal polyps were associated with higher likelihood of remission in the first year, aligning with stronger response to biologic therapy in these patients reported by Wechsler et al. (2024), but these factors where not significantly associated with sustained remission in our study population. We detected that males had higher chance of sustaining remission over time, which was also shown as positively associated with remission in the first year following biologic initiation in a previous study (McDowell et al., 2023).

Meeting remission criteria in the first year following biologic therapy initiation was associated with better key clinical outcomes of asthma in further years of follow-up, even after adjusting for pre-biologic measures of corresponding outcomes. Varying across the remission definitions used, patients in remission in the first year following biologic initiation, and compared to those who were not, had 3 to 5 times less exacerbations, 2 to 4 times higher odds of having well controlled asthma, 7 to 10 percentage point higher FEV_1 percent of predicted value, and >5 times lower odds of using LTOCS in follow-up years. These numerically strong and statistically significant results indicate that the remission status in the first year following biologic initiation is key when trying to predict the long-term asthma outcomes in patients with severe asthma, irrespective of the remission definition. Of strong interest, the remission status in the first year following biologic initiation informed on the long-term clinical outcomes of asthma over and above differences in baseline patient characteristics that correlate with remission status in the first year following biologic initiation. This indicates that early remission might be a key predictor of a successful biologic therapy initiation in the long run, and that failing meeting remission criteria in the first year following biologic initiation is a poor outcome that might predict limited chance of reaching remission thereafter. In other words, the remission status in the first year following biologic initiation is a marker of the long-term success of the therapy, implying that lack of early response to the therapy is a marker of difficulties for the patients and their physicians to find alternatives for better outcomes.

While surpassing any RCT or real-world studies so far since none investigated clinical outcomes of asthma more than a year after biologic initiation, our study had several limitations. First, the proportion of patients with missing data was large and this might have biased the estimates of sustaining remission proportions if lack of data was associated with lower or higher likelihood of sustaining remission. This is unfortunately not possible to assess in the study population selected for our study. Additional longitudinal data collection within ISAR, with information on the reasons why data are missing will be able to investigate this point.

However, the ISAR setting is currently the largest database available to date for assessing these long-term remission patterns. Moreover, the association analyses conducted are unlikely to be biased by missing data, as shown by consistent results across remission definitions where the study population varied by geographical setting and calendar time. For example, the USA-NJH setting had limited information on asthma symptom control and hence did not contribute much to the analyses when asthma symptom control was a criterion of the remission definition, and calendar time that overlap with the COVID-19 pandemics lacked lung function assessment for obvious reasons.

Another limitation of this study is the intention-to-treat design, in that stopping or switching biologics was not accounting for in our analyses. This bias could go both ways, in that excluding stoppers would inflate the sustained remission prevalence (as stopping might be due to lack of efficiency), while switching biologics could inflate the proportions of patients remaining in remission from year to year (when switching was decided due to losing remission or response). This will warrant further investigation; however, the current approach is conservative in terms of assessing remission sustainability. Chances of reaching remission in further years of follow-up when switching from one biologic to another is an endeavour that is warranted, to investigate whether this would correlate with the subsets of patients who switched from no remission to remission over time.

Finally, here we did not consider the class of biologics initiated. This again could lead to underestimating or overestimating the global proportion of patient sustaining remission over time if the biologic class is correlated with that outcome. Again, this warrants further investigation, as the first choice of biologic class is both linked to severe asthma phenotype and biologic agent access in each geographic setting.

9.0 Conclusion

In adult patients with severe asthma who initiated biologic therapy, achieving remission in the first year of follow-up was strongly associated with better asthma-related outcomes in further years of follow-up. This warrants a close monitoring of asthma remission criteria early after biologic initiation, as meeting these criteria correlates with longer-term outcomes of asthma.

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, have formed the Advisory Group.

No	Name	Country / Institution
1	Jorge Máspero	Argentina
2	Benjamin Emmanuel	AstraZeneca
3	Andrew N. Menzies-Gow	AstraZeneca
4	Amit D. Parulekar	AstraZeneca
5	Trung N. Tran	AstraZeneca
6	Tancy C. Zhang	AstraZeneca
7	Peter G. Gibson	Australia
8	Mark Hew	Australia
9	Matthew J. Peters	Australia
10	Florence Schleich	Belgium
11	Paulo Márcio Pitrez	Brazil
12	George C. Christoff	Bulgaria
13	Todor A. Popov	Bulgaria
14	Simon Couillard	Canada
15	Carlos A. Torres-Duque	Colombia
16	Celeste M. Porsbjerg	Denmark
17	Ivan Cherrez-Ojeda	Ecuador
18	Alan Altraja	Estonia
19	Arnaud Bourdin	France
20	Camille Taillé	France
21	Christian Taube	Germany
22	Maria Kallieri	Greece
23	Konstantinos Kostikas	Greece
24	Nikolaos G. Papadopoulos	Greece
25	Sundeep Salvi	India
26	Richard W. Costello	Ireland
27	Patrick D. Mitchell	Ireland
28	Giorgio Walter Canonica	Italy
29	Enrico Heffler	Italy
30	Takashi Iwanaga	Japan
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13.0 List of Tables and Figures

14.0 Appendices

14.1 Appendix 1: Patient disposition by geographical setting

Suppl. Table 1: Patient disposition by geographical setting.

	Overall		Argentina		Belgium		Brazil		Bulgaria	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total patients considered for inclusion	11,798	-	62	-	296	-	200	-	66	-
Sequential exclusions										
Age <18	274	(2.3)	0	(0.0)	5	(1.7)	30	(15.0)	0	(0.0)
Missing biologic initiation date	1,114	(9.4)	7	(11.3)	0	(0.0)	18	(9.0)	0	(0.0)
Biologic initiated less than a year before dataset closure date (31-07-2025)	169	(1.4)	0	(0.0)	3	(1.0)	6	(3.0)	0	(0.0)
Less than 1 year of follow-up	1,882	(16.0)	19	(30.6)	53	(17.9)	28	(14.0)	32	(48.5)
Missing data for both 3-domain remission definitions at 1st year of follow-up	4,046	(34.3)	25	(40.3)	111	(37.5)	92	(46.0)	28	(42.4)
Missing data for all 4 domains in the 2nd year of follow-up	935	(7.9)	11	(17.7)	19	(6.4)	15	(7.5)	4	(6.1)
Missing age	6	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Missing sex	1	(<0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Eligible	3,371	(28.6)	0	(0.0)	105	(35.5)	11	(5.5)	2	(3.0)

Suppl. Table 1 (cont'd).

	Canada		Colombia		Denmark		Estonia		Greece	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total patients considered for inclusion	443	-	256	-	1,362	-	29	-	117	-
Sequential exclusions										
Age <18	1	(0.2)	8	(3.1)	17	(1.2)	0	(0.0)	0	(0.0)
Missing biologic initiation date	10	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)
Biologic initiated less than a year before dataset closure date (31-07-2025)	0	(0.0)	2	(0.8)	23	(1.7)	0	(0.0)	0	(0.0)
Less than 1 year of follow-up	29	(6.5)	25	(9.8)	88	(6.5)	7	(24.1)	30	(25.6)
Missing data for both 3-domain remission definitions at 1st year of follow-up	290	(65.5)	127	(49.6)	241	(17.7)	3	(10.3)	37	(31.6)
Missing data for all 4 domains in the 2nd year of follow-up	15	(3.4)	14	(5.5)	154	(11.3)	18	(62.1)	26	(22.2)
Missing age	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Missing sex	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Eligible	98	(22.1)	80	(31.2)	839	(61.6)	1	(3.4)	23	(19.7)

Suppl. Table 1 (cont'd).

	India		Ireland-Beaumont		Ireland-Tallaght		Italy		Japan	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total patients considered for inclusion	8	-	3	-	53	-	2,492	-	158	-
Sequential exclusions										
Age <18	0	(0.0)	0	(0.0)	0	(0.0)	26	(1.0)	6	(3.8)
Missing biologic initiation date	3	(37.5)	0	(0.0)	0	(0.0)	0	(0.0)	5	(3.2)
Biologic initiated less than a year before dataset closure date (31-07-2025)	0	(0.0)	0	(0.0)	0	(0.0)	73	(2.9)	0	(0.0)
Less than 1 year of follow-up	4	(50.0)	1	(33.3)	9	(17.0)	568	(22.8)	9	(5.7)
Missing data for both 3-domain remission definitions at 1st year of follow-up	1	(12.5)	1	(33.3)	37	(69.8)	905	(36.3)	66	(41.8)
Missing data for all 4 domains in the 2nd year of follow-up	0	(0.0)	0	(0.0)	6	(0.0)	230	(9.2)	9	(5.7)
Missing age	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Missing sex	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.6)
Eligible	0	(0.0)	1	(33.3)	1	(1.9)	690	(39.2)	62	(39.2)

Suppl. Table 1 (cont'd).

	Kuwait		Mexico		Norway		Poland		Portugal	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total patients considered for inclusion	228	-	422	-	94	-	483	-	142	-
Sequential exclusions										
Age <18	6	(2.6)	58	(13.7)	2	(2.1)	4	(0.8)	8	(5.6)
Missing biologic initiation date	0	(0.0)	12	(2.8)	1	(1.1)	4	(0.8)	1	(0.7)
Biologic initiated less than a year before dataset closure date (31-07-2025)	0	(0.0)	0	(0.0)	0	(0.0)	24	(5.0)	0	(0.0)
Less than 1 year of follow-up	16	(7.0)	92	(21.8)	13	(13.8)	140	(29.0)	26	(18.3)
Missing data for both 3-domain remission definitions at 1st year of follow-up	152	(66.7)	188	(44.5)	20	(21.3)	209	(43.3)	86	(60.6)
Missing data for all 4 domains in the 2nd year of follow-up	30	(13.2)	28	(6.6)	14	(14.9)	19	(3.9)	10	(7.0)
Missing age	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Missing sex	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Eligible	24	(10.5)	44	(10.4)	44	(46.8)	83	(17.2)	11	(7.7)

Suppl. Table 1 (cont'd).

	Saudi Arabia		Singapore		South Korea		Spain		Taiwan	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total patients considered for inclusion	244	-	66	-	54	-	988	-	121	-
Sequential exclusions										
Age <18	3	(1.2)	0	(0.0)	0	(0.0)	29	(2.9)	1	(0.8)
Missing biologic initiation date	7	(2.9)	0	(0.0)	0	(0.0)	13	(1.3)	3	(2.5)
Biologic initiated less than a year before dataset closure date (31-07-2025)	12	(4.9)	0	(0.0)	0	(0.0)	5	(0.5)	0	(0.0)
Less than 1 year of follow-up	95	(38.9)	16	(24.2)	18	(33.3)	169	(17.1)	29	(24.0)
Missing data for both 3-domain remission definitions at 1st year of follow-up	84	(34.4)	17	(25.8)	14	(25.9)	550	(55.7)	22	(18.2)
Missing data for all 4 domains in the 2nd year of follow-up	7	(2.9)	13	(19.7)	11	(20.4)	39	(3.9)	20	(16.5)
Missing age	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Missing sex	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Eligible	36	(14.8)	20	(30.3)	11	(20.4)	183	(18.5)	46	(38.0)

Suppl. Table 1 (cont'd).

	UAE		UK		USA-Michigan		USA-NJH	
	N	(%)	N	(%)	N	(%)	N	(%)
Total patients considered for inclusion	194	-	804	-	44	-	2,369	-
Sequential exclusions								
Age <18	2	(1.0)	0	(0.0)	0	(0.0)	68	(2.9)
Missing biologic initiation date	8	(4.1)	24	(3.0)	0	(0.0)	997	(42.1)
Biologic initiated less than a year before dataset closure date (31-07-2025)	0	(0.0)	21	(2.6)	0	(0.0)	0	(0.0)
Less than 1 year of follow-up	80	(41.2)	110	(13.7)	0	(0.0)	176	(7.4)
Missing data for both 3-domain remission definitions at 1st year of follow-up	67	(34.5)	272	(33.8)	27	(61.4)	374	(15.8)
Missing data for all 4 domains in the 2nd year of follow-up	24	(12.4)	102	(12.7)	2	(4.5)	95	(4.0)
Missing age	0	(0.0)	0	(0.0)	0	(0.0)	6	(0.3)
Missing sex	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Eligible	13	(6.7)	275	(34.2)	15	(34.1)	653	(27.6)

14.2 Appendix 2: Remission status over time since biologic initiation for the 3 main remission definitions and 13 additional remission definitions

Remission status in follow-up years	Remission status at Year 1		
	Yes	No	Total
Four-domain remission: no exacerbations, no LTOCS use, well or partly controlled, and percent predicted FEV_1 ≥80%			
Year 1	-	-	1,396
Yes	-	-	363 (26.00)
No	-	-	1,033 (74.00)
Year 2	363	1,033	1,396
Yes	261 (71.90)	147 (14.23)	408 (29.23)
No	102 (28.10)	886 (85.77)	988 (70.77)
Year 3	190	563	753
Yes	133 (70.00)	107 (19.01)	240 (31.87)
No	57 (30.00)	456 (80.99)	513 (68.13)
Year 4	91	296	387
Yes	66 (72.53)	63 (21.28)	129 (33.33)
No	25 (27.47)	233 (78.72)	258 (66.67)
Year 5	36	157	193
Yes	27 (75.00)	32 (20.38)	59 (30.57)
No	9 (25.00)	125 (79.62)	134 (69.43)
Three-domain remission: no exacerbations, no LTOCS use, and well or partly controlled			
Year 1	-	-	1,824
Yes	-	-	732 (40.13)
No	-	-	1,092 (59.87)
Year 2	732	1,092	1,824
Yes	584 (79.78)	261 (23.90)	845 (46.43)
No	148 (20.22)	831 (76.10)	979 (53.67)
Year 3	427	635	1,062
Yes	334 (78.22)	195 (30.71)	529 (49.81)
No	93 (21.78)	440 (69.29)	533 (50.19)
Year 4	220	362	582
Yes	175 (79.55)	136 (37.57)	311 (53.44)
No	45 (20.45)	226 (62.43)	271 (46.56)
Year 5	102	199	301
Yes	78 (76.47)	77 (38.69)	155 (51.50)
No	24 (23.53)	122 (61.31)	146 (48.50)
Three-domain remission: no exacerbations, no LTOCS use, and percent predicted FEV_1 ≥80%			
Year 1	-	-	2,015
Yes	-	-	612 (30.37)
No	-	-	1,403 (69.63)
Year 2	612	1,403	2,015
Yes	456 (74.51)	225 (16.04)	681 (33.80)
No	156 (25.49)	1,178 (83.96)	1,334 (66.20)
Year 3	346	815	1,161
Yes	246 (71.10)	159 (19.51)	405 (34.88)
No	100 (28.90)	656 (80.49)	756 (65.12)
Year 4	183	483	666
Yes	132 (72.13)	105 (21.74)	237 (35.59)
No	51 (27.87)	378 (78.26)	429 (64.41)
Year 5	101	279	380
Yes	72 (71.29)	52 (18.64)	124 (32.63)
No	29 (28.71)	227 (81.36)	256 (67.37)

Remission status in follow-up years	Remission status at Year 1		
	Yes	No	Total
Three-domain remission: no exacerbations, no LTOCS use, and well controlled			
Year 1	-	-	1,824
Yes	-	-	532 (29.17)
No	-	-	1,292 (70.83)
Year 2	532	1,292	1,824
Yes	386 (72.56)	233 (18.03)	619 (33.94)
No	146 (27.44)	1,059 (81.97)	1,205 (66.06)
Year 3	301	761	1,062
Yes	224 (74.42)	175 (23.00)	399 (37.57)
No	77 (25.58)	586 (77.00)	663 (62.43)
Year 4	146	436	582
Yes	108 (73.97)	124 (28.44)	232 (39.86)
No	38 (26.03)	312 (71.56)	350 (60.14)
Year 5	67	234	301
Yes	48 (71.64)	73 (31.20)	121 (40.20)
No	19 (28.36)	161 (68.80)	180 (59.80)
Three-domain remission: no exacerbations, no LTOCS use, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV1 decline)			
Year 1	-	-	1,771
Yes	-	-	884 (49.92)
No	-	-	887 (50.08)
Year 2	884	887	1,771
Yes	654 (73.98)	273 (30.78)	927 (52.34)
No	230 (26.02)	614 (69.22)	844 (47.66)
Year 3	505	516	1,021
Yes	377 (74.65)	224 (43.41)	601 (58.86)
No	128 (25.35)	292 (56.59)	420 (41.14)
Year 4	280	299	579
Yes	211 (75.36)	126 (42.14)	337 (58.20)
No	69 (24.64)	173 (57.86)	242 (41.80)
Year 5	158	176	334
Yes	113 (71.52)	66 (37.50)	179 (53.59)
No	45 (28.48)	110 (62.50)	155 (46.41)
Four-domain remission: no exacerbations, no LTOCS use, well controlled, and percent predicted FEV_1 ≥80%			
Year 1	-	-	1,396
Yes	-	-	274 (19.63)
No	-	-	1,122 (80.37)
Year 2	274	1,122	1,396
Yes	189 (68.98)	123 (10.96)	312 (22.35)
No	85 (31.02)	999 (89.04)	1,084 (77.65)
Year 3	139	614	753
Yes	96 (69.06)	95 (15.47)	191 (25.37)
No	43 (30.94)	519 (84.53)	562 (74.63)
Year 4	58	329	387
Yes	42 (72.41)	54 (16.41)	96 (24.81)
No	16 (27.59)	275 (83.59)	291 (75.19)
Year 5	24	169	193
Yes	15 (62.50)	29 (17.16)	44 (22.80)
No	9 (37.50)	140 (82.84)	149 (77.20)

Remission status in follow-up years	Remission status at Year 1		
	Yes	**No**	**Total**
Four-domain remission: no exacerbations, no LTOCS use, well/partly controlled, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV1 decline)			
Year 1	-	-	1,200
Yes	-	-	478 (39.83)
No	-	-	722 (60.17)
Year 2	478	722	1,200
Yes	346 (72.38)	158 (21.88)	504 (42.00)
No	132 (27.62)	564 (78.12)	696 (58.00)
Year 3	254	397	651
Yes	181 (71.26)	119 (29.97)	300 (46.08)
No	73 (28.74)	278 (70.03)	351 (53.92)
Year 4	125	203	328
Yes	92 (73.60)	71 (34.98)	163 (49.07)
No	33 (26.40)	132 (65.02)	165 (50.30)
Year 5	82	111	163
Yes	37 (71.15)	33 (29.73)	70 (42.94)
No	15 (28.85)	78 (70.27)	93 (57.06)
Four-domain remission: no exacerbations, no LTOCS use, well controlled, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV1 decline)			
Year 1	-	-	1,200
Yes	-	-	343 (28.58)
No	-	-	857 (71.42)
Year 2	343	857	1,200
Yes	235 (68.51)	135 (15.75)	370 (30.83)
No	108 (31.49)	722 (84.25)	830 (69.17)
Year 3	176	475	651
Yes	125 (71.02)	104 (21.89)	229 (35.18)
No	51 (28.98)	371 (78.11)	422 (64.82)
Year 4	75	253	328
Yes	58 (77.33)	63 (24.90)	121 (36.89)
No	17 (22.67)	190 (75.10)	207 (63.11)
Year 5	29	134	163
Yes	19 (65.52)	30 (22.39)	49 (30.06)
No	10 (34.48)	104 (77.61)	114 (69.94)
Three-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, and well/partly controlled			
Year 1	-	-	1,797
Yes	-	-	767 (42.68)
No	-	-	1,030 (57.32)
Year 2	767	1,030	1,797
Yes	606 (79.01)	266 (25.83)	872 (48.53)
No	161 (20.99)	764 (74.17)	925 (51.47)
Year 3	454	593	1,047
Yes	354 (77.97)	206 (34.74)	560 (53.49)
No	100 (22.03)	387 (65.26)	487 (46.51)
Year 4	233	342	575
Yes	183 (78.54)	143 (41.81)	326 (56.70)
No	50 (21.46)	199 (58.19)	249 (43.30)
Year 5	104	192	296
Yes	78 (75.00)	84 (43.75)	162 (54.73)
No	26 (25.00)	108 (56.25)	134 (45.27)

Remission status in follow-up years	Remission status at Year 1		
	Yes	**No**	**Total**
Three-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, and well controlled			
Year 1	-	-	1,797
Yes	-	-	553 (30.77)
No	-	-	1,244 (69.23)
Year 2	553	1,244	1,797
Yes	399 (72.15)	240 (19.29)	639 (35.56)
No	154 (27.85)	1,004 (80.71)	1,158 (64.44)
Year 3	319	728	1,047
Yes	232 (72.73)	186 (25.55)	418 (39.92)
No	87 (27.27)	542 (74.45)	629 (60.08)
Year 4	156	419	575
Yes	115 (73.72)	129 (30.79)	244 (42.43)
No	41 (26.28)	290 (69.21)	331 (57.57)
Year 5	69	227	296
Yes	49 (71.01)	80 (35.24)	129 (43.58)
No	20 (28.99)	147 (64.76)	167 (56.42)
Three-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, and percent predicted FEV_1 ≥80%			
Year 1	-	-	1,984
Yes	-	-	620 (31.25)
No	-	-	1,364 (68.75)
Year 2	620	1,364	1,984
Yes	462 (74.52)	221 (16.20)	683 (34.43)
No	158 (25.48)	1,143 (83.80)	1,301 (65.57)
Year 3	348	797	1,145
Yes	246 (70.69)	172 (21.58)	418 (36.51)
No	102 (29.31)	625 (78.42)	727 (63.49)
Year 4	186	469	655
Yes	133 (71.51)	109 (23.24)	242 (36.95)
No	53 (28.49)	390 (76.76)	413 (63.05)
Year 5	100	277	377
Yes	69 (69.00)	58 (20.94)	127 (33.69)
No	31 (31.00)	219 (79.06)	250 (66.31)
Three-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, and percent predicted FEV_1 ≥80% and/or stabilization			
Year 1	-	-	1,744
Yes	-	-	909 (52.12)
No	-	-	835 (47.88)
Year 2	909	835	1,744
Yes	670 (73.71)	270 (32.34)	940 (53.90)
No	239 (26.29)	565 (67.66)	804 (46.10)
Year 3	512	495	1,007
Yes	382 (74.61)	234 (47.27)	616 (61.17)
No	130 (25.39)	261 (52.73)	391 (38.83)
Year 4	284	284	568
Yes	214 (75.35)	132 (46.48)	346 (60.92)
No	70 (24.65)	152 (53.52)	222 (39.08)
Year 5	152	176	328
Yes	107 (70.39)	79 (44.89)	186 (56.71)
No	45 (29.61)	97 (55.1)	142 (43.29)

Remission status in follow-up years	Remission status at Year 1		
	Yes	No	Total
Four-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, well/partly controlled, and percent predicted FEV_1 ≥80%			
Year 1	-	-	1,372
Yes	-	-	373 (27.19)
No	-	-	999 (72.81)
Year 2	373	999	1,372
Yes	272 (72.92)	140 (14.01)	412 (30.03)
No	101 (27.08)	859 (85.99)	960 (69.97)
Year 3	197	543	740
Yes	137 (69.54)	112 (20.63)	249 (33.65)
No	60 (30.46)	431 (79.37)	491 (66.35)
Year 4	94	287	381
Yes	65 (69.15)	63 (21.95)	128 (33.60)
No	29 (30.85)	224 (78.05)	253 (66.40)
Year 5	37	154	191
Yes	25 (67.57)	35 (22.73)	60 (31.41)
No	12 (32.43)	119 (77.27)	131 (68.59)
Four-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, well controlled, and percent predicted FEV_1 ≥80%			
Year 1	-	-	1,372
Yes	-	-	281 (20.48)
No	-	-	1,091 (79.52)
Year 2	281	1,091	1,372
Yes	194 (69.04)	124 (11.37)	318 (23.18)
No	87 (30.96)	967 (88.63)	1,054 (76.82)
Year 3	142	598	740
Yes	94 (66.20)	100 (16.72)	194 (26.22)
No	48 (33.80)	498 (83.28)	546 (73.78)
Year 4	60	321	381
Yes	43 (71.67)	53 (16.51)	96 (25.20)
No	17 (28.33)	268 (83.49)	285 (74.80)
Year 5	25	166	191
Yes	15 (60.00)	31 (18.67)	46 (24.08)
No	10 (40.00)	135 (81.33)	145 (75.92)
Four-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, well/partly controlled, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV1 decline)			
Year 1	-	-	1,179
Yes	-	-	501 (42.49)
No	-	-	678 (57.51)
Year 2	501	678	1,179
Yes	366 (73.05)	150 (22.12)	516 (43.77)
No	135 (26.95)	528 (77.88)	663 (56.23)
Year 3	266	374	640
Yes	192 (72.18)	121 (32.35)	313 (48.91)
No	74 (27.82)	253 (67.65)	327 (51.09)
Year 4	129	193	322
Yes	94 (72.87)	73 (37.82)	167 (51.86)
No	35 (27.13)	120 (62.18)	155 (48.14)
Year 5	51	109	160
Yes	34 (66.67)	37 (33.94)	71 (44.38)
No	17 (33.33)	72 (66.06)	89 (55.62)

Remission status in follow-up years	Remission status at Year 1		
	Yes	No	Total
Four-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, well controlled, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV1 decline)			
Year 1	-	-	1,179
Yes	-	-	357 (30.28)
No	-	-	822 (69.72)
Year 2	357	822	1,179
Yes	244 (68.35)	134 (16.30)	378 (32.06)
No	113 (31.65)	688 (83.70)	801 (67.94)
Year 3	183	457	640
Yes	127 (69.40)	109 (23.85)	236 (36.88)
No	56 (30.60)	348 (76.15)	404 (63.12)
Year 4	79	243	322
Yes	61 (77.22)	63 (25.93)	124 (38.51)
No	18 (22.78)	180 (74.07)	198 (61.49)
Year 5	30	130	160
Yes	19 (63.33)	32 (24.62)	51 (31.88)
No	11 (36.67)	98 (75.38)	109 (68.12)

14.3 Appendix 3: Remission status transitions over time since biologic initiation, stratified by remission status at Year 1, for 13 additional remission definitions

Suppl. Table 2. Remission status transitions over time since biologic initiation, stratified by remission status at Year 1, for 13 additional remission definitions.

Remission transitions	Patients in remission at Year 1				Patients not in remission at Year 1			
	Year 1 to 2	Year 2 to 3	Year 3 to 4	Year 4 to 5	Year 1 to 2	Year 2 to 3	Year 3 to 4	Year 4 to 5
Three-domain remission: no exacerbations, no LTOCS use, and well controlled								
Patients in remission in the previous year, N	532	218	115	53	0	134	105	44
Maintained remission: n (%)	386 (72.56)	188 (86.24)	93 (80.87)	42 (79.25)	N/A	84 (62.69)	73 (69.52)	26 (59.09)
Changed from remission to no remission: n (%)	146 (27.44)	30 (13.76)	22 (19.13)	11 (20.75)	N/A	50 (37.31)	32 (30.48)	18 (40.91)
Patients not in remission in the previous year, N	0	83	31	14	1,292	627	331	119
Remained below remission criteria: n (%)	N/A	47 (56.63)	16 (51.61)	8 (57.14)	1,059 (81.97)	536 (85.49)	280 (84.59)	101 (84.87)
Changed from no remission to remission: n (%)	N/A	36 (43.37)	15 (48.39)	6 (42.86)	233 (18.03)	91 (14.51)	51 (15.41)	18 (15.13)
Three-domain remission: no exacerbations, no LTOCS use, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV1 decline)								
Patients in remission in the previous year, N	884	369	207	118	0	163	125	73
Maintained remission: n (%)	654 (73.98)	295 (79.95)	168 (81.16)	98 (83.05)	N/A	117 (71.78)	82 (65.60)	40 (54.79)
Changed from remission to no remission: n (%)	230 (26.02)	74 (20.05)	39 (18.84)	20 (16.95)	N/A	46 (28.22)	43 (34.40)	33 (45.21)
Patients not in remission in the previous year, N	0	136	73	40	887	353	174	103
Remained below remission criteria: n (%)	N/A	54 (39.71)	30 (41.10)	25 (62.50)	614 (69.22)	246 (69.69)	130 (74.71)	77 (74.26)
Changed from no remission to remission: n (%)	N/A	82 (60.29)	43 (58.90)	15 (37.50)	273 (30.78)	107 (30.31)	44 (25.29)	26 (25.24)
Four-domain remission: no exacerbations, no LTOCS use, well controlled, and percent predicted FEV_1 ≥80%								
Patients in remission in the previous year, N	274	100	45	18	0	64	51	25
Maintained remission: n (%)	189 (68.98)	83 (83.00)	37 (82.22)	12 (66.67)	N/A	40 (62.50)	26 (50.98)	13 (52.00)
Changed from remission to no remission: n (%)	85 (31.02)	17 (17.00)	8 (17.78)	6 (33.33)	N/A	24 (37.50)	25 (49.02)	12 (48.00)
Patients not in remission in the previous year, N	0	39	13	6	1,122	550	278	144
Remained below remission criteria: n (%)	N/A	26 (66.67)	8 (61.54)	3 (50.00)	999 (89.04)	495 (90.00)	250 (89.93)	128 (88.89)
Changed from no remission to remission: n (%)	N/A	13 (33.33)	5 (38.46)	3 (50.00)	123 (10.96)	55 (10.00)	28 (10.07)	16 (11.11)
Four-domain remission: no exacerbations, no LTOCS use, well/partly controlled, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV1 decline)								
Patients in remission in the previous year, N	478	189	94	37	0	88	57	36
Maintained remission: n (%)	346 (72.38)	154 (81.48)	75 (79.79)	29 (78.38)	N/A	57 (64.77)	43 (75.44)	21 (58.33)
Changed from remission to no remission: n (%)	132 (27.62)	35 (18.52)	19 (20.21)	8 (21.62)	N/A	31 (35.23)	14 (24.56)	15 (41.67)
Patients not in remission in the previous year, N	0	65	31	15	722	309	146	75
Remained below remission criteria: n (%)	N/A	38 (58.46)	14 (45.16)	7 (46.67)	564 (78.12)	247 (79.94)	118 (80.82)	63 (84.00)
Changed from no remission to remission: n (%)	N/A	27 (41.54)	17 (54.84)	8 (53.33)	158 (21.88)	62 (20.06)	28 (19.18)	12 (16.00)
Four-domain remission: no exacerbations, no LTOCS use, well controlled, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV1 decline)								
Patients in remission in the previous year, N	343	127	57	23	0	75	56	31
Maintained remission: n (%)	235 (68.51)	107 (84.25)	49 (85.96)	17 (73.91)	N/A	41 (54.67)	33 (58.93)	14 (45.16)
Changed from remission to no remission: n (%)	108 (31.49)	20 (15.75)	8 (14.04)	6 (26.09)	N/A	34 (45.33)	23 (41.07)	17 (54.84)
Patients not in remission in the previous year, N	0	49	18	6	857	400	197	103
Remained below remission criteria: n (%)	N/A	31 (63.27)	9 (50.00)	4 (66.67)	722 (84.25)	337 (84.25)	167 (84.77)	87 (84.47)
Changed from no remission to remission: n (%)	N/A	18 (36.73)	9 (50.00)	2 (33.33)	135 (15.75)	63 (15.75)	30 (15.23)	16 (15.53)
Three-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, and well/partly controlled								
Patients in remission in the previous year, N	771	357	188	82	0	159	125	84
Maintained remission: n (%)	608 (78.86)	304 (85.15)	157 (83.51)	65 (79.27)	N/A	113 (71.07)	98 (78.40)	63 (75.00)
Changed from remission to no remission: n (%)	163 (21.14)	53 (14.85)	31 (16.49)	17 (20.73)	N/A	46 (28.93)	27 (21.60)	21 (25.00)
Patients not in remission in the previous year, N	0	97	45	22	1,039	435	217	108
Remained below remission criteria: n (%)	N/A	47 (48.45)	19 (42.22)	9 (40.91)	773 (74.40)	342 (78.62)	172 (79.26)	87 (80.56)
Changed from no remission to remission: n (%)	N/A	50 (51.55)	26 (57.78)	13 (59.09)	266 (25.60)	93 (21.38)	45 (20.74)	21 (19.44)
Three-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, and well controlled								
Patients in remission in the previous year, N	556	230	118	56	0	139	113	73
Maintained remission: n (%)	399 (71.76)	192 (83.48)	95 (80.51)	43 (76.79)	N/A	90 (64.75)	81 (71.68)	50 (68.49)
Changed from remission to no remission: n (%)	157 (28.24)	38 (16.52)	23 (19.49)	13 (23.21)	N/A	49 (35.25)	32 (28.32)	23 (31.51)
Patients not in remission in the previous year, N	0	89	38	13	1,254	590	306	154
Remained below remission criteria: n (%)	N/A	49 (55.06)	18 (47.37)	7 (53.85)	1,014 (80.86)	494 (83.73)	258 (84.31)	124 (80.52)
Changed from no remission to remission: n (%)	N/A	40 (44.94)	20 (52.63)	6 (46.15)	240 (19.14)	96 (16.27)	48 (15.69)	30 (19.48)
Three-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, and percent predicted FEV_1 ≥80%								
Patients in remission in the previous year, N	624	261	130	72	0	129	96	60
Maintained remission: n (%)	463 (74.20)	209 (80.08)	106 (81.54)	56 (77.78)	N/A	88 (68.22)	61 (63.54)	36 (60.00)
Changed from remission to no remission: n (%)	161 (25.80)	52 (19.92)	24 (18.46)	16 (22.22)	N/A	41 (31.78)	35 (36.46)	24 (40.00)
Patients not in remission in the previous year, N	0	87	56	28	1,374	669	373	217
Remained below remission criteria: n (%)	N/A	50 (57.47)	29 (51.79)	15 (53.57)	1,153 (83.92)	585 (87.44)	325 (87.13)	195 (89.86)
Changed from no remission to remission: n (%)	N/A	37 (42.53)	27 (48.21)	13 (46.43)	221 (16.08)	84 (12.56)	48 (12.87)	22 (10.14)

Suppl. Table 2 (cont'd).

Remission transitions	Patients in remission at Year 1				Patients not in remission at Year 1			
	Year 1 to 2	Year 2 to 3	Year 3 to 4	Year 4 to 5	Year 1 to 2	Year 2 to 3	Year 3 to 4	Year 4 to 5
Three-domain remission: no LTOCS use or daily dose ≤5mg equivalent-prednisone, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV1 decline)								
Patients in remission in the previous year, N	916	375	210	113	0	166	130	83
Maintained remission: n (%)	672 (73.36)	299 (79.73)	172 (81.90)	91 (80.53)	N/A	116 (69.88)	89 (68.46)	50 (60.24)
Changed from remission to no remission: n (%)	244 (26.64)	76 (20.27)	38 (18.10)	22 (19.47)	N/A	50 (30.12)	41 (31.54)	33 (39.76)
Patients not in remission in the previous year, N	0	138	74	39	841	329	154	93
Remained below remission criteria: n (%)	N/A	55 (39.86)	32 (43.24)	23 (58.97)	570 (67.78)	211 (64.13)	111 (72.08)	64 (68.82)
Changed from no remission to remission: n (%)	N/A	83 (60.14)	42 (56.76)	16 (41.03)	271 (32.22)	118 (35.87)	43 (27.92)	29 (31.18)
Four-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, well/partly controlled, and percent predicted FEV_1 ≥80%								
Patients in remission in the previous year, N	375	145	66	27	0	84	60	31
Maintained remission: n (%)	273 (72.80)	117 (80.69)	52 (78.79)	20 (74.07)	N/A	55 (65.48)	40 (66.67)	21 (67.74)
Changed from remission to no remission: n (%)	102 (27.20)	28 (19.31)	14 (21.21)	7 (25.93)	N/A	29 (34.52)	20 (33.33)	10 (32.26)
Patients not in remission in the previous year, N	0	52	28	10	1,009	460	227	123
Remained below remission criteria: n (%)	N/A	32 (61.54)	15 (53.57)	5 (50.00)	869 (86.12)	403 (87.61)	204 (89.87)	109 (88.62)
Changed from no remission to remission: n (%)	N/A	20 (38.46)	13 (46.43)	5 (50.00)	140 (13.88)	57 (12.39)	23 (10.13)	14 (11.38)
Four-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, well controlled, and percent predicted FEV_1 ≥80%								
Patients in remission in the previous year, N	283	102	43	19	0	71	54	25
Maintained remission: n (%)	194 (68.55)	80 (78.43)	35 (81.40)	12 (63.16)	N/A	45 (63.38)	29 (53.70)	15 (60.00)
Changed from remission to no remission: n (%)	89 (31.45)	22 (21.57)	8 (18.60)	7 (36.84)	N/A	26 (36.62)	25 (46.30)	10 (40.00)
Patients not in remission in the previous year, N	0	40	17	6	1,101	528	267	141
Remained below remission criteria: n (%)	N/A	26 (65.00)	9 (52.94)	3 (50.00)	977 (88.74)	473 (89.58)	243 (91.01)	125 (88.65)
Changed from no remission to remission: n (%)	N/A	14 (35.00)	8 (47.06)	3 (50.00)	124 (11.26)	55 (10.42)	24 (8.99)	16 (11.35)
Four-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, well/partly controlled, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV1 decline)								
Patients in remission in the previous year, N	504	198	96	37	0	89	62	55
Maintained remission: n (%)	367 (72.82)	160 (80.81)	76 (79.17)	26 (70.27)	N/A	57 (64.04)	47 (75.81)	35 (63.64)
Changed from remission to no remission: n (%)	137 (27.18)	38 (19.19)	20 (20.83)	11 (29.73)	N/A	32 (35.96)	15 (24.19)	20 (36.36)
Patients not in remission in the previous year, N	0	68	33	14	686	286	131	99
Remained below remission criteria: n (%)	N/A	36 (52.94)	15 (45.45)	6 (42.86)	536 (78.13)	222 (77.62)	105 (80.15)	80 (80.81)
Changed from no remission to remission: n (%)	N/A	32 (47.06)	18 (54.55)	8 (57.14)	150 (21.87)	64 (22.38)	26 (19.85)	19 (19.19)
Four-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, well controlled, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV1 decline)								
Patients in remission in the previous year, N	360	131	57	25	0	78	60	31
Maintained remission: n (%)	244 (67.78)	106 (80.92)	49 (85.96)	17 (68.00)	N/A	45 (57.69)	37 (61.67)	16 (51.61)
Changed from remission to no remission: n (%)	116 (32.22)	25 (19.08)	8 (14.04)	8 (32.00)	N/A	33 (42.31)	23 (38.33)	15 (48.39)
Patients not in remission in the previous year, N	0	52	22	5	830	380	183	99
Remained below remission criteria: n (%)	N/A	31 (59.62)	10 (45.45)	3 (60.00)	696 (83.86)	316 (83.16)	157 (85.79)	83 (83.84)
Changed from no remission to remission: n (%)	N/A	21 (40.38)	12 (54.55)	2 (40.00)	134 (16.14)	64 (16.84)	26 (14.21)	16 (16.16)

N/A: not applicable.

14.4 Appendix 4: Proportions of patients that remained in remission over 3, 4, and 5 years, in patients who met remission criteria in the first year post-biologic initiation, for 13 additional remission definitions

Suppl. Table 3. Proportions of patients that remained in remission over 3, 4, and 5 years, in patients who met remission criteria in the first year post-biologic initiation, for 13 additional remission definitions.

Over 3 years		Over 4 years		Over 5 years	
Denominator	**n (%)**	**Denominator**	**n (%)**	**Denominator**	**n (%)**
Three-domain remission: no exacerbations, no LTOCS use, and well controlled					
301	188 (62.5)	146	82 (56.2)	67	32 (47.8)
Three-domain remission: no exacerbations, no LTOCS use, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV_1 decline)					
505	295 (58.4)	280	137 (48.9)	158	70 (44.3)
Four-domain remission: no exacerbations, no LTOCS use, well controlled, and percent predicted FEV1 ≥80%					
139	83 (59.7)	58	33 (56.9)	24	10 (41.7)
Four-domain remission: no exacerbations, no LTOCS use, well/partly controlled, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV_1 decline)					
254	154 (60.6)	125	61 (48.8)	52	20 (38.5)
Four-domain remission: no exacerbations, no LTOCS use, well controlled, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV_1 decline)					
176	107 (60.8)	75	42 (56.0)	29	13 (44.8)
Three-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, and well/partly controlled					
454	307 (67.0)	233	135 (57.9)	104	51 (49.0)
Three-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, and well controlled					
319	192 (60.2)	156	80 (52.6)	69	32 (46.4)
Three-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, and percent predicted FEV_1 ≥80%					
348	209 (60.1)	186	93 (50.0)	100	42 (42.0)
Three-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV_1 decline)					
513	299 (58.3)	284	138 (48.6)	152	667 (44.1)
Four-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, well/partly controlled, and percent predicted FEV_1 ≥80%					
197	117 (59.4)	94	44 (46.8)	37	16 (43.2)
Four-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, well controlled, and percent predicted FEV_1 ≥80%					
142	80 (56.3)	60	31 (51.7)	25	10 (40.0)
Four-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, well/partly controlled, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV_1 decline)					
266	160 (60.2)	129	61 (47.3)	51	19 (37.3)
Four-domain remission: no exacerbations, no LTOCS use or daily dose ≤5mg equivalent-prednisone, well controlled, and percent predicted FEV_1 ≥80% and/or stabilization (i.e. not greater than 10% or 100mL of FEV_1 decline)					
183	106 (57.9)	79	41 (51.9)	30	13 (43.3)

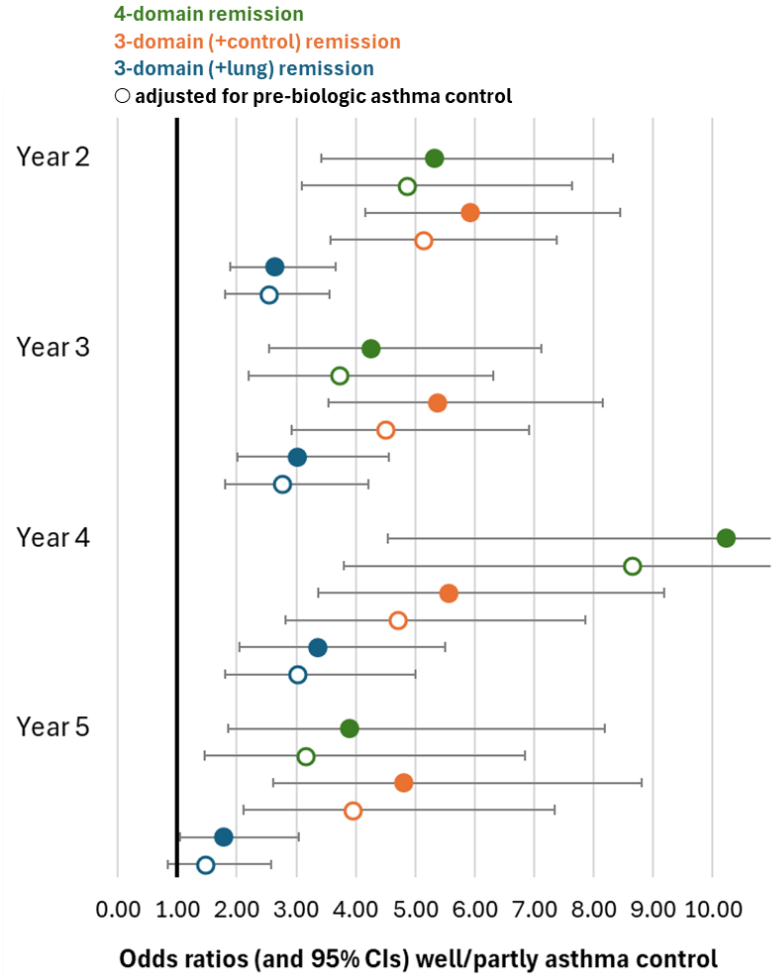
14.5 Appendix 5: Minimally adjusted association analysis results without restricting on study population with available pre-biologic measure of the outcome of interest

Remission at Year 1	Year 2			Year 3			Year 4			Year 5		
	Outcome: Exacerbations rates in further years											
	N	RR	(95% CI)	N	RR	(95% CI)	N	RR	(95% CI)	N	RR	(95% CI)
4-domain												
No	1,308	4.52	(3.27-6.24)	960	2.87	(2.03-4.06)	674	4.68	(2.61-8.39)	461	3.05	(1.59-5.88)
Yes	490	-	Ref.	322	-	Ref.	186	-	Ref.	115	-	Ref.
3-domain (+control)												
No	1,214	4.78	(3.87-5.90)	864	3.22	(2.47-4.19)	607	4.64	(3.12-6.90)	408	3.83	(2.30-6.38)
Yes	875	-	Ref.	595	-	Ref.	369	-	Ref.	223	-	Ref.
3-domain (+lung)												
No	1,629	4.07	(3.30-5.03)	1,260	2.79	(2.15-3.61)	925	2.50	(1.79-3.51)	676	3.26	(2.09-5.07)
Yes	788	-	Ref.	536	-	Ref.	338	-	Ref.	228	-	Ref.
	Outcome: Absence of exacerbations in further years											
	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)
4-domain												
No	1,308	-	Ref.	960	-	Ref.	674	-	Ref.	461	-	Ref.
Yes	490	5.32	(3.96-7.15)	322	3.27	(2.20-4.88)	186	3.62	(2.01-6.50)	115	2.65	(1.35-5.19)
3-domain (+control)												
No	1,214	-	Ref.	864	-	Ref.	607	-	Ref.	408	-	Ref.
Yes	875	4.59	(3.60-5.86)	595	3.53	(2.61-4.77)	369	3.10	(2.08-4.62)	223	3.23	(1.91-5.47)
3-domain (+lung)												
No	1,629	-	Ref.	1,260	-	Ref.	925	-	Ref.	676	-	Ref.
Yes	788	3.87	(3.06-4.91)	536	2.67	(2.01-3.55)	338	2.67	(1.85-3.84)	228	2.65	(1.69-4.15)
	Outcome: Well/partly controlled asthma in further years											
	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)
4-domain												
No	1,380	-	Ref.	981	-	Ref.	687	-	Ref.	494	-	Ref.
Yes	474	4.69	(3.39-6.48)	321	3.91	(2.68-5.69)	196	4.73	(2.91-7.68)	131	3.49	(2.04-5.99)
3-domain (+control)												
No	1,296	-	Ref.	924	-	Ref.	640	-	Ref.	455	-	Ref.
Yes	858	5.86	(4.51-7.62)	580	4.02	(2.99-5.39)	371	4.36	(3.03-6.28)	247	4.19	(2.72-6.47)
3-domain (+lung)												
No	1,402	-	Ref.	1,026	-	Ref.	746	-	Ref.	551	-	Ref.
Yes	625	2.18	(1.72-2.77)	430	2.54	(1.90-3.39)	271	2.80	(1.97-3.98)	203	1.96	(1.34-2.86)
	Outcome: Well controlled asthma in further years											
	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)
4-domain												
No	1,380	-	Ref.	981	-	Ref.	687	-	Ref.	494	-	Ref.
Yes	474	4.11	(3.23-5.23)	321	3.92	(2.91-5.28)	196	3.30	(2.28-4.78)	131	2.63	(1.69-4.09)
3-domain (+control)												
No	1,296	-	Ref.	924	-	Ref.	640	-	Ref.	455	-	Ref.
Yes	858	4.25	(3.48-5.20)	580	3.68	(2.89-4.70)	371	3.18	(2.36-4.28)	247	2.51	(1.75-3.61)
3-domain (+lung)												
No	1,402	-	Ref.	1,026	-	Ref.	746	-	Ref.	551	-	Ref.
Yes	625	2.44	(1.98-3.00)	430	2.79	(2.17-3.60)	271	2.31	(1.70-3.15)	203	2.05	(1.44-2.93)
	Outcome: Percent predicted FEV_1 (continuous) in further years											
	N	Diff.	(95% CI)	N	Diff.	(95% CI)	N	Diff.	(95% CI)	N	Diff.	(95% CI)
4-domain												
No	1,331	-	Ref.	940	-	Ref.	675	-	Ref.	505	-	Ref.
Yes	444	+20.5	(+18.2, +22.8)	303	+20.3	(+17.5, +23.0)	199	+18.2	(+14.9, +21.6)	121	+18.6	(+14.5, +22.6)
3-domain (+control)												
No	1,158	-	Ref.	818	-	Ref.	605	-	Ref.	441	-	Ref.
Yes	752	+9.2	(+7.1, +11.4)	527	+9.0	(+6.5, +11.5)	354	+7.0	(+4.1, +10.0)	231	+5.3	(+1.8, +8.8)
3-domain (+lung)												
No	1,588	-	Ref.	1,153	-	Ref.	848	-	Ref.	633	-	Ref.
Yes	685	+22.0	(+20.2, +23.8)	477	+21.5	(+19.3, +23.7)	327	+22.3	(+19.8, +24.8)	228	+21.7	(+18.7, +24.7)

Remission at Year 1	Year 2			Year 3			Year 4			Year 5		
	Outcome: Percent predicted FEV_1 ≥80% in further years											
	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)
4-domain												
No	1,331	-	Ref.	940	-	Ref.	675	-	Ref.	505	-	Ref.
Yes	444	9.78	(7.20-13.3)	303	8.01	(5.58-11.5)	199	7.78	(5.03-12.0)	121	9.80	(5.55-17.3)
3-domain (+control)												
No	1,158	-	Ref.	818	-	Ref.	605	-	Ref.	441	-	Ref.
Yes	752	1.95	(1.60-2.38)	527	1.94	(1.53-2.46)	354	1.78	(1.34-2.36)	231	1.64	(1.17-2.31)
3-domain (+lung)												
No	1,588	-	Ref.	1,153	-	Ref.	848	-	Ref.	633	-	Ref.
Yes	685	11.30	(8.86-14.5)	477	9.71	(7.29-13.0)	327	11.00	(7.78-15.6)	228	10.30	(6.90-15.3)
	Outcome: Absence of LTOCS use (or stopping using) in further years											
	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)
4-domain												
No	1,486	-	Ref.	1,110	-	Ref.	807	-	Ref.	575	-	Ref.
Yes	501	31.7	(11.7-85.7)	337	15.3	(6.16-38.1)	207	13.6	(4.28-43.5)	129	8.23	(2.54-26.7)
3-domain (+control)												
No	1,414	-	Ref.	1,026	-	Ref.	746	-	Ref.	528	-	Ref.
Yes	896	37.9	(18.6-77.3)	620	20.4	(10.3-40.6)	400	21.6	(8.70-53.6)	246	12.7	(5.04-32.2)
3-domain (+lung)												
No	1,856	-	Ref.	1,436	-	Ref.	1,089	-	Ref.	811	-	Ref.
Yes	804	30.2	(13.4-68.2)	562	18.8	(8.20-43.3)	366	15.8	(5.76-43.1)	248	9.23	(3.33-25.6)

Diff.: difference in percentage points; OR: odds ratio; RR: rate ratio; CI: confidence interval.

14.6 Appendix 6: Association between remission status at Year 1 and having well or partly controlled asthma in further years of follow-up, adjusting for age, sex, and geographical setting, +/- pre-biologic asthma control



Remission status at Year 1 (N)				
No*	Yes		OR (95% CI)	p
775	276	4-domain remission	5.33 (3.42-8.32)	<0.001
			4.85 (3.09-7.63)	<0.001
711	491	3-domain (+control) remission	5.93 (4.16-8.45)	<0.001
			5.14 (3.58-7.38)	<0.001
754	351	3-domain (+lung) remission	2.63 (1.89-3.66)	<0.001
			2.53 (1.80-3.55)	<0.001
563	189	4-domain remission	4.26 (2.55-7.12)	<0.001
			3.72 (2.20-6.31)	<0.001
515	342	3-domain (+control) remission	5.37 (3.54-8.16)	<0.001
			4.50 (2.93-6.91)	<0.001
553	245	3-domain (+lung) remission	3.02 (2.01-4.55)	<0.001
			2.76 (1.81-4.21)	<0.001
390	121	4-domain remission	10.22 (4.54-22.98)	<0.001
			8.65 (3.80-16.68)	<0.001
353	226	3-domain (+control) remission	5.56 (3.37-9.18)	<0.001
			4.71 (2.82-7.86)	<0.001
387	157	3-domain (+lung) remission	3.36 (2.05-5.51)	<0.001
			3.01 (1.81-5.01)	<0.001
281	79	4-domain remission	3.90 (1.85-8.19)	<0.001
			3.16 (1.46-6.84)	0.003
260	151	3-domain (+control) remission	4.80 (2.62-8.80)	<0.001
			3.94 (2.11-7.35)	<0.001
281	111	3-domain (+lung) remission	1.78 (1.05-3.04)	0.033
			1.47 (0.84-2.57)	0.171

14.7 Appendix 7: Association between remission status at Year 1 and several asthma-related outcomes after restricting the study population to patients who had maintained the same biologic throughout the study period of interest (adjusting for age, sex, geographical setting, and pre-biologic measure of the outcome of interest)

Remission at Year 1	Year 2			Year 3			Year 4			Year 5		
	Outcome: Exacerbations rates in further years											
	N	RR	(95% CI)	N	RR	(95% CI)	N	RR	(95% CI)	N	RR	(95% CI)
4-domain												
No	761	4.49	(3.06-6.60)	508	3.14	(1.91-5.18)	345	4.97	(2.18-11.30)	223	2.69	(1.10-6.61)
Yes	321	-	Ref.	200	-	Ref.	117	-	Ref.	69	-	Ref.
3-domain (+control)												
No	655	4.20	(3.20-5.54)	420	2.74	(1.89-3.99)	287	3.43	(2.05-5.73)	189	2.83	(1.46-5.47)
Yes	581	-	Ref.	375	-	Ref.	232	-	Ref.	133	-	Ref.
3-domain (+lung)												
No	910	3.39	(2.56-4.44)	638	2.82	(1.94-4.11)	445	2.68	(1.61-4.47)	295	2.59	(1.36-4.94)
Yes	486	-	Ref.	306	-	Ref.	188	-	Ref.	117	-	Ref.
	Outcome: Absence of exacerbations in further years											
	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)
4-domain												
No	761	-	Ref.	508	-	Ref.	345	-	Ref.	223	-	Ref.
Yes	321	4.82	(3.11-7.48)	200	3.61	(2.05-6.33)	117	5.09	(2.09-12.42)	69	2.56	(0.99-6.58)
3-domain (+control)												
No	655	-	Ref.	420	-	Ref.	287	-	Ref.	189	-	Ref.
Yes	581	3.95	(2.89-5.41)	375	2.66	(1.79-3.97)	232	2.94	(1.69-5.12)	133	2.92	(1.41-6.05)
3-domain (+lung)												
No	910	-	Ref.	638	-	Ref.	445	-	Ref.	295	-	Ref.
Yes	486	3.16	(2.30-4.35)	306	3.04	(2.00-4.62)	188	3.24	(1.82-5.78)	117	1.91	(1.00-3.65)
	Outcome: Well/partly controlled asthma in further years											
	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)
4-domain												
No	591	-	Ref.	375	-	Ref.	249	-	Ref.	164	-	Ref.
Yes	245	7.06	(3.98-12.52)	160	3.92	(2.09-7.34)	94	12.70	(4.35-37.05)	61	6.28	(2.07-19.06)
3-domain (+control)												
No	527	-	Ref.	336	-	Ref.	216	-	Ref.	144	-	Ref.
Yes	443	6.18	(4.06-9.38)	282	5.02	(2.99-8.44)	177	5.42	(2.91-10.11)	116	7.93	(3.16-19.92)
3-domain (+lung)												
No	578	-	Ref.	366	-	Ref.	249	-	Ref.	166	-	Ref.
Yes	302	2.89	(1.94-4.30)	200	2.97	(1.78-4.98)	117	5.03	(2.55-9.93)	81	2.30	(1.09-4.88)
	Outcome: Well controlled asthma in further years											
	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)
4-domain												
No	591	-	Ref.	375	-	Ref.	249	-	Ref.	164	-	Ref.
Yes	245	4.53	(3.14-6.53)	160	3.79	(2.37-6.05)	94	3.91	(2.12-7.23)	61	2.37	(1.11-5.03)
3-domain (+control)												
No	527	-	Ref.	336	-	Ref.	216	-	Ref.	144	-	Ref.
Yes	443	4.23	(3.12-5.73)	282	3.79	(2.55-5.62)	177	2.55	(1.57-4.15)	116	2.23	(1.20-4.14)
3-domain (+lung)												
No	578	-	Ref.	366	-	Ref.	249	-	Ref.	166	-	Ref.
Yes	302	2.70	(1.96-3.71)	200	3.09	(2.03-4.70)	117	2.57	(1.51-4.36)	81	1.82	(0.96-3.44)
	Outcome: Percent predicted FEV_1 (continuous) in further years											
	N	Diff.	(95% CI)	N	Diff.	(95% CI)	N	Diff.	(95% CI)	N	Diff.	(95% CI)
4-domain												
No	743	-	Ref.	461	-	Ref.	308	-	Ref.	217	-	Ref.
Yes	266	+9.4	(+7.2; +11.7)	177	+10.5	(+7.8; +13.2)	109	+9.1	(+5.6; +12.7)	65	+9.7	(+5.3; +14.1)
3-domain (+control)												
No	616	-	Ref.	383	-	Ref.	261	-	Ref.	179	-	Ref.
Yes	459	+4.8	(+2.9; +6.7)	300	+5.0	(+2.6; +7.4)	194	+4.2	(+1.2; +7.2)	127	+2.3	(-1.3; +6.0)
3-domain (+lung)												
No	919	-	Ref.	593	-	Ref.	399	-	Ref.	283	-	Ref.
Yes	411	+10.6	(+8.7; +12.4)	276	+11.1	(+8.8; +13.3)	171	+11.9	(+9.0; +14.8)	121	+12.2	(+8.7; +15.6)

Remission at Year 1	Year 2			Year 3			Year 4			Year 5		
	Outcome: Percent predicted FEV_1 ≥80% in further years											
	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)
4-domain												
No	743	-	Ref.	461	-	Ref.	308	-	Ref.	217	-	Ref.
Yes	266	6.33	(3.94-10.17)	177	4.58	(2.70-7.77)	109	3.98	(2.06-7.70)	65	6.84	(2.59-18.01)
3-domain (+control)												
No	616	-	Ref.	383	-	Ref.	261	-	Ref.	179	-	Ref.
Yes	459	1.59	(1.14-2.21)	300	1.53	(1.03-2.28)	194	1.51	(0.93-2.45)	127	1.15	(0.63-2.08)
3-domain (+lung)												
No	919	-	Ref.	593	-	Ref.	399	-	Ref.	283	-	Ref.
Yes	411	7.45	(5.12-10.82)	276	6.07	(3.97-9.26)	171	7.10	(4.07-12.39)	121	7.86	(3.91-15.81)
	Outcome: Absence of LTOCS use (or stopping using) in further years											
	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)
4-domain												
No	942	-	Ref.	629	-	Ref.	421	-	Ref.	273	-	Ref.
Yes	355	34.7	(8.34-144.0)	225	11.1	(3.36-36.8)	135	18.1	(2.36-138.8)	77	model not converging	
3-domain (+control)												
No	863	-	Ref.	555	-	Ref.	371	-	Ref.	242	-	Ref.
Yes	641	30.3	(12.0-76.2)	418	10.5	(4.65-23.7)	261	14.7	(4.36-49.6)	150	13.5	(2.99-61.2)
3-domain (+lung)												
No	1,154	-	Ref.	801	-	Ref.	556	-	Ref.	374	-	Ref.
Yes	540	37.9	(10.5-136.7)	346	21.3	(5.12-88.9)	218	21.4	(2.87-160.0)	135	model not converging	

Diff.: difference in percentage points; OR: odds ratio; RR: rate ratio; CI: confidence interval.