Exploring Definitions and Predictors of Severe Asthma Clinical Remission Post-Biologic in Adults

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At a Glance Commentary

Scientific knowledge on the subject: Asthma remission has been defined in many ways. Previous studies to identify predictors of remission have predominantly been retrospective or *post-hoc* analyses from randomized controlled trials, limited to single jurisdiction, have included relatively small numbers of patients, and/or investigated remission achievable with a single biologic.

What this study adds to the field: In this longitudinal cohort real life study including data from 23 countries, 20.3-50.2% of patients with severe asthma met criteria for clinical remission within 1-year of biologic treatment depending upon domains included in the remission definition. Patients with less severe disease and shorter duration of asthma pre-biologic-initiation had a better chance of achieving remission post-biologic. Our results suggest the need to consider earlier intervention with biologics for patients with severe asthma prior to significant and irreversible lung function impairment (partly as a consequence of repeated exacerbations) and before initiation of long-term oral corticosteroid treatment. Recognition that remission is more likely to occur if targeted earlier in the asthma life cycle, may influence biologic prescription criteria, and herald a paradigm shift away from targeting response in those with more severe asthma, towards the promotion of remission in those with less severe disease but at risk of developing severe asthma, but this will need to be confirmed.

This article has an online data supplement, which is accessible at the Supplements tab.

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Abstract

Rationale: There is no consensus on criteria to include in an asthma remission definition in real-life. Factors associated with achieving remission post-biologic-initiation remain poorly understood.

Objectives: To quantify the proportion of adults with severe asthma achieving multi-domain-defined remission post-biologic-initiation and identify pre-biologic characteristics associated with achieving remission which may be used to predict it.

Methods: This was a longitudinal cohort study using data from 23 countries from the International Severe Asthma Registry. Four asthma outcome domains were assessed in the 1-year pre- and post-biologic-initiation. *A priori*-defined remission cut-offs were: 0 exacerbations/year, no long-term oral corticosteroid (LTOCS), partly/well-controlled asthma, and percent predicted forced expiratory volume in one second ≥80%. Remission was defined using 2 (exacerbations + LTOCS), 3 (+control or +lung function) and 4 of these domains. The association between pre-biologic characteristics and post-biologic remission was assessed by multivariable analysis.

Measurements and main results: 50.2%, 33.5%, 25.8% and 20.3% of patients met criteria for 2, 3 (+control), 3 (+lung function) and 4-domain-remission, respectively. The odds of achieving 4-domain remission decreased by 15% for every additional 10-years asthma duration (odds ratio: 0.85; 95% CI: 0.73, 1.00). The odds of remission increased in those with fewer exacerbations/year, lower LTOCS daily dose, better control and better lung function pre-biologic-initiation.

Conclusions: One in 5 patients achieved 4-domain remission within 1-year of biologic-initiation. Patients with less severe impairment and shorter asthma duration at initiation

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had a greater chance of achieving remission post-biologic, indicating that biologic treatment should not be delayed if remission is the goal.

Key words: anti-IgE; anti-IL5/5R; anti-IL4Rα; exacerbation, lung function

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Introduction

Clinical studies and asthma treatment goals for adults with severe asthma have focused on biologic effectiveness and disease control, respectively, rather than remission as a therapeutic target.(1) The existence of spontaneous remission in the adult asthma population,(2–5) coupled with the chronic inflammatory nature of asthma, and a similar treatment development trajectory as other chronic inflammatory conditions where remission on treatment is well defined,(6–8) led to the hope that the asthma management paradigm could undergo a similar shift from asthma control to asthma remission.(9) Indeed, recently, there has been a shift in asthma management, with the concept of remission included in four national guidelines.(10) To date, remission is not included as a therapeutic target by the Global Initiative of Asthma (GINA), although good control of symptoms, normal activity levels, and minimization of exacerbations, persistent airflow limitation and side-effects are listed as long-term goals.(1)

Remission has been defined as ‘clinical’, ‘functional’, ‘immunological’ and ‘deep’ (all criteria) remission.(11) Expert consensus also defined ‘clinical’ remission as the absence of asthma symptoms, optimization/stabilization of lung function, patient/provider agreement regarding disease remission and no systemic oral corticosteroid (OCS; minimum duration of 12 months). Objective resolution of asthma-related inflammation and, if appropriate, negative bronchial hyperresponsiveness was additionally required for complete remission.(6) Recently updated national asthma guidelines from Germany, Spain and Italy all agree on no exacerbations, no systemic corticosteroids, good asthma control or no asthma-related symptoms and stable lung function as remission criteria.(10) In Italy, OCS use was considered the central tenant of ‘partial’ and ‘complete’ clinical remission; the latter requiring the complete absence of

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asthma symptoms, exacerbations and stable lung function for ≥12 months, and the former requiring any 2 of these criteria over the same timeframe.(12) These definitions will be part of the 2023 GINA Italy update.(10)

There is, however, some variability in remission domains and cut-offs recommended by these guidelines. For example, a lung function criterion was not incorporated into the 2023 update of the Japanese Practical Guidelines for Asthma Management.(10) Moreover good asthma control definitions ranged from 'no asthma-related symptoms' in the German and Spanish guidelines, to an Asthma Control Test (ACT) score of ≥23 or ≥20 in the Japanese and Italian guidelines, respectively.(10) Like our study, others have used an Asthma Control Questionnaire (ACQ)-5 cut-off of <1.5 as corresponding to GINA partly or well-controlled.(13) Most recently, a US expert consensus panel increased the rigor of current definitions to also include no missed work and limited inhaled corticosteroid (ICS) dose (low-medium) and short-acting β_2-agonist (SABA) use (≤1/month).(14)

The achievement of clinical remission following biologic treatment has varied widely, ranging from 12-43%,(11, 13, 15–22) most likely due to the wide range of criteria used to define it, but also due to differences in study methodology and heterogeneity among study populations. Identified predictors of remission have included younger age, shorter duration of asthma, less comorbidity, preserved lung function at biologic initiation, and no (or low dose) maintenance OCS. Patients with an elevated blood eosinophil count (BEC) and fractional exhaled nitric oxide (FeNO) levels have also reached remission more frequently.(11, 13, 16, 17, 20) However, these studies have utilised retrospective or *post-hoc* analyses and/or have included relatively small numbers of patients.

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Further research is needed to explore and test consensus-derived remission definitions, to align on criteria to include in a global definition, to ascertain the impact of each domain included, and to identify factors which predict severe asthma remission following biologic treatment in real-life. The International Severe Asthma Registry (ISAR), offers a unique opportunity to do that.(23–26) Our study aimed to quantify the proportion of adult patients with severe asthma achieving multi-domain-defined remission when treated with biologic therapy in real-life (overall and by biologic class), and to identify pre-biologic characteristics associated with remission in these patients. Some of the results of this study have been previously reported in the form of abstracts.(27, 28)

Methods

Study design and data source

This was a longitudinal, pre-to-post biologic-initiation, cohort study including data from 23 countries which shared data with ISAR (**Table E1**)(23, 25, 29) from 05.01.17 up to 01.25.23 2023. Biologic class categorization was based on first biologic used during the study period, regardless of subsequent changes (stop or switch) during follow-up (intention-to-treat approach). Pre- and post-biologic-initiation outcomes were described across four domains, in the 1-year pre-biologic and as close as possible to 1-year post-biologic-initiation (**Figure E1; Table 1**).

Patients

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Patients were required to be ≥18 years old at biologic initiation and have severe asthma (i.e. receiving treatment at GINA 2018 Step 5 or with uncontrolled asthma at GINA Step 4).(30) Uncontrolled asthma for registry inclusion was defined as having severe asthma symptoms or frequent exacerbations (≥2/year) requiring OCS. Patients were also required to be treated with anti-IgE, anti-IL5/5R, or anti-IL4Rα, have available registry data prior to, or on, biologic initiation date for ≥1 study domain, and follow-up data (as close to 1-year as possible). The presence of significant disease impairment at baseline was not required. Those with a history of bronchial thermoplasty were excluded.

Variables

Key patient demographic (e.g. age, sex, body mass index [BMI], smoking history) and pre-biologic asthma clinical characteristics (e.g. asthma onset and duration, biomarker levels, treatment and comorbidity history) were collected **(Table 2A and 2B)**.

Asthma outcome domains, timing of assessments and remission definitions

Definitions and timing of pre- and post-biologic outcomes are provided in **Table 1**. The asthma outcome domains used to define remission included exacerbation rate, long-term OCS (LTOCS) daily dose, asthma control (assessed using either GINA control criteria, ACT or ACQ; **Table E2**), and percent predicted forced expiratory volume in one second (ppFEV_1). ACQ and/or ACT control categories were fitted to GINA 2020 control categories as follows – mean ACQ: well controlled (≤0.75), partly controlled (>0.75 to < 1.5), uncontrolled (≥1.5); total ACT: well controlled (>19), partly controlled (>15 to ≤19), uncontrolled (≤15). Similar cut-offs and correlations (31, 32) have been described and used by others.(12, 13, 22) For forced expiratory volume in one second (FEV_1) we used post-bronchodilator measures if available,

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and pre-bronchodilator measures otherwise, while ensuring that pre- and post-biologic measures were both either pre- or post-bronchodilator. Post-bronchodilator measurements were used for 61.6% of patients with available pre-biologic $ppFEV_1$ (N=2,705). The remaining 38.4% of patients were all treated with ICS/long-acting β_2-agonist (LABA; i.e. bronchodilator not specifically withheld).

Domain choice was informed *a priori* by a previous ISAR study which examined pre-to-post biologic change in exacerbation rate, LTOCS use, asthma control and lung function in patients categorized according to degree of pre-biologic impairment, and which assessed the magnitude of improvement according to starting point and outcome assessed.(33) Our domain choice and remission cut-offs were also informed by expert consensus (52 experts from 25 countries)(33) and aligned with findings of the expert consensus framework for asthma remission of Menzies-Gow et al, (i.e. 0 exacerbations, no LTOCS use, absence of significant symptoms and optimized lung function).(6) Remission was characterized using 2 domains (i.e. exacerbation rate & LTOCS), 3 domains (i.e. exacerbation rate + LTOCS + asthma control OR exacerbation rate + LTOCS + $ppFEV_1$) or all 4 asthma outcomes (**Table 1**). Remission cut-offs for each of these domains were also defined *a priori* and categorized as 'strict' or 'relaxed' (**Figure 1)**. In this article 'remission' refers to 'strict' remission in those who initiated biologics.

Statistical analyses

The statistical analysis plan was pre-defined. R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) was used.(34) The observed proportions of patients who met the criteria for each remission definition were described overall and by biologic class. A *post-hoc*

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analysis was conducted to assess the proportion of patient meeting remission criteria in those with FEV_1/forced vital capacity (FVC) < and ≥ 0.7 No formal comparison between biologic classes was intended for these descriptive analyses. The associations between pre-biologic characteristics and remission were analysed using multivariable logistic regressions with remission (yes/no) as the outcome variable, using all proposed remission definitions. Patients with missing data for all asthma-related outcomes were excluded from the study, as well as patients with missing age and/or sex. However, patients with missing data for some but not all asthma-related outcomes were included in the analysis for the relevant outcomes. We did not conduct imputation of missing values. Significance was tested through log-likelihood ratios. Variables assessed for association with remission in the multivariable analyses included pre-biologic characteristics that were statistically significant ($p<.05$) in a univariate analysis for any domain assessed (data not shown) or those informed by literature review and expert consensus. Analyses were adjusted for pre-biologic asthma-related outcome included in the considered remission definition, age, and sex. Pre-biologic asthma-related outcomes, biomarkers, asthma duration, and BMI were analyzed as continuous variables.'. The models were fitted overall and for each biologic class (not anti-IL4Rα due to small sample size). To test for difference between anti-IgE and anti-IL5/5R patients, a single model was fitted in these patients adding biologic class as an interaction term with the variables of interest.

Results

Patients

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As of 25th Jan 2023, 14,284 patients were enrolled in ISAR. Of these, 6,816 initiated biologics and 3,717 met all inclusion criteria and were included in ≥1 analysis (**Figure E2**). Most exclusions occurred due to lack of pre- (n=715; 10.5%), or post-biologic data (n=1956; 28.7%) (**Table E3**). A total of 1,390, 2,021 and 306 patients received anti-IgE, anti-IL5/R, and anti-IL4Rα, respectively. The median duration of treatment was 1 year. Biologic interruption or switching was reported in 6.6% and 3.2% of patients, respectively (**Table E4**). The USA (n=1,131; 30.4%), UK (n=487; 13.1%), and Italy (n=438; 11.8%) contributed most patients (**Table E1**). The number of patients included in each analysis varied according to data availability for multiple domains (**Figure E2**).

Patient demographic and clinical characteristics pre-biologic

Patients were predominantly White (80.6%; n=2,616/3,246), with a tendency for more females (62.0%; n=2,305/3,715) and never-smokers (67.9%; n=1,827/2,692), with a median age of 30 (Q1, Q3: 14, 44) years at asthma onset and an asthma duration of 19 (Q1, Q3: 9, 34) years (**Table 2A**). Median age and BMI at study entry were 54 years (Q1, Q3: 43, 63) and 28.1 kg/m^2 (Q1, Q3: 24.4, 32.9), respectively. Biomarkers indicative of T2-high disease were all elevated, and 84.9% (n=2,709/2,901) had an eosinophilic phenotype. Most patients (79.7%; n=1,378/1,730) had a positive allergy test (i.e. to dust mite, grass mix, cat hair, mould mix, dog hair, aspergillus, weed mix, trees, food mix, animal mix, and/or others), with 96.9% of patients (n=1040/1073) with available data for at least one category (excluding UK which does not provide type of allergen data to ISAR) testing positive to an aeroallergen. The prevalence of T2-related comorbidities was 52.4% (n=1,274/2,430), 51.4% (n=1,471/2,860) and 28.1% (n=842/2,997) for allergic rhinitis (AR), chronic rhinosinusitis (CRS), and nasal polyposis (NP), respectively (**Table 2A**). In 2,278 patients with information on both AR and CRS, 700 (30.7%)

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reported both comorbidities. The prevalence of other comorbidities is provided in **Table E1.** Pre-biologic, 45.5% of patients (n=1,070/2,351) experienced ≥1 exacerbation requiring hospitalization or ≥3 exacerbations in total, 40.1% (n=1,242/3,094) were treated with LTOCS, 72.5% (n=1,310/1,808) had uncontrolled asthma, and 58.4% (n=1,579/2,705) had a ppFEV$_1$ <80% (**Table 2B)**. Patients, who subsequently initiated anti-IL5/5R, tended to have more severe disease in terms of greater exacerbation burden and LTOCS use, and those who subsequently initiated anti-IL4Rα had less severe disease for all considered domains (**Table 2B**). Those, who subsequently achieved remission (any definition) post-biologic-initiation, also had less severe disease at baseline than those who did not subsequently meet remission criteria, and also tended to have a lower BMI, be older at asthma onset, have shorter disease duration, and have a higher BEC, a positive allergen test, and CRS pre-biologic (**Table E5**).

Proportion of patients in remission

The percentage of patients in remission was dependent upon number of asthma outcome domains included in the definition, highest (50.2%; n=1,076/2,142) for 2-domain remission and lowest (20.3%; n=215/1,059) for 4-domain remission (**Figure 2; Table E6**). The addition of lung function to the 2-domain remission definition decreased the remission rate (25.8%, n=435/1,688) to a greater degree than the addition of control status (33.5%, n=414/1,235) (**Figure 2; Table E6**). Remission was also achievable in those with evidence of irreversible airflow limitation, albeit less likely; 11.3% (n=50/444) of those with pre-biologic FEV$_1$/FVC <0.7 achieved 4-domain remission and 25.4% (n=88/347) of those with FEV$_1$/FVC ≥0.7 (**Table E7**). A small proportion of patients met remission criteria pre-biologic-initiation, highest for 2-domain remission (8.4%; n=106/1258) and lowest for 4-domain remission (1.0%; n= 6/585)

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(**Figure 2; Table E8**). Remission prevalence for patients treated with anti-IgE, anti-IL5/5R and anti-IL4Rα ranged from 19.3-55.1%, 20.6-43.4% and 22.6-71.0%, respectively (**Figure 3**).

The prevalence of post-biologic-initiation remission defined using the relaxed cut-offs was higher, ranging from 29.1% to 75.2% (**Figure E3**). By biologic class remission rates, using relaxed cut-offs, ranged from 25.7-78.0% for anti-IgE, 30.8-70.6% for anti-IL5/5R and 29.0-90.0% for anti-IL4Rα (**Figure E4**). See **Tables E6 and E8** for a detailed breakdown of remission prevalence pre- and post-biologic therapy.

Association between pre-biologic characteristics and remission (multivariable analyses)

Disease severity

In general, the odds of remission were increased in those with less severe disease evidenced by: fewer exacerbations/year, lower LTOCS daily dose, better asthma control, and better lung function in the 1-year pre-biologic-initiation period (**Figure 4A and B; Table E9**). For 4-domain remission, the odds of remission decreased by 12% (95% CI 0.80, 0.97) for each additional exacerbation/year experienced pre-biologic, and by 41% (95% CI: 0.45, 0.77) for each additional 5 mg/day increment of LTOCS received pre-biologic-initiation. The odds of achieving 4-domain remission increased by 1.34 (95% CI: 0.91, 1.97) and by 1.29 (95% CI 1.20, 1.38) for each GINA control category improvement, and each 5% $ppFEV_1$ increment improvement pre-biologic-initiation, respectively (**Figure 4B**). A similar association pattern was noted for 2-domain (**Figure E5A**) and 3-domain (+ lung function) remission (**Figure E5B**) and for both anti-IgE and anti-IL5/5R, but generally with greater odds of remission for the latter (**Figure E6-9**). Similar findings were also noted when results were adjusted by country, although the exacerbation OR was attenuated (**Table E10)**.

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Biomarkers

Higher BEC levels (but not blood IgE or FeNO) were associated with greater odds of remission (**Figure 4; Figure E5A & B**), particularly noted for anti-IL5/5R (**Figure E6-E9**), and slightly attenuated when adjusted by country although the trend remained (**Table E10**).

Asthma duration

Shorter asthma duration was also associated with greater odds of remission (all definitions except 3-domain remission (+control); **Figure 4 and Figure E5**). Patients had a 15% lower odds of achieving 4-domain remission (OR: 0.85; 95% CI: 0.73, 1.00) (**Figure 4B**). The same estimate was achieved when adjusted by country (**Table E10**). Similar findings were observed when restricting the study population to patients aged ≥20 years at asthma onset (OR: 0.87; 95% CI: 0.67, 1.14) and was not solely driven by lung function, being still apparent (although attenuated) when adjusted for pre-biologic-initiation $ppFEV_1$ (0.94, 95% CI: 0.79, 1.13) (**Table E9**).

Other pre-biologic variables

Neither BMI nor smoking status were associated with remission (any definition). Prescription for theophylline (but not leukotriene receptor antagonist or macrolide) was negatively associated with the odds of remission, with similar findings noted on country adjustment (**Table E10**). Although T2-related co-morbidity score was not associated with remission (without or without country adjustment), those without a history of osteoporosis, and with a history of sleep apnea or anxiety/depression tended to have a greater odds of achieving remission, although the confidence intervals were wide (**Figure 4; Figure E5**).

Discussion

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To our knowledge, this is the largest study reporting prevalence of remission pre- and post-biologic-initiation and correlates of remission post-biologic for patients with severe asthma in real-life. Multiple domain severe asthma remission was achievable in real-life, along a gradation according to number and type of domains included in its definition, in a broad, heterogeneous severe asthma population; many of whom would be excluded from randomized controlled trials (RCTs). One in 5 patients with severe asthma met the criteria for clinical remission in all 4 domains within 1-year of biologic initiation, increasing to 1 in 2 patients when remission included exacerbation + LTOCS outcome domains only (indicative of bronchial inflammation and most effectively targeted by biologic therapy). These findings lend further weight to GINA recommendations to avoid LTOCS if possible in severe asthma (i.e. due to potential for adverse events, many of which do not reverse upon discontinuation, plus now with a negative association with remission). Importantly, patients with less severe disease and shorter duration of asthma pre-biologic-initiation had a better chance of achieving remission post-biologic.

To date, several studies have assessed the remission of severe asthma post-biologic therapy.(11, 13, 15–18, 21, 22) Three-domain biologic associated remission rates (excluding lung function), were remarkably similar across studies; 37.6% using data from the German Asthma Net severe asthma cohort,(17) 37.0% in a *post-hoc* analysis using data from the real-world Effectiveness and safety of mepolizumab study,(16) and 33.5% in the current study. Although remission definitions used in these studies frequently included the same domains, domain-specific criteria differed between them, making cross-comparisons difficult.(10, 13–16) The prevalence of 4-domain biologic associated remission (including lung function) ranged from 14.5 to 43.0%, (20.3% in the current study),(13, 15–18, 20–22) varying according

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to lung function criterion applied, patient cohort, and biologic. Examples of previously used lung function remission criteria include FEV_1>80% predicted (as in the present study),(22) an objective assessment of normal lung function,(2) and an FEV_1 above the lower limit of normal or no more than 100 mL less than baseline.(13) We consider inclusion of a high lung function hurdle an important component of clinical remission as it is representative of lung function optimization,(6) and may encourage earlier intervention with targeted treatment prior to irreversible lung damage. We also acknowledge the difficulty in achieving it in patients who frequently exhibit limited reversibility,(35–37), the lack of consensus in defining lung function optimization/stabilization,(38) and the ongoing debate on whether a lung function domain, used in sentinel remission papers (39) and national guidelines(10) should be included as a remission criterion. Of note, a reduced FEV_1 can be due to other non-asthma factors and, therefore, be unrelated to the presence of remission.

Although severe asthma remission is achievable in some patients when treated with a biologic in real-life, other patients receiving the same treatment failed to achieve it.(13, 22) This is likely due to a complex interplay of factors, including the heterogeneity of asthma itself, the timing of biologic intervention and assessment of remission, the presence of non-reversible airflow obstruction and the negative impact of comorbidities on asthma control.(40) Understanding why certain patients with severe asthma treated with biologics fail to achieve remission is arguably just as important as predicting those who do achieve it. This represents an important unmet need which requires consideration of the pathway to remission and national variability in biologic access,(26) but may also warrant the adoption of an alternative concept of remission (e.g. personalized remission), and/or a different approach to achieve it (e.g. more effective or alternative interventions).

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Some important points emerged when remission rate was assessed by biologic class. Firstly, remission was noted for all classes assessed. Secondly, the addition of the lung function domain (to exacerbations plus LTOCS) had a consistently greater negative impact on remission rate than the addition of asthma control. And thirdly, although the 2- and 3-domain remission [+ control or + lung function] rates appeared higher for IL4Rα, caution in interpretation should be employed due to small patient numbers, less severe impairment pre-biologic-initiation, and the greater prevalence of patients in remission pre-treatment in this group. Notably, when the more stringent 4-domain remission definition was applied, remission rates were similar across all biologic classes (approx. 20%) irrespective of inherent inter-group differences. We also noted a small proportion of patients in remission pre-biologic-initiation (up to 1.5% for 4-domain remission) which may be indicative of differences in biologics we use worldwide,(26) an artifact of under-reporting during the COVID pandemic, better management in severe asthma centres, including optimization of inhaled treatments and comorbidity management, and improved adherence pre-biologic.(20) Also, it is possible that some patients were incorrectly categorized as 'in remission' pre-biologic-initiation.

Pre-biologic correlates of remission were consistent across remission definitions. However, in contrast to what has been formerly observed with biologic response, where greater response is associated with greater pre-biologic-initiation disease severity,(41–43) for remission those with less impairment pre-biologic had greater odds of achieving remission. Patients had a 29% increased odds of achieving 4-domain remission for every 5% greater ppFEV_1, and were 41% less likely, respectively, to achieve remission for every additional 5 mg/day of LTOCS prescribed pre-biologic-initiation. Others reported similar findings, but these studies have

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been small by comparison, national in scope, have investigated remission achievable with a single biologic, and/or assessed remission predictors by univariate analysis.(11, 13, 16) A *post-hoc* analysis of the REDES study, for example, found that compared to those who did not achieve clinical remission, those who achieved 4-domain remission were more likely to have better pre-biologic asthma control (ACT score: 15.9 vs 13.7), lower median OCS dose (10.0 vs 6.3 mg/day) and better lung function (ppFEV$_1$: 71.2% vs 86.9%).(16) Similarly, a study in Japanese patients with severe asthma found that those with a ppFEV$_1$ ≥75% were 3.38 times more likely to achieve 3-domain clinical remission.(11) A UK study found that the odds of remission were 7.44-fold higher in patients with high T2-biomakers and lower for those who were female, obese or had poorly controlled severe asthma pre-biologic initiation.(13)

The shorter duration of asthma as a remission predictor in the current study is particularly relevant and could indicate that the path to remission should start as early as possible. Our finding has been corroborated by data from both the UK and from Denmark, the former showing that the likelihood of remission reduced by 14% for every 10-year increase in disease duration.(13, 22) Others reported that patients with an asthma diagnosis made after the age of 12 years were 1.9 times more likely to achieve 3-domain clinical remission,(17) and that greater improvements in lung function when treated with tezepelumab compared to placebo were observed in patients with a disease duration <20 years.(44) This phenomenon is likely a consequence of accelerated lung function decline in those patients who frequently exacerbate (most marked in those <40 years),(45) or due to limited efficacy of ICS in preventing long-term lung function decline in some patients (or due to poor adherence or under prescription). Indeed, the odds ratios for asthma duration were attenuated when adjusted for pre-biologic ppFEV$_1$. In contrast to response, elevated FeNO levels were not

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consistently associated with increased odds of remission in our study, possibly as this biomarker may be better at predicting those who do badly without treatment, rather than in predicting those who will do better while treated, or due to the fact that anti-IL4Rα is under-represented in our study. An association with persistently high FeNO levels may have been observed but requires further study. The finding of a positive association of elevated BEC and higher odds of remission (particularly for anti-IL5/5R) is notable and an important treatable trait, although a selection bias for those with elevated BEC in the anti-IL5/5R group cannot be discounted.

Limitations of the current study include missing data, the relatively small number of anti-IL4Rα treated patients, lack of patient matching between biologic classes, and the risk of multiplicity. Assessing generalizability is difficult, so although our study included a large cohort of severe asthma patients from 23 countries, caution should be employed when extrapolating results to the wider asthma population. Use of three tools to assess asthma control (i.e. GINA, ACT and ACQ) could be considered a limitation. However, these are all validated with good inter-test correlation,(31, 32) and reflect inter-country variability in how asthma control is assessed in real-life, including variability in control tools required for biologic eligibility and reimbursement, although this has been mitigated to some extent by adjusting for country. Additionally, while remission can also be defined as a prolonged period with low to no disease activity this goes beyond the scope of our study which assessed disease activity at ~1-year post-biologic-initiation. Inclusion of a patient-reported outcome measure in a remission definition may also strengthen our concept of what remission means to patients.

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Strengths included use of routinely collected clinical and functional domains to define remission, facilitating replication and validation globally. We included a large, real-life and heterogenous severe asthma population treated with biologic therapy, with sufficient data to categorize remission using multiple domain definitions and using both strict and relaxed cut-offs, for biologics overall and by class. The very low prevalence of remission pre-biologic-initiation coupled with the observed negative association of pre-biologic impairment with odds of remission, indicates that the results were unlikely affected by inclusion of patients already in remission at baseline. Our study also investigated the likelihood of achieving remission using a large number of pre-biologic variables used in routine management and included many patients not eligible for inclusion in RCTs. New directions and opportunities for future research include the assessment of remission duration (on treatment), since the occurrence of temporary remission cannot be discounted.(46, 47) Remission prevalence at later timepoints and according to the American Thoracic Society definition,(14), the persistence of remission upon treatment discontinuation, and the impact of earlier biologic initiation on disease trajectory should also be investigated. Future studies could also investigate the concepts of complete and long-term remission, including objective resolution of asthma-related inflammation and lung function stabilization (rather than optimization) as remission criteria, in line with the remission consensus framework(6) and recent national asthma management guidelines.(10)

Our findings have tested the sensitivity of asthma remission definitions in the largest severe asthma cohort in the world, shown how the proportion of patients categorized as in remission is affected by some domains more than others and, by identifying a wide range of pre-biologic factors associated with remission, brought us one step closer to accurate remission prediction

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in real-life. Although, remission is the ultimate goal of asthma management, it occurs in a relatively small proportion of patients treated with current biologics. This may suggest the need to consider switching biologic therapies if remission is not achieved, use of biologic combinations, and use of biologics earlier to give patients the best chance of achieving remission, but further research is needed. If remission is the target, guidelines should reflect that, and treatment approaches/strategies in selected patients most likely to achieve it may be recommended (pending confirmation).

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Figure Legends

Figure 1: Definitions of remission post-biologic therapy using strict and relaxed domain cut-offs.

Abbreviations: LTOCS: long-term oral corticosteroid; $ppFEV_1$: percent predicted forced expiratory volume in one second. * prednisolone equivalent;† Control was assessed by GINA control criteria; Asthma Control Questionnaire or Asthma Control Test; ‡Post-bronchodilator used if available, and pre-bronchodilator used otherwise, while ensuring that pre- and post-biologic measures were both either pre- or post-bronchodilator. Post-bronchodilator measurements were used for 61.6% of patients with available pre-biologic $ppFEV_1$ (N=2,705). The remaining 38.4% of patients were all treated with ICS/LABA (i.e. bronchodilator not specifically withheld).

Figure 2: Percentage of patients in remission (strict criteria) pre- and post-biologic treatment.

Abbreviations: $ppFEV_1$: percent predicted forced expiratory volume in one second; LTOCS: long-term oral corticosteroid.

Figure 3: Percentage of patients in remission (strict criteria) pre- and post-treatment with anti-IgE, anti-IL5/5R, or anti-IL4Rα.

Abbreviations: $ppFEV_1$: percent predicted forced expiratory volume in one second; LTOCS: long-term oral corticosteroid.

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Figure 4: Association between selected pre-biologic characteristics and (A) 3-domain and (B) 4 domain asthma remission in patients with severe asthma.

Abbreviations: BEC: blood eosinophil count; BMI: body mass index; CI: confidence interval; FeNO: fractional exhaled nitric oxide; GINA: Global Initiative for Asthma; LTOCS: long-term oral corticosteroids; LTRA: leukotriene receptor antagonist; OR: odds ratio; $ppFEV_1$: percent predicted forced expiratory volume in one second.

3-domain remission: 0 exacerbations/year + no LTOCS + well or partly-controlled asthma

4-domain remission: 0 exacerbations/year + no LTOCS + well or partly-controlled asthma + $ppFEV_1$ ≥80%

Grey zones highlight association patterns.

* Pre-biologic lung function adjustment removed

Asthma duration: age at biologic initiation minus reported age at asthma onset

All ORs were adjusted for pre-biologic asthma-related outcome including in the considered remission definition, as well as for age and sex.

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Table 1: Asthma outcome domain definitions and timing of pre- and post-biologic assessment

Outcome	Definition	Pre-biologic	Post- biologic
Annualized Exacerbation rate	• asthma-related hospital attendance/admission; AND/OR • asthma-related ER attendance; AND/OR • acute OCS course ≥3 days	1 year pre-biologic (or 48 weeks minimum)	Annualized post-biologic (number of events assessed for a minimum of 48 weeks and a maximum of 80 weeks post-biologic)
Asthma control*	• GINA control test,(1) OR • ACT Test(48) OR • ACQ(49)	At biologic initiation (or assessment closest to biologic initiation up to a maximum of 1 year pre-biologic)	Closest to 1-year post biologic (24 weeks minimum and 80 weeks maximum)
Daily LTOCS dose†	• Continuous OCS use ≥3 months duration • Daily LTOCS (prednisolone equivalent) dose (mg)	At biologic initiation	Closest to 1-year post biologic (24 weeks minimum and 80 weeks maximum)

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Lung function‡	• $ppFEV_1$	At biologic initiation (or assessment closest to biologic initiation up to a maximum of 1 year pre-biologic)	Closest to 1-year post biologic (24 weeks minimum and 80 weeks maximum)

Abbreviations: ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; GINA: Global Initiative for Asthma; LTOCS: long-term oral corticosteroid; OCS: oral corticosteroid; $ppFEV_1$: percent predicted forced expiratory volume in one second

* Some countries use ACQ and/or ACT to assess control. In these instances, ACQ and/or ACT control categories were fitted to GINA 2020 control categories as follows:
Mean ACQ: well controlled (≤0.75); partly controlled (>0.75 to < 1.5); uncontrolled (≥1.5)
Total ACT: well controlled (>19); partly controlled (>15 to ≤19); uncontrolled (≤15). A summary of control test utilised by each country is provided in the online supplement (**Table E2**).

† In cases when there were different periods with different doses pre-biologic, the most recent dose (i.e. closest to biologic initiation) was used. For post-biologic dose and if changed from pre-biologic, the new dose closest to 1-year post-biologic initiation (minimum 24 weeks, maximum 80 weeks) was used and the date of change used to calculate the follow-up time.

‡ Post-bronchodilator used if available, and pre-bronchodilator used otherwise, while ensuring that pre- and post-biologic measures were both either pre- or post-bronchodilator.

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Post-bronchodilator measurements were used for 61.6% of patients with available pre-biologic ppFEV$_1$ (N=2,705). The remaining 38.4% of patients were all treated with ICS/LABA (i.e. bronchodilator not specifically withheld).

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Table 2A: Patient demographic and clinical characteristics pre-biologic overall and by biologic class

	Total (N=3717)	Anti-IgE (N=1390)	Anti-IL5/5R (N=2021)	Anti-IL4Rα (N=306)
Age at biologic initiation, yrs				
Median (Q1, Q3)	54 (43, 63)	50 (40, 59)	56 (46, 65)	52 (41, 62)
Sex, N	3715	1389	2020	306
Female, n (%)	2305 (62.0)	902 (64.9)	1214 (60.1)	189 (61.8)
Ethnicity, N	3717	1390	2021	306
Caucasian, n (%)	2616 (70.4)	982 (70.6)	1438 (71.2)	196 (64.1)
South East Asian, n (%)	118 (3.2)	59 (4.2)	52 (2.6)	7 (2.3)
N East Asian, n (%)	108 (2.9)	25 (1.8)	70 (3.5)	13 (4.2)
African, n (%)	95 (2.6)	36 (2.6)	49 (2.4)	10 (3.3)
Mixed, n (%)	68 (1.8)	55 (4.0)	7 (0.3)	6 (2.0)
Other, n (%)	241 (6.4)	89 (6.4)	130 (6.4)	22 (7.2)
Unknown/missing, n (%)	471 (12.7)	144 (10.4)	275 (13.6)	52 (17.0)
BMI, kg/m^2, N	3467	1270	1895	302
Median	28.1	28.8	27.5	28.9
(Q1, Q3)	(24.4, 32.9)	(25.1, 33.7)	(24.0, 32.0)	(24.8, 33.8)
Smoking status at Bx initiation, N	2692	978	1479	235
Current smoker, n (%)	74 (2.7)	38 (3.9)	29 (2.0)	7 (3.0)
Ex-smoker, n (%)	791 (29.4)	232 (23.7)	479 (32.4)	80 (34.0)
Never smoker, n (%)	1827 (67.9)	708 (72.4)	971 (65.7)	148 (63.0)

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	Total (N=3717)	Anti-IgE (N=1390)	Anti-IL5/5R (N=2021)	Anti-IL4Rα (N=306)
Age-of-asthma onset, yrs, N	2289	823	1366	100
Median (Q1, Q3)	30 (14, 44)	24 (10, 39)	33 (18, 47)	26 (10, 43)
Asthma duration,* yrs, N	2289	823	1366	100
Median (Q1, Q3)	19 (9, 34)	20 (11, 34)	18 (9, 34)	22 (7, 34)
FEV_1/FVC <0.7, N	2646	1390	1433	238
n (%)	1398 (52.8)	479 (49.1)	811 (56.6)	108 (45.4)
Pre-Bx highest BEC, 10^9 cells/L, N	2420	843	1388	189
Median (Q1, Q3)	455 (230,	300 (200, 600)	550 (300, 900)	400 (200,
Pre-Bx latest FeNO, ppb, N	1603	441	1017	145
Median (Q1, Q3)	34 (18, 66)	26 (14, 51)	39 (21, 73)	28 (16, 57)
Pre-Bx latest blood IgE count,				
IU/mL, N	2294	927	1203	164
Median (Q1, Q3)	188 (75, 489)	253 (114, 576)	145 (53, 385)	134 (33, 500)
Positive test to any allergen†, N	1730	739	892	99
Yes, n (%)	1378 (79.7)	701 (94.9)	609 (68.3)	68 (68.7)
Medication use in the year				
preceding Bx initiation, N	3121	1223	1599	299
LAMA, n (%)	104 (3.3)	46 (3.8)	50 (3.1)	8 (2.7)
Theophylline, n (%)	274 (8.8)	114 (9.3)	154 (9.6)	6 (2.0)
LTRA, n (%)	1378 (44.2)	566 (46.3)	659 (41.2)	153 (51.2)
Macrolide, n (%)	368 (11.8)	145 (11.9)	170 (10.6)	53 (17.7)
History of AR, N	2430	987	1186	257

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	Total (N=3717)	Anti-IgE (N=1390)	Anti-IL5/5R (N=2021)	Anti-IL4Rα (N=306)
Yes, n (%)	1274 (52.4%)	600 (60.8%)	570 (48.1%)	104 (40.5%)
History of CRS, N	2860	1063	1543	254
Yes, n (%)	1471 (51.4)	458 (43.1)	880 (57.0)	133 (52.4)
History of NP, N	2997	1100	1639	258
Yes, n (%)	842 (28.1)	196 (17.8)	566 (34.5)	80 (31.0)
History of osteoporosis, N	3154	1259	1604	291
Yes, n (%)	485 (15.4)	195 (15.5)	258 (16.1)	32 (11.0)
History of anxiety/depression, N	3172	1226	1669	277
Yes, n (%)	481 (15.2)	182 (14.8)	245 (14.7)	54 (19.5)
Eosinophilic gradient‡(50)**, N**	2901	714	2021	166
Grade 0, n (%)	5 (0.2)	5 (0.7)	0 (0.0)	0 (0.0)
Grade 1, n (%)	62 (2.1)	53 (7.4)	0 (0.0)	9 (5.4)
Grade 2, n (%)	125 (4.3)	109 (15.3)	0 (0.0)	16 (9.6)
Grade 3, n (%)	2709 (84.9)	547 (76.6)	2021 (100.0)	141 (84.9)

Abbreviations: AR: allergic rhinitis; Bx: biologic; BEC: blood eosinophil concentration; CRS: chronic rhinosinusitis; FeNO: fractional exhaled nitric oxide; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; NP: nasal polyps; Q: quartile

*age at biologic initiation minus reported age at asthma onset

†Except for the UK patients for whom no detail is available to ISAR (n=471, 64.8% with a positive allergy test), ISAR collects data on test results for allergens in 11 categories: dust mite, grass mix, cat hair, mould mix, dog hair, aspergillus, weed mix, trees, food mix, animal

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mix, and others. Patients with a reported positive test in at least one category were reported as positive; patients with at least one negative record and no positive records were reported as negative. A total of 1,230 patients had data available for at least two categories, of whom 256 (20.8%) were negative on all recorded tests, 250 (20.3%) were positive for one category only, and 724 (58.9%) were positive for at least 2 categories

‡Note that patients receiving anti-IL5/5R were all categorized as 'Most likely' by the algorithm. Grade 0 (unlikely/non-eosinophilic); Grade 1 (least likely); Grade 2 (likely); Grade 3 (most likely)

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Table 2B: pre-biologic asthma-related outcomes used in remission definitions

	Total (N=3717)	Anti-IgE (N=1390)	Anti-IL5/5R (N=2021)	Anti-IL4Rα (N=306)
Pre-Bx exacerbations*, N	2351	777	1382	192
0, n (%)	610 (25.9)	221 (28.4)	286 (20.7)	103 (53.6)
1 (not hospitalized), n (%)	364 (15.5)	126 (16.2)	191 (13.8)	47 (24.5)
2 (not hospitalized), n (%)	307 (13.1)	100 (12.9)	186 (13.5)	21 (10.9)
≥1 (hospitalized) or ≥3 in total, n (%)	1070 (45.5)	330 (42.5)	719 (52.0)	21 (10.9)
Pre-Bx LTOCS* dose, N	3094	1076	1824	194
0 mg/day (non-user), n (%)	1852 (59.9)	729 (67.8)	974 (53.4)	149 (76.8)
≤ 5mg/day, n (%)	332 (10.7)	98 (9.1)	218 (12.0)	16 (8.2)
>5 to 10mg/day, n (%)	365 (11.8)	100 (9.3)	252 (13.8)	13 (6.7)
>10mg/day, n (%)	362 (11.7)	105 (9.8)	242 (13.3)	15 (7.7)
User but missing dose, n (%)	183 (5.9)	44 (4.1)	138 (7.6)	1 (0.5)
Pre-Bx asthma control †‡, N	1808	637	1095	76
Well controlled, n (%)	189 (10.5)	73 (11.5)	104 (9.5)	12 (15.8)
Partly controlled, n (%)	309 (17.1)	88 (13.8)	202 (18.4)	19 (25.0)
Uncontrolled, n (%)	1310 (72.5)	476 (74.7)	789 (72.1)	45 (59.2)

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Pre-Bx ppFEV$_1$ †#, N	2705	995	1472	238
≥80%, n (%)	1126 (41.6)	412 (41.4)	599 (40.7)	115 (48.3)
<80%, n (%)	1579 (58.4)	583 (58.6)	873 (59.3)	123 (51.7)

* In the year preceding biologic initiation;

†in the year preceding and closest to biologic initiation.

‡Assessed using either GINA control criteria,(30) Asthma Control Test(48) or Asthma Control Questionnaire(49). ACQ and/or ACT control categories were fitted to GINA 2020 control categories as follows: Mean ACQ: well controlled (≤0.75); partly controlled (>0.75 to < 1.5); uncontrolled (≥1.5) Total ACT: well controlled (>19); partly controlled (>15 to ≤19); uncontrolled (≤15).

Post-bronchodilator used if available, and pre-bronchodilator used otherwise, while ensuring that pre- and post-biologic measures were both either pre- or post-bronchodilator. Post-bronchodilator measurements were used for 61.6% of patients with available pre-biologic ppFEV$_1$ (N=2,705). The remaining 38.4% of patients were all treated with ICS/LABA (i.e. bronchodilator not specifically withheld).

Abbreviations: Bx: biologic; ppFEV$_1$: percent predicted forced expiratory volume in one second; LTOCS: long-term oral corticosteroid

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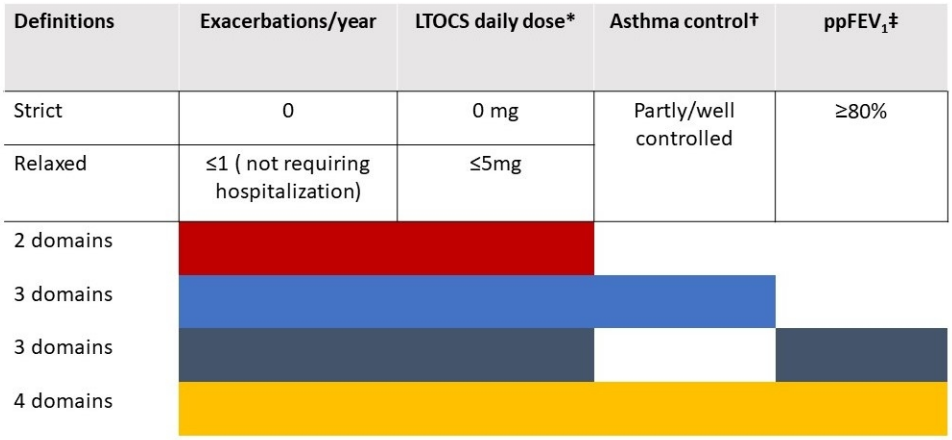

Figure 1: Definitions of remission post-biologic therapy using strict and relaxed domain cut-offs.

183x87mm (144 x 144 DPI)

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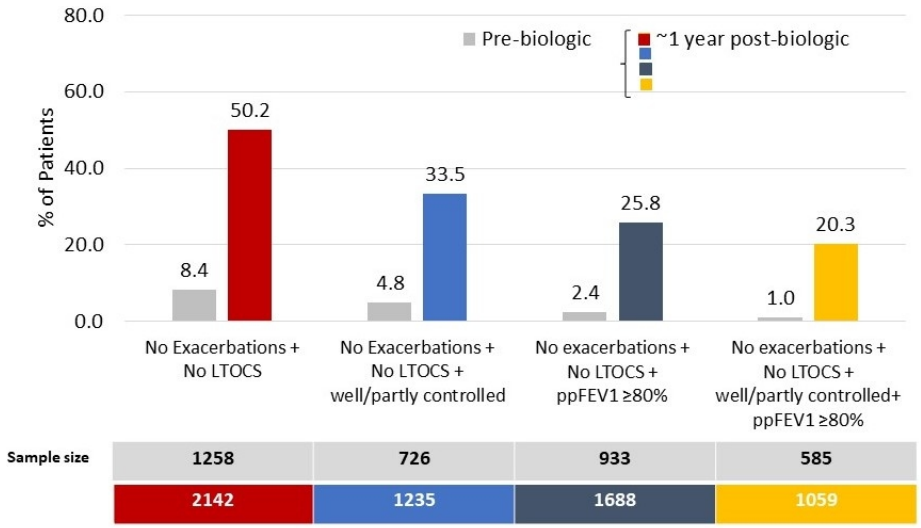

Figure 2: Percentage of patients in remission (strict criteria) pre- and post-biologic treatment.

165x96mm (144 x 144 DPI)

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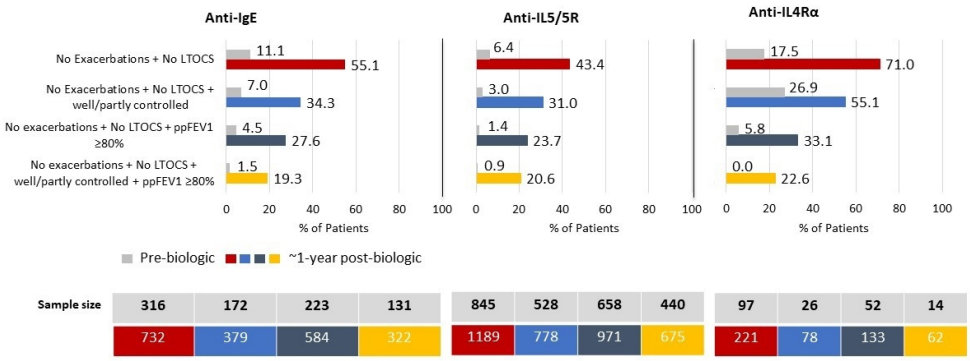

Figure 3: Percentage of patients in remission (strict criteria) pre- and post-treatment with anti-IgE, anti-IL5/5R, or anti-IL4Rα.

214x86mm (144 x 144 DPI)

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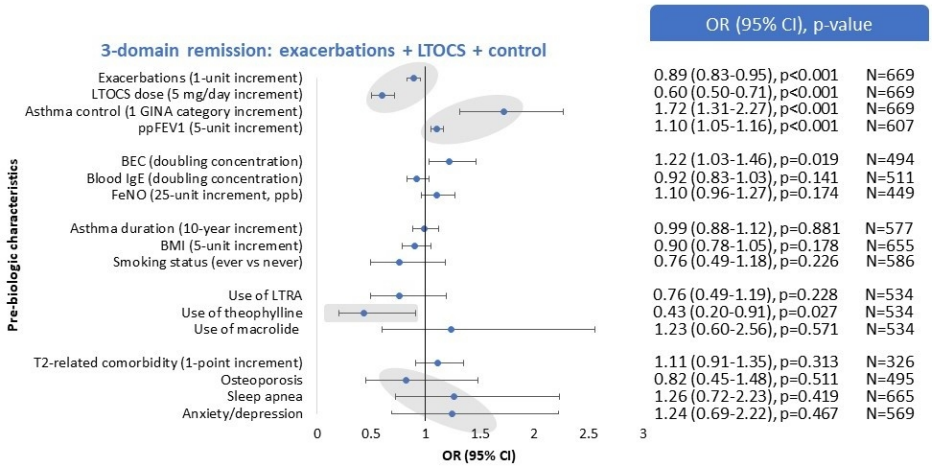

Figure 4A: Association between selected pre-biologic characteristics and 3-domain asthma remission in patients with severe asthma.

183x95mm (144 x 144 DPI)

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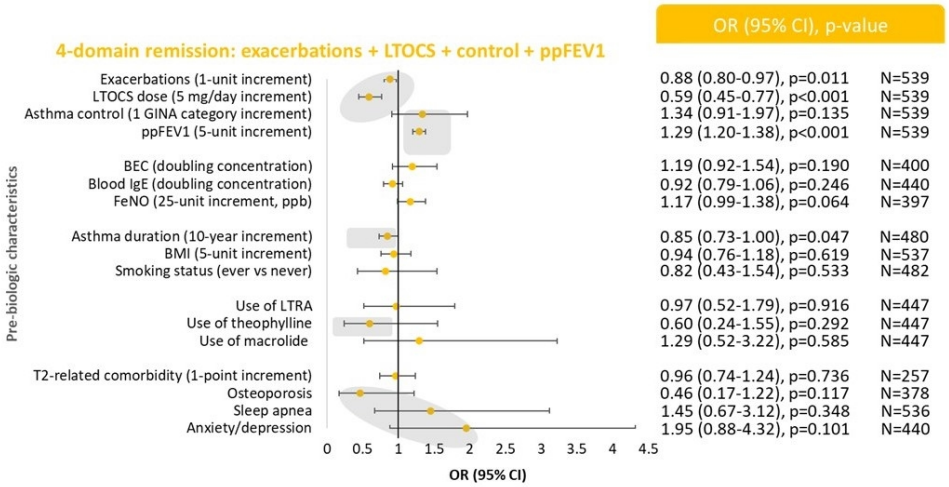

Figure 4B: Association between selected pre-biologic characteristics and 4 domain asthma remission in patients with severe asthma.

189x99mm (144 x 144 DPI)

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Exploring Definitions and Predictors of Severe Asthma Clinical Remission Post-Biologic in Adults

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ONLINE DATA SUPPLEMENT

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Study registration and Ethics approval

The study was registered with the European Network Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP; EUPAS 104132), designed, implemented, and reported in compliance with the ENCePP and with all applicable local and international laws and regulations and approved by the International Severe Asthma Registry (ISAR) Steering Committee, and approved by the ISAR Steering Committee. Ethics approval was obtained from the Anonymized Data Ethics Protocols and Transparency Committee (ADEPT0922). The ISAR database has ethical approval from ADEPT committee (ADEPT0218) and is registered with the European Union Electronic Register of Post-Authorization studies (ENCEPP/DSPP/23720).

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Table E1: Patient data contributed by country and comorbidity prevalence overall and by biologic class

	Anti-IgE (N=1390)	Anti-IL5/5R (N=2021)	Anti-IL4Rα (N=306)	Total (N=3717)
Country				
Argentina	2 (0.1%)	4 (0.2%)	8 (2.6%)	14 (0.4%)
Australia	65 (4.7%)	120 (5.9%)	5 (1.6%)	190 (5.1%)
Bulgaria	6 (0.4%)	2 (0.1%)	0 (0.0%)	8 (0.2%)
Canada	36 (2.6%)	133 (6.6%)	13 (4.2%)	182 (4.9%)
Colombia	40 (2.9%)	20 (1.0%)	13 (4.2%)	73 (2.0%)
Denmark	62 (4.5%)	227 (11.2%)	2 (0.7%)	291 (7.8%)
Greece	24 (1.7%)	27 (1.3%)	0 (0.0%)	51 (1.4%)
India	0 (0.0%)	1 (0.0%)	0 (0.0%)	1 (0.0%)
Ireland	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Italy	133 (9.6%)	305 (15.1%)	0 (0.0%)	438 (11.8%)
Japan	10 (0.7%)	42 (2.1%)	15 (4.9%)	67 (1.8%)
Kuwait	171 (12.3%)	16 (0.8%)	6 (2.0%)	193 (5.2%)

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	Anti-IgE (N=1390)	Anti-IL5/5R (N=2021)	Anti-IL4Rα (N=306)	Total (N=3717)
Mexico	60 (4.3%)	3 (0.1%)	5 (1.6%)	68 (1.8%)
Poland	58 (4.2%)	84 (4.2%)	0 (0.0%)	142 (3.8%)
Portugal	2 (0.1%)	20 (1.0%)	0 (0.0%)	22 (0.6%)
Saudi Arabia	20 (1.4%)	24 (1.2%)	1 (0.3%)	45 (1.2%)
Singapore	4 (0.3%)	10 (0.5%)	0 (0.0%)	14 (0.4%)
South Korea	7 (0.5%)	7 (0.3%)	2 (0.7%)	16 (0.4%)
Spain	41 (2.9%)	116 (5.7%)	0 (0.0%)	157 (4.2%)
Taiwan	45 (3.2%)	26 (1.3%)	1 (0.3%)	72 (1.9%)
UAE	22 (1.6%)	9 (0.4%)	23 (7.5%)	54 (1.5%)
UK	104 (7.5%)	382 (18.9%)	1 (0.3%)	487 (13.1%)
USA	477 (34.3%)	443 (21.9%)	211 (69.0%)	1131 (30.4%)
History of allergic rhinitis	987	1186	257	2430
Yes, n (%)	600 (60.8%)	570 (48.1%)	104 (40.5%)	1274 (52.4%)
History of chronic rhinosinusitis	1063	1543	254	2860

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	Anti-IgE (N=1390)	Anti-IL5/5R (N=2021)	Anti-IL4Rα (N=306)	Total (N=3717)
Yes, n (%)	458 (43.1%)	880 (57.0%)	133 (52.4%)	1471 (51.4%)
History of nasal polyposis	1100	1639	258	2997
Yes, n (%)	196 (17.8%)	566 (34.5%)	80 (31.0%)	842 (28.1%)
History of osteoporosis	1259	1604	291	3154
Yes, n (%)	195 (15.5%)	258 (16.1%)	32 (11.0%)	485 (15.4%)
History of sleep apnea	1362	1976	296	3634
Yes, n (%)	260 (19.1%)	300 (15.2%)	83 (28.0%)	643 (17.7%)
History of anxiety/depression	1226	1669	277	3172
Yes, n (%)	182 (14.8%)	245 (14.7%)	54 (19.5%)	481 (15.2%)
History of pneumonia	1080	1167	283	2530
Yes, n (%)	115 (10.6%)	163 (14.0%)	37 (13.1%)	315 (12.5%)
History of eczema/AD	1100	1635	258	2993
Yes, n (%)	130 (11.8%)	150 (9.2%)	48 (18.6%)	328 (11.0%)
History of diabetes	1371	1978	305	3654

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	Anti-IgE (N=1390)	**Anti-IL5/5R (N=2021)**	**Anti-IL4Rα (N=306)**	**Total (N=3717)**
Yes, n (%)	174 (12.7%)	161 (8.1%)	35 (11.5%)	370 (10.1%)
History of cataract	1196	1349	300	2845
Yes, n (%)	38 (3.2%)	79 (5.9%)	3 (1.0%)	120 (4.2%)
History of heart failure and/or myocardial infarction	1095	1112	267	2474
Yes, n(%)	37 (3.4%)	58 (5.2%)	6 (2.2%)	101 (4.1%)
History of peptic ulcer	1098	1131	296	2525
Yes, n (%)	42 (3.8%)	39 (3.4%)	6 (2.0%)	87 (3.4%)
History of chronic kidney disease	1069	1106	262	2437
Yes, n (%)	27 (2.5%)	34 (3.1%)	5 (1.9%)	66 (2.7%)
History of glaucoma	1194	1336	303	2833
Yes	14 (1.2%)	25 (1.9%)	3 (1.0%)	42 (1.5%)
History of PE/venous thromboembolism	1244	1559	297	3100

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	Anti-IgE (N=1390)	**Anti-IL5/5R (N=2021)**	**Anti-IL4Rα (N=306)**	**Total (N=3717)**
Yes, n (%)	20 (1.6%)	23 (1.5%)	9 (3.0%)	52 (1.7%)
History of CVA	1143	1185	298	2626
Yes, n (%)	8 (0.7%)	7 (0.6%)	4 (1.3%)	19 (0.7%)

Abbreviations: AD: atopic dermatitis; CVA: cerebrovascular accident; PE: pulmonary embolism

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Table E2: asthma control test utilized by country

Country	N	Proportions of patients by asthma control assessment tool used
Argentina, Bulgaria, Canada, Colombia, Greece, India, Japan, Kuwait, Mexico, Poland, Portugal, Saudi Arabia, Singapore, South Korea, Taiwan, UAE	415	GINA: 100%
Australia	135	ACQ: 100%
Denmark	194	ACQ: 77.8% ACT: 22.2%
Italy	333	GINA: 80.2% ACQ: 19.8%
Spain	46	ACT: 100%
UK	467	ACQ: 100%
USA	218	ACT: 100%
TOTAL	1808	GINA: 37.7% ACQ: 45.3% ACT: 17.0%

ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; GINA: Global Initiative for Asthma; UAE: United Arab Emirates

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Table E3: Number and proportion of patients excluded from the analysis by sequential exclusion criteria and by country.

Countries (N of biologic patients in ISAR database)	Sequential exclusion criteria						Eligible
	1. Age <18 at biologic initiation	2. Missing date at biologic initiation	3. Missing age at biologic initiation	4. Had bronchial thermoplasty	5. No post-biologic data available	6. No pre-biologic data available	
Total (N=6816)	148 (2.2%)	209 (3.1%)	50 (0.7%)	21 (0.3%)	1956 (28.7%)	715 (10.5%)	3717 (54.3%)
Argentina (N=61)	0 (0.0%)	19 (31.1%)	3 (4.9%)	0 (0.0%)	14 (23.0%)	11 (18.0%)	14 (23.0%)
Australia (N=322)	2 (0.6%)	25 (7.8%)	4 (1.2%)	12 (3.7%)	71 (22.0%)	18 (5.6%)	190 (59.0%)
Bulgaria (N=65)	0 (0.0%)	2 (3.1%)	0 (0.0%)	0 (0.0%)	45 (69.2%)	10 (15.4%)	8 (12.3%)
Canada (N=266)	1 (0.4%)	21 (7.9%)	1 (0.4%)	0 (0.0%)	43 (16.2%)	18 (6.8%)	182 (68.4%)
Colombia (N=166)	3 (1.8%)	26 (15.7%)	1 (0.6%)	0 (0.0%)	50 (30.1%)	13 (7.8%)	73 (44.0%)
Denmark (N=334)	4 (1.2%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	27 (8.1%)	11 (3.3%)	291 (87.1%)
Greece (N=92)	0 (0.0%)	5 (5.4%)	0 (0.0%)	0 (0.0%)	33 (35.9%)	3 (3.3%)	51 (55.4%)
India (N=6)	0 (0.0%)	3 (50.0%)	0 (0.0%)	0 (0.0%)	2 (33.3%)	0 (0.0%)	1 (16.7%)
Ireland (N=3)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	1 (33.3%)	1 (33.3%)
Italy (N=1138)	16 (1.4%)	3 (0.3%)	0 (0.0%)	0 (0.0%)	396 (34.8%)	285 (25.0%)	438 (38.5%)

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Japan (N=146)	6 (4.1%)	6 (4.1%)	0 (0.0%)	0 (0.0%)	41 (28.1%)	26 (17.8%)	67 (45.9%)
Kuwait (N=231)	6 (2.6%)	5 (2.2%)	3 (1.3%)	0 (0.0%)	11 (4.8%)	13 (5.6%)	193 (83.5%)
Mexico (N=175)	6 (3.4%)	28 (16.0%)	6 (3.4%)	0 (0.0%)	57 (32.6%)	10 (5.7%)	68 (38.9%)
Poland (N=274)	3 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	99 (36.1%)	30 (10.9%)	142 (51.8%)
Portugal (N=95)	3 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	51 (53.7%)	19 (20.0%)	22 (23.2%)
Saudi Arabia (N=112)	1 (0.9%)	34 (30.4%)	0 (0.0%)	1 (0.9%)	26 (23.2%)	5 (4.5%)	45 (40.2%)
Singapore (N=25)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (24.0%)	5 (20.0%)	14 (56.0%)
South Korea (N=35)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	13 (37.1%)	5 (14.3%)	16 (45.7%)
Spain (N=582)	22 (3.8%)	10 (1.7%)	2 (0.3%)	1 (0.2%)	302 (51.9%)	88 (15.1%)	157 (27.0%)
Taiwan (N=111)	1 (0.9%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	24 (21.6%)	10 (9.0%)	72 (64.9%)
UAE (N=155)	2 (1.3%)	12 (7.7%)	0 (0.0%)	0 (0.0%)	74 (47.7%)	13 (8.4%)	54 (34.8%)
UK (N=575)	1 (0.2%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	85 (14.8%)	0 (0.0%)	487 (84.7%)
USA (N=1847)	71 (3.8%)	4 (0.2%)	29 (1.6%)	6 (0.3%)	485 (26.3%)	121 (6.6%)	1131 (61.2%)

Abbreviations: ISAR: International Severe Asthma Registry; UAE: United Arab Emirates

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Table E4: Duration and adherence to biologic therapy during the study

Biologic therapy adherence over 1 year post-initiation	Total (N=3686)	Anti-IgE (N=1375)	Anti-IL5/5R (N=2007)	Anti-IL4Rα (N=304)
Duration: median (range)	1 yr (1 day – 1 yr)	1 yr (1 day – 1 yr)	1 yr (1 day – 1 yr)	1 yr (1 day – 1 yr)
Interrupted therapy: n (%)	244 (6.62%)	123 (8.95%)	88 (4.38%)	33 (10.86%)
Switch to another biologic class: n (%)	119 (3.23%)	63 (4.58%)	45 (2.24%)	11 (3.62%)

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Table E5. Patient demographic and clinical characteristics pre-biologic by post-biologic remission status using 4 remission definitions.

Characteristics	2-domain definition: no exacerbation + no LTOCS			3-domain definition 1 no exacerbation + no LTOCS + well/partly controlled			3-domain definition 2: no exacerbation + no LTOCS + $ppFEV_1$ ≥80%			4-domain definition: no exacerbation + no LTOCS + well/partly controlled+ $ppFEV_1$		
	Remission (N=1076)	**No remission (N=1066)**	**p***	**Remission (N=414)**	**No remission (N=821)**	**p***	**Remission (N=435)**	**No remission (N=1253)**	**p***	**Remission (N=215)**	**No remission (N=844)**	**p***
Age at biologic initiation, yrs												
Median (Q1, Q3)	54 (42, 64)	54 (44, 62)	0.658	54 (45, 64)	54 (44, 62)	0.151	54 (44, 64)	55 (44, 63)	0.632	54 (46, 64)	54 (44, 62)	0.234
Sex												
Female, n (%)	641 (59.6)	662 (62.1)	0.231	238 (57.5)	502 (61.1)	0.216	269 (61.8)	752 (60.0)	0.503	129 (60.0)	503 (59.6)	0.914
Ethnicity, N	1027	1017	0.238	382	772	0.321	416	1187	0.031	197	787	0.007
Caucasian, n (%)	745 (72.5)	736 (72.4)		270 (70.7)	545 (70.6)		315 (75.7)	867 (73.0)		147 (74.6)	557 (70.8)	
South East Asian, n (%)	33 (3.2)	32 (3.1)		21 (5.5)	33 (4.3)		16 (3.8)	38 (3.2)		12 (6.1)	36 (4.6)	
North East Asian, n (%)	36 (3.5)	38 (3.7)		25 (6.5)	47 (6.1)		18 (4.3)	46 (3.9)		14 (7.1)	49 (6.2)	
African, n (%)	23 (2.2)	40 (3.9)		7 (1.8)	26 (3.4)		4 (1.0)	48 (4.0)		1 (0.5)	28 (3.6)	
Mixed, n (%)	10 (1.0)	6 (0.6)		7 (1.8)	5 (0.6)		6 (1.4)	7 (0.6)		6 (3.0)	6 (0.8)	
Other, n (%)	63 (6.1)	69 (6.8)		35 (9.2)	74 (9.6)		21 (5.0)	79 (6.7)		14 (7.1)	75 (9.5)	
Unknown/missing, n (%)	117 (11.4)	96 (9.4)		17 (4.4)	42 (5.4)		36 (8.6)	102 (8.6)		3 (1.5)	36 (4.6)	

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BMI, kg/m², N	1062	1039		409	799		432	1243		214	837	
Median (Q1, Q3)	28.1 (24.3,	28.1 (24.4,	0.201	26.9 (23.5,	28.2 (24.4,	<0.001	27.7 (23.9,	28.1 (24.3,	0.013	26.2 (23.1,	28.1 (24.3,	<0.001
Smoking status at Bx initiation, N	850	871	0.971	282	640	0.715	340	1013	0.101	149	644	0.124
Current smoker, n (%)	24 (2.8)	25 (2.9)		5 (1.8)	17 (2.7)		3 (0.9)	29 (2.9)		1 (0.7)	18 (2.8)	
Ex-smoker, n (%)	273 (32.1)	275 (31.6)		86 (30.5)	196 (30.6)		107 (31.5)	327 (32.3)		40 (26.8)	205 (31.8)	
Never smoker, n (%)	553 (65.1)	571 (65.6)		191 (67.7)	427 (66.7)		230 (67.6)	657 (64.9)		108 (72.5)	421 (65.4)	
Age-of-asthma onset, yrs, N	437	620		303	626		199	661		155	624	
Median (Q1, Q3)	31 (15, 45)	27 (10, 43)	0.075	31 (16, 45)	28 (11, 45)	0.339	35 (20, 46)	27 (11, 42)	0.002	35 (20, 49)	27 (11, 43)	0.002
Asthma duration§ yrs, N	437	620		303	626		199	661		155	624	
Median (Q1, Q3)	19 (9, 34)	22 (9, 36)	0.213	20 (9, 35)	21 (9, 35)	0.661	17 (6, 33)	21 (10, 35)	0.022	16 (7, 32)	21 (9, 35)	0.066
Pre-Bx highest BEC, 10^9 cells/L, N	691	744		276	565		278	855		141	579	
Median (Q1, Q3)	460 (200, 795)	400 (200, 722)	0.562	500 (300, 815)	430 (200, 750)	0.048	500 (290, 813)	410 (200, 730)	0.019	520 (310, 840)	450 (210, 776)	0.040
Pre-Bx latest FeNO, ppb, N	484	569		193	485		209	675		110	506	
Median (Q1, Q3)	32 (17, 64)	37 (20, 68)	0.362	33 (21, 60)	38 (21, 64)	0.970	32 (19, 70)	34 (19, 63)	0.160	36 (23, 73)	36 (21, 62)	0.060
Pre-Bx latest blood IgE count, IU/mL, N	676	735		266	578		284	862		151	600	
Median (Q1, Q3)	155 (68, 505)	183 (65, 437)	0.428	161 (66, 516)	182 (66, 434)	0.264	134 (64, 505)	171 (63, 425)	0.549	139 (63, 559)	180 (66, 431)	0.931

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Positive test to any allergen, N	385	521		144	441		161	580		76	430	
Yes, n (%)	365 (94.8)	426 (81.8)	<0.001	129 (89.6)	352 (79.8)	0.008	147 (91.3)	493 (85.0)	0.039	65 (85.5)	349 (81.2)	0.363
Medication use in the year preceding Bx initiation, N	940	962		314	702		372	1140		163	733	
LAMA, n (%)	37 (3.9)	35 (3.6)	0.734	7 (2.2)	25 (3.6)	0.261	10 (2.7)	50 (4.4)	0.145	2 (1.2)	28 (3.8)	0.096
Theophylline, n (%)	40 (4.3)	113 (11.7)	<0.001	21 (6.7)	103 (14.7)	<0.001	17 (4.6)	120 (10.5)	<0.001	12 (7.4)	105 (14.3)	0.017
LTRA, n (%)	483 (51.4)	461 (47.9)	0.131	128 (40.8)	308 (43.9)	0.355	197 (53.0)	556 (48.8)	0.161	71 (43.6)	327 (44.6)	0.807
Macrolide, n (%)	127 (13.5)	161 (16.7)	0.050	26 (8.3)	69 (9.8)	0.433	46 (12.4)	186 (16.3)	0.066	12 (7.4)	78 (10.6)	0.208
History of AR, N	867	668		265	422		343	830		139	439	
Yes, n (%)	434 (50.1)	325 (48.7)	0.585	159 (60.0)	250 (59.2)	0.844	181 (52.8)	406 (48.9)	0.230	84 (60.4)	254 (57.9)	0.592
History of CRS, N	890	905		281	645		360	1066		155	662	
Yes, n (%)	468 (52.6)	471 (52.0)	0.819	157 (55.9)	322 (49.9)	0.096	210 (58.3)	549 (51.5)	0.025	91 (58.7)	336 (50.8)	0.074
History of NP, N	918	946		304	691		364	1100		156	699	
Yes, n (%)	220 (24.0)	252 (26.6)	0.185	111 (36.5)	222 (32.1)	0.177	99 (27.2)	279 (25.4)	0.488	60 (38.5)	225 (32.2)	0.133
History of osteoporosis, N	924	874		346	624		357	1020		170	636	
Yes, n (%)	126 (13.6)	173 (19.8)	<0.001	44 (12.7)	109 (17.5)	0.052	52 (14.6)	206 (20.20)	0.019	21 (12.3)	118 (18.5)	0.057
History of anxiety/depression, N	866	890		362	671		338	1017		177	684	
Yes, n (%)	156 (18.0)	144 (16.2)	0.307	43 (11.9)	98 (14.6)	0.223	55 (16.3)	173 (17.0)	0.753	20 (11.3)	98 (14.3)	0.296

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Eosinophilic gradient,(1) N	776	885	0.045	342	699	0.026	326	1001	0.165	181	713	0.242
Grade 0: Unlikely/non eosinophilic, n (%)	1 (0.1)	0 (0.0)		1 (0.3)	0 (0.0)		1 (0.3)	0 (0.0)		1 (0.5)	0 (0.0)	
Grade 1: Least likely, n (%)	24 (3.1)	11 (1.2)		14 (4.1)	11 (1.6)		7 (2.1)	21 (2.1)		3 (1.7)	16 (2.2)	
Grade 2: Likely, n (%)	27 (3.5)	32 (3.6)		15 (4.4)	23 (3.3)		7 (2.1)	38 (3.8)		6 (3.3)	25 (3.5)	
Grade 3: Most likely, n (%)	724 (93.3)	842 (95.1)		312 (91.2)	665 (95.1)		311 (95.4)	942 (94.1)		171 (94.5)	672 (94.2)	
Pre-Bx exacerbations[†], N	689	772	<0.001	285	620	<0.001	276	893	0.006	146	629	0.330
0, n (%)	284 (41.2)	175 (22.7)		83 (29.1)	122 (19.7)		96 (34.8)	241 (27.0)		38 (26.0)	127 (20.2)	
1 (not hospitalized), n (%)	138 (20.0)	112 (14.5)		47 (16.5)	68 (11.0)		53 (19.2)	135 (15.1)		19 (13.0)	69 (11.0)	
2 (not hospitalized), n (%)	94 (13.6)	101 (13.1)		43 (15.1)	84 (13.5)		35 (12.7)	125 (14.0)		19 (13.0)	91 (14.5)	
≥1 (hospitalized) or ≥3 in total, n (%)	173 (25.1)	384 (49.7)		112 (39.3)	346 (55.8)		92 (33.3)	392 (43.9)		70 (48.0)	342 (54.4)	
Pre-Bx LTOCS dose[††], N	710	920	<0.001	377	764	<0.001	310	1012	<0.001	192	778	<0.001
0 mg/day (non-user), n (%)	569 (80.1)	374 (40.6)		303 (80.4)	357 (46.7)		242 (78.1)	504 (49.8)		147 (76.6)	404 (51.9)	
≤ 5mg/day, n (%)	40 (5.6)	150 (16.3)		15 (4.0)	107 (14.0)		21 (6.8)	141 (13.9)		9 (4.7)	94 (12.1)	
>5 to 10mg/day, n (%)	37 (5.2)	191 (20.8)		18 (4.8)	132 (17.3)		14 (4.5)	170 (16.8)		11 (5.7)	119 (15.3)	
>10mg/day, n (%)	36 (5.1)	140 (15.2)		22 (5.8)	113 (14.8)		17 (5.5)	135 (13.3)		12 (6.2)	108 (13.9)	
User but missing dose, n (%)	28 (3.9)	65 (7.1)		19 (5.0)	55 (7.2)		16 (5.2)	62 (6.1)		13 (6.8)	53 (6.8)	

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Pre-Bx asthma control[††], N	403	581	<0.001	242	576	<0.001	177	643	<0.001	126	570	<0.001
Well controlled, n (%)	60 (14.9)	43 (7.4)		40 (16.5)	36 (6.2)		34 (19.1)	47 (7.3)		27 (21.4)	36 (6.3)	
Partly controlled, n (%)	87 (21.6)	79 (13.6)		58 (24.0)	77 (13.4)		46 (26.0)	92 (14.3)		34 (27.0)	76 (13.3)	
Uncontrolled, n (%)	256 (63.5)	459 (79.0)		144 (59.5)	463 (80.4)		97 (54.8)	504 (78.4)		65 (51.6)	458 (80.3)	
Pre-Bx ppFEV$_1$[††], N	862	876	<0.001	270	636	0.001	347	1070	<0.001	145	672	<0.001
≥80%, n (%)	411 (47.7)	316 (36.1)		143 (53.0)	228 (35.8)		262 (75.5)	300 (28.0)		112 (77.2)	216 (32.1)	
<80%, n (%)	451 (52.3)	560 (63.9)		127 (47.0)	408 (61.2)		85 (24.5)	770 (72.0)		33 (22.8)	456 (67.9)	

*Kruskal-Wallis rank sum test for continuous variables; Pearson's chi-squared test for categorical variables.

[†]In the year preceding biologic initiation.

[††]In the year preceding and closest to biologic initiation. Assessed using either GINA control criteria,(2) Asthma Control Test(3) or Asthma Control Questionnaire(4). ACQ and/or ACT control categories were fitted to GINA 2020 control categories as follows: Mean ACQ: well controlled (≤0.75); partly controlled (>0.75 to < 1.5); uncontrolled (≥1.5) Total ACT: well controlled (>19); partly controlled (>15 to ≤19); uncontrolled (≤15).

§age at biologic initiation minus reported age at asthma onset

Abbreviations: AR: allergic rhinitis; BEC: blood eosinophil concentration; Bx: biologic; CRS: chronic rhinosinusitis; FeNO: fractional exhaled nitric oxide; LAMA: long-acting muscarinic antagonist; LTOCS: long-term oral corticosteroid; LTRA: leukotriene receptor antagonist; NP: nasal polyps; ppFEV$_1$: percent predicted forced expiratory volume in one second; Q: quartile

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Table E6. Proportion of patients categorized as in remission at 1-year post-biologic initiation according to different definitions, overall and by biologic class.

	Overall (N=3717)	Anti-IgE (N=1390)	Anti-IL5/5R (N=2021)	Anti-IL4Rα (N=306)
Exacerbations remission				
N	2163	738	1199	226
None	1366 (63.2%)	476 (64.5%)	713 (59.5%)	177 (78.3%)
1 that did not require hospitalisation	415 (19.2%)	144 (19.5%)	237 (19.8%)	34 (15.0%)
2 that did not require hospitalisation	148 (6.8%)	52 (7.0%)	89 (7.4%)	7 (3.1%)
>=1 that required hospitalisation or >=3 in total	234 (10.8%)	66 (8.9%)	160 (13.3%)	8 (3.5%)
Follow-up duration for exac (wks)				
Median	52.14	52.14	54.14	52.14
Q1, Q3	52.14, 52.57	52.14, 52.14	52.14, 55.21	52.14, 52.14
LTOCS remission				
N	3695	1384	2011	300
Non user	2720 (73.6%)	1108 (80.1%)	1343 (66.8%)	269 (89.7%)
<=5mg/day	355 (9.6%)	92 (6.6%)	249 (12.4%)	14 (4.7%)
>5 to 10mg/day	265 (7.2%)	85 (6.1%)	171 (8.5%)	9 (3.0%)
>10mg/day	212 (5.7%)	62 (4.5%)	144 (7.2%)	6 (2.0%)

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User but missing dose	143 (3.9%)	37 (2.7%)	104 (5.2%)	2 (0.7%)
Follow-up duration for LTOCS (weeks)				
Median	52.14	52.14	52.14	52.14
Q1, Q3	52.14, 52.14	52.14, 52.14	52.14, 52.14	49.75, 52.29
Asthma control remission*				
N	1882	571	1199	112
Well controlled	675 (35.9%)	177 (31.0%)	444 (37.0%)	54 (48.2%)
Partly controlled	505 (26.8%)	163 (28.5%)	315 (26.3%)	27 (24.1%)
Uncontrolled	702 (37.3%)	231 (40.5%)	440 (36.7%)	31 (27.7%)
Follow-up duration for asthma control (weeks)				
Median	51.57	50.43	52.00	48.43
Q1, Q3	43.71, 58.54	42, 58.29	45.00, 58.71	37.68, 57.93
Lung function remission				
N	2323	782	1369	172
ppFEV$_1$ ≥80%	1104 (47.5%)	356 (45.5%)	652 (47.6%)	96 (55.8%)
ppFEV$_1$ <80%	1219 (52.5%)	426 (54.5%)	717 (52.4%)	76 (44.2%)
Follow-up duration for lung function (weeks)				
Median	50.86	50.43	51.00	47.57

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Q1, Q3	42.00, 58.00	42.57, 58.00	42.57, 58.00	36.71, 58.93
Remission in exacerbations and LTOCS (strict definition)				
N	2142	732	1189	221
No exacerbation & no LTOCS	1076 (50.2%)	403 (55.1%)	516 (43.4%)	157 (71.0%)
Other combinations	1066 (49.8%)	329 (44.9%)	673 (56.6%)	64 (29.0%)
Remission in exacerbations and LTOCS (relaxed definition)				
N	2073	717	1137	219
<=1 exacerbation (no hospitalisation) and LTOCS <=5mg/day	1559 (75.2%)	559 (78.0%)	803 (70.6%)	197 (90.0%)
Other combinations	514 (24.8%)	158 (22.0%)	334 (29.4%)	22 (10.0%)
Remission in exacerbations, LTOCS, and asthma control* (strict definition)				
N	1235	379	778	78
No exacerbation, no LTOCS, and partly/well controlled	414 (33.5%)	130 (34.3%)	241 (31.0%)	43 (55.1%)
Other combinations	821 (66.5%)	249 (65.7%)	537 (69.0%)	35 (44.9%)
Remission in exacerbations, LTOCS, and asthma control* (relaxed definition)				
N	1186	368	740	78
<=1 exacerbation (no hospitalisation), LTOCS <=5mg/day, and partly/well controlled	590 (49.7%)	177 (48.1%)	362 (48.9%)	51 (65.4%)

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Other combinations	596 (50.3%)	191 (51.9%)	378 (51.1%)	27 (34.6%)
Remission in exacerbations, LTOCS, and lung function (strict definition)				
N	1688	584	971	133
No exacerbation, no LTOCS, and ppFEV$_1$ ≥80%	435 (25.8%)	161 (27.6%)	230 (23.7%)	44 (33.1%)
Other combinations	1253 (74.2%)	423 (72.4%)	741 (76.3%)	89 (66.9%)
Remission in exacerbations, LTOCS, and lung function (relaxed definition)				
N	1632	573	927	132
<=1 exacerbation (no hospitalisation), LTOCS <=5mg/day, and ppFEV$_1$ ≥80%	612 (37.5%)	214 (37.3%)	335 (36.1%)	63 (47.7%)
Other combinations	1020 (62.5%)	359 (62.7%)	592 (63.9%)	69 (52.3%)
Remission in exacerbations, LTOCS, asthma control,* and lung function (strict definition)				
N	1059	322	675	62
No exacerbation, no LTOCS, partly/well controlled, and ppFEV$_1$ ≥80%	215 (20.3%)	62 (19.3%)	139 (20.6%)	14 (22.6%)
Other combinations	844 (79.7%)	260 (80.7%)	536 (79.4%)	48 (77.4%)
Remission in exacerbations, LTOCS, asthma control*, and lung function (relaxed definition)				
N	1019	315	642	62
<=1 exacerbation (no hospitalisation), LTOCS <=5mg/day, partly/well controlled, and ppFEV$_1$ ≥80%	297 (29.1%)	81 (25.7%)	198 (30.8%)	18 (29.0%)

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Other combinations	722 (70.9%)	234 (74.3%)	444 (69.2%)	44 (71.0%)

* Assessed using either GINA control criteria,(2) Asthma Control Test(3) or Asthma Control Questionnaire(4).

ACQ and/or ACT control categories were fitted to GINA 2020 control categories as follows: Mean ACQ: well controlled (≤0.75); partly controlled (>0.75 to < 1.5); uncontrolled (≥1.5) Total ACT: well controlled (>19); partly controlled (>15 to ≤19); uncontrolled (≤15).

Abbreviations: LTOCS: long-term oral corticosteroids; ppFEV_1: percent predicted forced expiratory volume in one second

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Table E7 Proportion of patients categorized as in remission at 1-year post-biologic initiation according to different definitions, stratified by pre-biologic FEV_1/FVC

Post-biologic remission criteria	Pre-biologic FEV_1/FVC ratio <0.70	Pre-biologic FEV_1/FVC ratio ≥ 0.70
No exacerbation, N n (%)	925 549 (59.4)	799 537 (67.2)
No LTOCS use, N n (%)	1393 983 (70.6)	1239 957 (77.2)
Partly/well controlled,* N n, (%)	647 381 (58.9)	521 297 (57.0)
$ppFEV_1$ ≥ 80%, N n (%)	942 280 (29.7)	760 518 (68.2)
2-domain (exacerbation + LTOCS), N n (%)	920 420 (45.7)	790 433 (54.8)
3-domain (exacerbation + LTOCS + control*), N n (%)	487 131 (26.9)	391 128 (32.7)
3-domain (exacerbation + LTOCS + $ppFEV_1$), N n (%)	771 109 (14.1)	617 231 (37.4)
4-domain (exacerbation + LTOCS + control* + $ppFEV_1$), N n (%)	444 50 (11.3)	347 88 (25.4)

*Assessed using either GINA control criteria,(2) Asthma Control Test(3) or Asthma Control Questionnaire(4).

ACQ and/or ACT control categories were fitted to GINA 2020 control categories as follows: Mean ACQ: well controlled (≤0.75); partly controlled (>0.75 to < 1.5); uncontrolled (≥1.5) Total ACT: well controlled (>19); partly controlled (>15 to ≤19); uncontrolled (≤15).

Abbreviations - FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; $ppFEV_1$: percent predicted forced expiratory volume in one second; LTOCS: long-term oral corticosteroid

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Table E8. Proportions of patients categorized as in remission pre-biologic initiation according to different definitions, overall and by biologic class, in patients with matching available data post-biologic.

	Overall (N=3569)	Anti-IgE (N=1323)	Anti-IL5/5R (N=1972)	Anti-IL4Rα (N=274)
Exacerbations remission				
N	1471	403	917	151
0. None	462 (31.4%)	165 (41.9%)	215 (23.4%)	82 (54.3%)
1 that did not require hospitalisation	252 (17.1%)	76 (18.9%)	141 (15.4%)	35 (23.2%)
2 that did not require hospitalisation	196 (13.3%)	56 (13.9%)	125 (13.6%)	15 (9.9%)
≥1 that required hospitalisation or ≥3 in total	561 (34.1%)	106 (26.3%)	436 (47.5%)	19 (12.6%)
LTOCS remission				
N	3086	1074	1820	192
Non user	1846 (59.8%)	727 (67.7%)	971 (53.4%)	148 (77.1%)
<=5mg/day	330 (10.7%)	98 (9.1%)	217 (11.9%)	15 (7.8%)
>5 to 10mg/day	365 (11.8%)	100 (9.3%)	252 (13.8%)	13 (6.8%)
>10mg/day	362 (11.7%)	105 (9.8%)	242 (13.3%)	15 (7.8%)
User but missing dose	183 (5.9%)	44 (4.1%)	138 (7.6%)	1 (0.5%)
Asthma control* remission				

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N	1165	301	820	44
Well controlled	104 (8.9%)	35 (11.6%)	60 (7.3%)	9 (20.5%)
Partly controlled	218 (18.7%)	57 (18.9%)	151 (18.4%)	10 (22.7%)
Uncontrolled	843 (72.4%)	209 (69.4%)	609 (74.3%)	25 (56.8%)
Lung function remission				
N	1741	568	1042	131
$ppFEV_1$ ≥80%	704 (40.4%)	237 (41.7%)	409 (39.3%)	58 (44.3%)
$ppFEV_1$ <80%	1037 (59.6%)	331 (58.3%)	633 (60.7%)	73 (55.7%)
Remission in exacerbations and LTOCS (strict definition)				
N	1258	316	845	97
No exacerbation & no LTOCS	106 (8.4%)	35 (11.1%)	54 (6.4%)	17 (17.5%)
Other combinations	1152 (91.6%)	281 (88.9%)	791 (93.6%)	80 (82.5%)
Remission in exacerbations and LTOCS (relaxed definition)				
N	1174	302	775	97
<=1 exacerbation (no hospitalisation) and LTOCS <=5mg/day	358 (30.5%)	107 (35.4%)	194 (25.0%)	57 (58.8%)
Other combinations	816 (69.5%)	195 (64.6%)	581 (75.0%)	40 (41.2)
Remission in exacerbations, LTOCS, and asthma control* (strict definition)				
N	726	172	528	26

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No exacerbation, no LTOCS, and partly/well controlled	35 (4.8%)	12 (7.0)	16 (3.0)	7 (26.9)
Other combinations	691 (95.2%)	160 (93.0)	512 (97.0)	19 (73.1)
Remission in exacerbations, LTOCS, and asthma control* (relaxed definition)				
N	668	166	476	26
<=1 exacerbation (no hospitalisation), LTOCS <=5mg/day, and partly/well controlled	59 (8.8%)	22 (13.3)	29 (6.1)	8 (30.8)
Other combinations	609 (91.2%)	144 (86.7)	447 (93.9)	18 (69.2)
Remission in exacerbations, LTOCS, and lung function (strict definition)				
N	933	223	658	52
No exacerbation, no LTOCS, and $ppFEV_1$ ≥80%	22 (2.4%)	10 (4.5)	9 (1.4)	3 (5.8)
Other combinations	911 (97.6%)	213 (95.5)	649 (98.6)	49 (94.2)
Remission in exacerbations, LTOCS, and lung function (relaxed definition)				
N	870	216	602	52
<=1 exacerbation (no hospitalisation), LTOCS <=5mg/day, and $ppFEV_1$ ≥80%	86 (9.9%)	28 (13.0)	44 (7.3)	14 (26.9)
Other combinations	784 (90.1%)	188 (87.0)	558 (92.7)	38 (73.1)
Remission in exacerbations, LTOCS, asthma control*, and lung function (strict definition)				
N	585	131	440	14

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No exacerbation, no LTOCS, partly/well controlled, and ppFEV$_1$ ≥80%	6 (1.0%)	2 (1.5)	4 (0.9)	0 (0.0)
Other combinations	579 (99.0%)	129 (98.5)	436 (99.1)	14 (100.0)
Remission in exacerbations, LTOCS, asthma contro*l, and lung function (relaxed definition)				
N	536	126	396	14
<=1 exacerbation (no hospitalisation), LTOCS <=5mg/day, partly/well controlled, and ppFEV$_1$ >=80%	20 (3.7%)	8 (6.3)	11 (2.8)	1 (7.1)
Other combinations	516 (96.3%)	118 (93.7)	385 (97.2)	13 (93.9)

*Assessed using either GINA control criteria,(2) Asthma Control Test(3) or Asthma Control Questionnaire(4). ACQ and/or ACT control categories were fitted to GINA 2020 control categories as follows: Mean ACQ: well controlled (≤0.75); partly controlled (>0.75 to < 1.5); uncontrolled (≥1.5) Total ACT: well controlled (>19); partly controlled (>15 to ≤19); uncontrolled (≤15).

Abbreviations: LTOCS: long-term oral corticosteroid; ppFEV$_1$: percent predicted forced expiratory volume in one second

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Table E9: Association between selected pre-biologic variables and composite definitions of remission, adjusted for age, sex, and pre-biologic asthma-related outcomes included in the remission definition.

Pre-biologic factors	**Remission definitions**			
	No exacerbations & no LTOCS N OR (95% CI) p-value	**No exacerbations, no LTOCS, & partly/well controlled*** N OR (95% CI) p-value	**No exacerbations, no LTOCS, & $ppFEV_1$ ≥80%** N OR (95% CI) p-value	**No exacerbations, no LTOCS, partly/well controlled, & $ppFEV_1$ ≥80%** N OR (95% CI) p-value
All biologic classes				
Exacerbations (1-unit increment)	1157 0.85 (0.80-0.89) <0.001	669 0.89 (0.83-0.95) <0.001	870 0.90 (0.83-0.96) 0.004	539 0.88 (0.80-0.97) 0.011
LTOCS dose (5-mg/day increment)	1157 0.52 (0.46-0.60) <0.001	669 0.60 (0.50-0.71) <0.001	870 0.45 (0.36-0.58) <0.001	539 0.59 (0.45-0.77) <0.001
Asthma control (1-GINA category increment)	762 1.32 (1.03-1.70) 0.027	669 1.72 (1.31-2.27) <0.001	606 1.21 (0.86-1.70) 0.277	539 1.34 (0.91-1.97) 0.135
$ppFEV_1$ (5-unit increment)	1014 1.06 (1.03-1.10) <0.001	607 1.10 (1.05-1.16) <0.001	870 1.30 (1.24-1.37) <0.001	539 1.29 (1.20-1.38) <0.001
BEC (doubling in concentration)	812 1.10 (0.97-1.23) 0.127	494 1.22 (1.03-1.46) 0.019	615 1.18 (0.98-1.43) 0.080	400 1.19 (0.92-1.54) 0.190

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Pre-biologic factors	**Remission definitions**			
	No exacerbations & no LTOCS N OR (95% CI) p-value	**No exacerbations, no LTOCS, & partly/well controlled*** N OR (95% CI) p-value	**No exacerbations, no LTOCS, & $ppFEV_1$ ≥80%** N OR (95% CI) p-value	**No exacerbations, no LTOCS, partly/well controlled, & $ppFEV_1$ ≥80%** N OR (95% CI) p-value
Blood IgE level (doubling in concentration)	819 0.94 (0.87-1.01) 0.093	511 0.92 (0.83-1.03) 0.141	649 0.95 (0.85-1.06) 0.337	440 0.92 (0.79-1.06) 0.246
FeNO (25-unit increment, ppb)	662 1.05 (0.95-1.17) 0.329	449 1.10 (0.96-1.27) 0.174	547 1.09 (0.95-1.24) 0.232	397 1.17 (0.99-1.38) 0.064
Asthma duration* (10-year increment)	714 0.90 (0.82-1.00) 0.040	577 0.99 (0.88-1.12) 0.881	531 0.92 (0.79-1.07) 0.275 *Removing pre-bx lung function adjustment:* *582* *0.85 (0.75-0.96)* *0.008*	455 0.94 (0.79-1.13) 0.515 *Removing pre-bx lung function adjustment:* *480* *0.85 (0.73-1.00)* *0.047*
BMI (5-unit increment)	1136 0.97 (0.88-1.07) 0.534	655 0.90 (0.78-1.05) 0.178	868 1.10 (0.95-1.28) 0.196	537 0.94 (0.76-1.18) 0.619
Smoking status (ever vs. never)	1003 0.85 (0.63-1.14) 0.270	586 0.76 (0.49-1.18) 0.226	773 1.06 (0.69-1.62) 0.793	482 0.82 (0.43-1.54) 0.533

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Pre-biologic factors	**Remission definitions**			
	No exacerbations & no LTOCS N OR (95% CI) p-value	**No exacerbations, no LTOCS, & partly/well controlled*** N OR (95% CI) p-value	**No exacerbations, no LTOCS, & $ppFEV_1$ ≥80%** N OR (95% CI) p-value	**No exacerbations, no LTOCS, partly/well controlled, & $ppFEV_1$ ≥80%** N OR (95% CI) p-value
Use of LTRA (yes vs. no)	992 0.90 (0.68-1.19) 0.457	534 0.76 (0.49-1.19) 0.228	765 1.09 (0.72-1.66) 0.678	447 0.97 (0.52-1.79) 0.916
Use of theophylline (yes vs. no)	992 0.48 (0.29-0.82) 0.007	534 0.43 (0.20-0.91) 0.027	765 0.58 (0.26-1.31) 0.193	447 0.60 (0.24-1.55) 0.292
Use of macrolide antibiotics (yes vs. no)	992 0.75 (0.53-1.07) 0.112	534 1.23 (0.60-2.56) 0.571	765 0.82 (0.48-1.40) 0.472	447 1.29 (0.52-3.22) 0.585
Allergen test results (positive vs. negative)	717 1.50 (0.99-2.26) 0.053	469 1.67 (0.87-3.20) 0.121	574 1.56 (0.84-2.90) 0.160	393 1.09 (0.48-2.52) 0.832
Allergic rhinitis (ever vs. never)	789 1.14 (0.84-1.53) 0.397	374 1.18 (0.74-1.87) 0.486	583 1.20 (0.78-1.84) 0.400	281 0.86 (0.46-1.61) 0.632
Chronic rhinosinusitis (ever vs. never)	1059 1.04 (0.8-1.36) 0.749	619 1.43 (0.98-2.10) 0.067	839 0.94 (0.64-1.40) 0.772	514 1.27 (0.74-2.15) 0.384
Nasal polyposis (ever vs. never)	1104 1.12 (0.84-1.49) 0.432	662 1.46 (1.01-2.12) 0.046	859 1.20 (0.80-1.80) 0.375	534 1.32 (0.78-2.23) 0.310

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Pre-biologic factors	Remission definitions			
	No exacerbations & no LTOCS N OR (95% CI) p-value	**No exacerbations, no LTOCS, & partly/well controlled*** N OR (95% CI) p-value	**No exacerbations, no LTOCS, & $ppFEV_1$ ≥80%** N OR (95% CI) p-value	**No exacerbations, no LTOCS, partly/well controlled, & $ppFEV_1$ ≥80%** N OR (95% CI) p-value
Eczema/AD (ever vs. never)	1106 1.95 (1.25-3.04) 0.003	663 1.40 (0.80-2.46) 0.244	861 1.63 (0.90-2.96) 0.109	535 0.59 (0.24-1.46) 0.252
T2-related comorbidity score (1-point increment; 0 to 4 score system)	735 1.05 (0.92-1.20) 0.484	326 1.11 (0.91-1.35) 0.313	560 1.04 (0.86-1.26) 0.679	257 0.96 (0.74-1.24) 0.736
Osteoporosis (yes vs. no)	895 0.76 (0.52-1.11) 0.156	495 0.82 (0.45-1.48) 0.511	647 0.66 (0.36-1.19) 0.168	378 0.46 (0.17-1.22) 0.117
Sleep apnea (yes vs. no)	1134 1.11 (0.79-1.54) 0.459	665 1.26 (0.72-2.23) 0.419	854 0.98 (0.60-1.60) 0.949	536 1.45 (0.67-3.12) 0.348
Anxiety/depression (yes vs. no)	936 1.51 (1.03-2.23) 0.037	569 1.24 (0.69-2.22) 0.467	682 1.25 (0.69-2.28) 0.456	440 1.95 (0.88-4.32) 0.101

*Assessed using either GINA 2020 control criteria,(2) Asthma Control Test(3) or Asthma Control Questionnaire(4). ACQ and/or ACT control categories were fitted to GINA 2020 control categories as follows: Mean ACQ: well controlled (≤0.75); partly controlled (>0.75 to < 1.5); uncontrolled (≥1.5) Total ACT: well controlled (>19); partly controlled (>15 to ≤19); uncontrolled (≤15).

†age at biologic initiation minus reported age at asthma onset

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Abbreviations: AD: atopic dermatitis; BEC: blood eosinophil count; BMI: body mass index; Bx: biologic; CI: confidence interval; FeNO: fractional exhaled nitric oxide; GINA: Global Initiative for Asthma; LTRA: leukotriene receptor antagonist; LTOCS: long-term oral corticosteroid; OR: odds ratio; $ppFEV_1$: percent predicted forced expiratory volume in one second

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Table E10: Association between selected pre-biologic variables and composite definitions of remission, adjusted for age, sex, country*, and pre-biologic asthma-related outcomes included in the remission definition.

Pre-biologic factors	Remission definitions			
	No exacerbations & no LTOCS N OR (95% CI) p-value	**No exacerbations, no LTOCS, & partly/well controlled†** N OR (95% CI) p-value	**No exacerbations, no LTOCS, & $ppFEV_1$ ≥80%** N OR (95% CI) p-value	**No exacerbations, no LTOCS, partly/well controlled†, & $ppFEV_1$ ≥80%** N OR (95% CI) p-value
Exacerbations (1-unit increment)	1157 0.90 (0.85-0.95) <0.001	669 0.95 (0.89-1.02) 0.156	870 0.93 (0.86-1.01) 0.092	539 0.93 (0.84-1.04) 0.194
LTOCS dose (5-mg/day increment)	1157 0.60 (0.52-0.68) <0.001	669 0.67 (0.57-0.80) <0.001	870 0.52 (0.41-0.66) <0.001	539 0.69 (0.53-0.90) 0.006
Asthma control (1-GINA category increment)	762 1.44 (1.10-1.89) 0.008	669 1.86 (1.38-2.52) <0.001	606 1.34 (0.94-1.92) 0.108	539 1.51 (1.00-2.27) 0.047
$ppFEV_1$ (5-unit increment)	1014 1.06 (1.03-1.10) <0.001	607 1.09 (1.04-1.15) <0.001	870 1.31 (1.24-1.38) <0.001	539 1.28 (1.19-1.37) <0.001
BEC (doubling in concentration)	812 1.04 (0.92-1.18) 0.508	494 1.12 (0.94-1.34) 0.214	615 1.13 (0.93-1.37) 0.225	400 1.11 (0.84-1.45) 0.464
Blood IgE level (doubling in concentration)	819 0.96 (0.89-1.04) 0.292	511 0.95 (0.85-1.07) 0.421	649 0.96 (0.86-1.07) 0.465	440 0.94 (0.80-1.09) 0.411
FeNO (25-unit increment, ppb)	662 1.06 (0.95-1.18) 0.302	449 1.09 (0.94-1.27) 0.254	547 1.09 (0.95-1.26) 0.215	397 1.16 (0.98-1.37) 0.090
Asthma duration** (10-year increment)	714 0.89 (0.79-0.99) 0.038	577 0.99 (0.87-1.13) 0.895	531 0.92 (0.79-1.08) 0.297 *Removing pre-bx lung function adjustment:* *582* *0.85 (0.75-0.98)* *0.022*	455 0.94 (0.78-1.13) 0.515 *Removing pre-bx lung function adjustment:* *480* *0.87 (0.73-1.03)* *0.107*
BMI (5-unit increment)	1136 1.03 (0.93-1.14) 0.617	655 0.97 (0.82-1.13) 0.659	868 1.17 (1.00-1.36) 0.049	537 1.03 (0.81-1.30) 0.818
Smoking status (ever vs. never)	1003 0.77 (0.57-1.05) 0.099	586 0.69 (0.43-1.11) 0.128	773 1.03 (0.66-1.59) 0.902	482 0.74 (0.39-1.43) 0.377
Use of LTRA (yes vs. no)	992 0.88 (0.65-1.19) 0.416	534 0.79 (0.49-1.29) 0.354	765 1.10 (0.72-1.70) 0.652	447 0.96 (0.50-1.83) 0.903

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Use of theophylline (yes vs. no)	992 0.49 (0.27-0.89) 0.019	534 0.51 (0.23-1.13) 0.096	765 0.64 (0.27-1.50) 0.301	447 0.72 (0.27-1.93) 0.516
Use of macrolide antibiotics (yes vs. no)	992 0.68 (0.45-1.01) 0.057	534 1.17 (0.52-2.65) 0.709	765 0.84 (0.47-1.51) 0.564	447 1.39 (0.44-4.36) 0.570
Allergen test results (positive vs. negative)	717 1.17 (0.54-2.56) 0.691	469 1.14 (0.54-2.38) 0.736	574 1.29 (0.68-2.46) 0.437	393 0.73 (0.29-1.85) 0.504
Allergic rhinitis (ever vs. never)	789 1.08 (0.79-1.47) 0.626	374 1.10 (0.68-1.77) 0.697	583 1.17 (0.76-1.81) 0.470	281 0.85 (0.44-1.62) 0.616
Chronic rhinosinusitis (ever vs. never)	1059 0.86 (0.64-1.15) 0.303	619 1.09 (0.71-1.66) 0.707	839 0.80 (0.53-1.22) 0.297	514 0.98 (0.55-1.75) 0.948
Nasal polyposis (ever vs. never)	1104 1.02 (0.75-1.38) 0.895	662 1.27 (0.85-1.90) 0.239	859 1.06 (0.69-1.62) 0.798	534 1.09 (0.62-1.91) 0.759
Eczema/AD (ever vs. never)	1106 1.51 (0.94-2.43) 0.086	663 1.10 (0.59-2.05) 0.765	861 1.44 (0.77-2.69) 0.253	535 0.50 (0.19-1.32) 0.163
T2-related comorbidity score (1-point increment; 0 to 4 score system)	735 1.03 (0.89-1.18) 0.714	326 1.11 (0.90-1.35) 0.331	560 1.03 (0.85-1.25) 0.772	257 0.96 (0.74-1.24) 0.734
Osteoporosis (yes vs. no)	895 0.63 (0.42-0.94) 0.025	495 0.60 (0.31-1.13) 0.113	647 0.59 (0.32-1.08) 0.088	378 0.32 (0.11-0.91) 0.033
Sleep apnea (yes vs. no)	1134 1.04 (0.73-1.49) 0.827	665 1.04 (0.55-1.95) 0.904	854 0.97 (0.57-1.65) 0.915	536 1.28 (0.55-3.00) 0.564
Anxiety/depression (yes vs. no)	936 1.12 (0.74-1.68) 0.594	569 0.73 (0.39-1.36) 0.327	682 1.04 (0.56-1.93) 0.893	440 1.47 (0.63-3.42) 0.371

Abbreviations: AD: atopic dermatitis; BEC: blood eosinophil count; BMI: body mass index; Bx: biologic; CI: confidence interval; FeNO: fractional exhaled nitric oxide; GINA: Global Initiative for Asthma; LTRA: leukotriene receptor antagonist; LTOCS: long-term oral corticosteroid; OR: odds ratio; $ppFEV_1$: percent predicted forced expiratory volume in one second

*as a random effect.

**age at biologic initiation minus reported age at asthma onset

†Assessed using either GINA control criteria,(2) Asthma Control Test(3) or Asthma Control Questionnaire(4). ACQ and/or ACT control categories were fitted to GINA 2020 control categories as follows: Mean ACQ: well controlled (≤0.75); partly controlled (>0.75 to < 1.5); uncontrolled (≥1.5) Total ACT: well controlled (>19); partly controlled (>15 to ≤19); uncontrolled (≤15).

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Legend to E-Figures

Figure E1: Study design plus strict and relaxed remission criteria. Abbreviations: LTOCS: long-term oral corticosteroids; $ppFEV_1$: percent predicted forced expiratory volume in one second.

Figure E2: Subject disposition. Abbreviations: Bx: biologic; LTOCS: long-term oral corticosteroids; $ppFEV_1$: percent predicted forced expiratory volume in one second.

Figure E3: Percentage of patients in remission (relaxed criteria) pre- and post-biologic treatment. Abbreviations: LTOCS: long-term oral corticosteroids; $ppFEV_1$: percent predicted forced expiratory volume in one second.

Figure E4: Percentage of patients in remission (relaxed) pre- and post-treatment with anti-IgE, anti-IL5/5R, or anti-IL4Rα. Abbreviations: LTOCS: long-term oral corticosteroids; $ppFEV_1$: percent predicted forced expiratory volume in one second.

Figure E5: Association between selected pre-biologic characteristics with (A) 2-domain and (B) 3-domain remission in patients with severe asthma. Abbreviations: BEC: blood eosinophil count; BMI: body mass index; CI: confidence interval; FeNO: fractional exhaled nitric oxide; GINA: Global Initiative for Asthma; LTOCS: long-term oral corticosteroids; LTRA: leukotriene receptor antagonist; OR: odds ratio; $ppFEV_1$: percent predicted forced expiratory volume in one second.

Footnote: 2 domain remission (0 exacerbations + no LTOCS); 3 domain remission (0 exacerbations + no LTOCS + $ppFEV_1$ ≥80%). Grey zones highlight association patterns. * Pre-biologic lung function adjustment removed

Asthma duration: age at biologic initiation minus reported age at asthma onset

All ORs were adjusted for pre-biologic asthma-related outcome including in the considered remission definition, as well as for age and sex.

Figure E6: Association between selected pre-biologic characteristics and 2-domain remission (i.e. 0 exacerbation + no LTOCS) by biologic class in in patients with severe asthma.

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Figure E7: Association between selected pre-biologic characteristics and 3-domain remission (i.e. 0 exacerbation + no LTOCS + well or partly-well controlled asthma) by biologic class in in patients with severe asthma.

Figure E8: Association between selected pre-biologic characteristics and 3-domain remission (i.e. 0 exacerbations + no LTOCS + $ppFEV_1$ ≥80%) by biologic class in in patients with severe asthma.

Figure E9: Association between selected pre-biologic characteristics and 4-domain remission (i.e.0 exacerbations + no LTOCS + well or partly controlled asthma + $ppFEV_1$ ≥80%) by biologic class in in patients with severe asthma.

Abbreviations and footnotes for Figure E6-E9:

Abbreviations: BEC: blood eosinophil count; BMI: body mass index; CI: confidence interval; FeNO: fractional exhaled nitric oxide; GINA: Global Initiative for Asthma; LTOCS: long-term oral corticosteroids; LTRA: leukotriene receptor antagonist; OR: odds ratio; $ppFEV_1$: percent predicted forced expiratory volume in one second.

Grey zones highlight association patterns. * Pre-biologic lung function adjustment removed

Asthma duration: age at biologic initiation minus reported age at asthma onset

All ORs were adjusted for pre-biologic asthma-related outcome including in the considered remission definition, as well as for age and sex.

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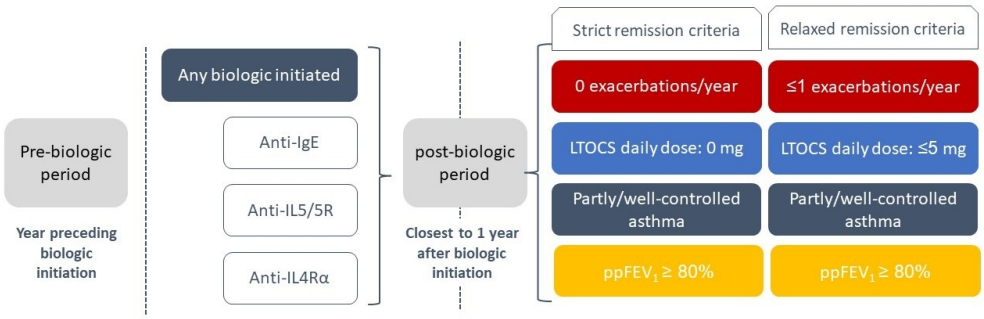

Figure E1: Study design plus strict and relaxed remission criteria.

225x86mm (144 x 144 DPI)

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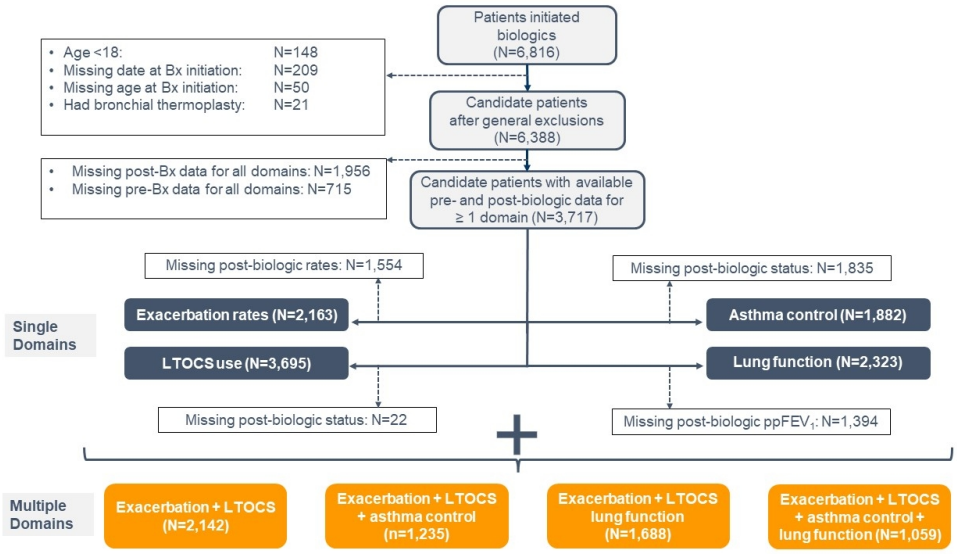

Figure E2: Subject disposition.

338x190mm (96 x 96 DPI)

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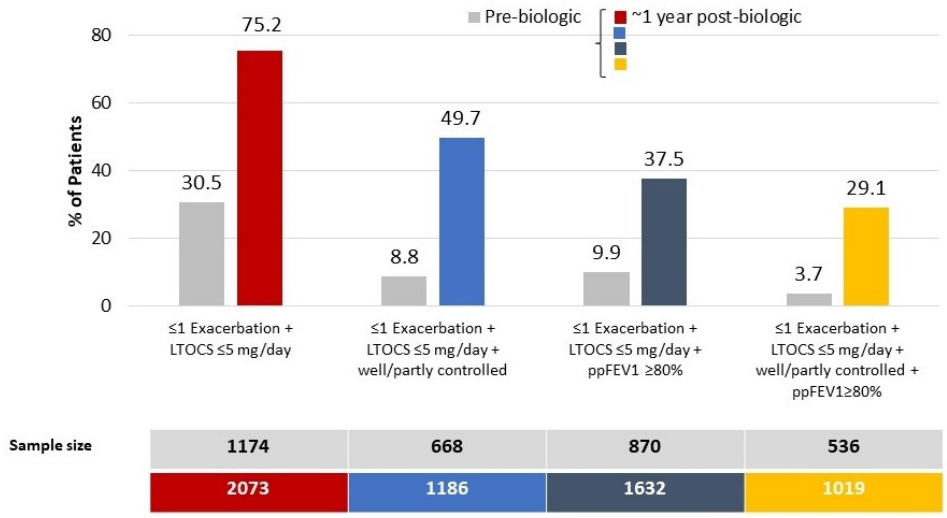

Figure E3: Percentage of patients in remission (relaxed criteria) pre- and post-biologic treatment.

164x94mm (144 x 144 DPI)

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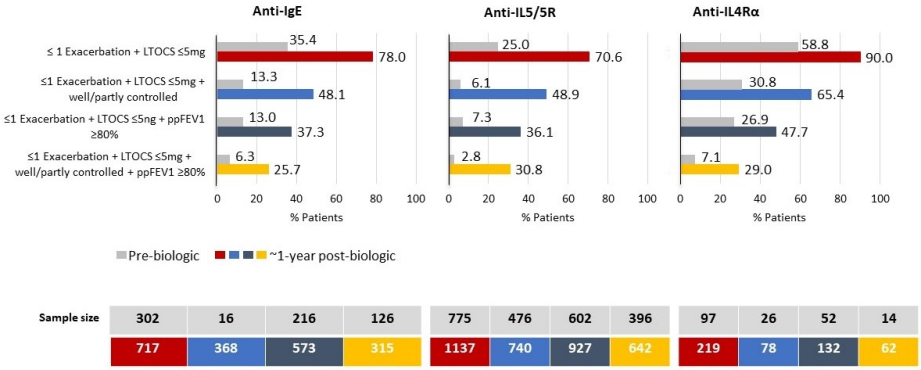

Figure E4: Percentage of patients in remission (relaxed) pre- and post-treatment with anti-IgE, anti-IL5/5R, or anti-IL4Rα.

225x94mm (144 x 144 DPI)

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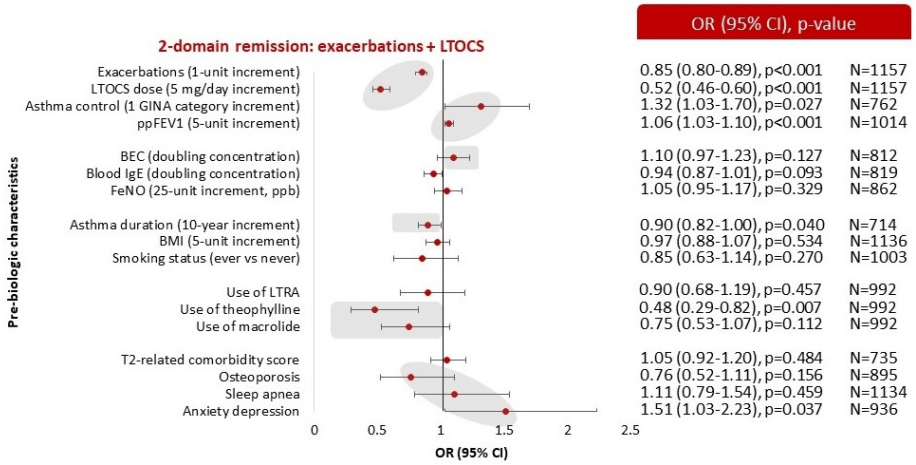

Figure E5A: Association between selected pre-biologic characteristics with 2-domain remission in patients with severe asthma.

185x95mm (144 x 144 DPI)

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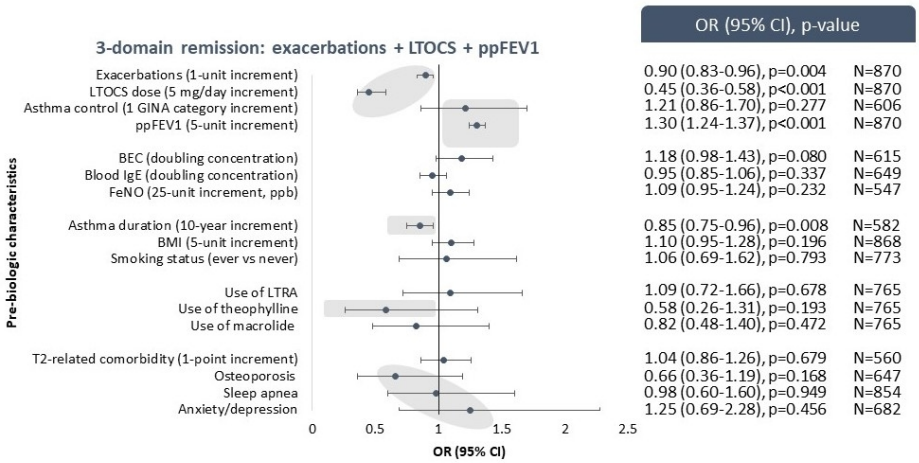

Figure E5B: Association between selected pre-biologic characteristics with 3-domain remission in patients with severe asthma.

186x92mm (144 x 144 DPI)

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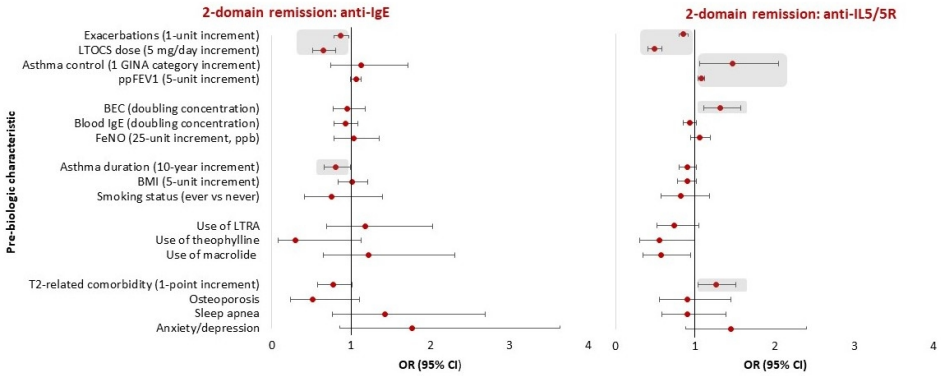

Figure E6: Association between selected pre-biologic characteristics and 2-domain remission (i.e. 0 exacerbation + no LTOCS) by biologic class in in patients with severe asthma.

214x92mm (144 x 144 DPI)

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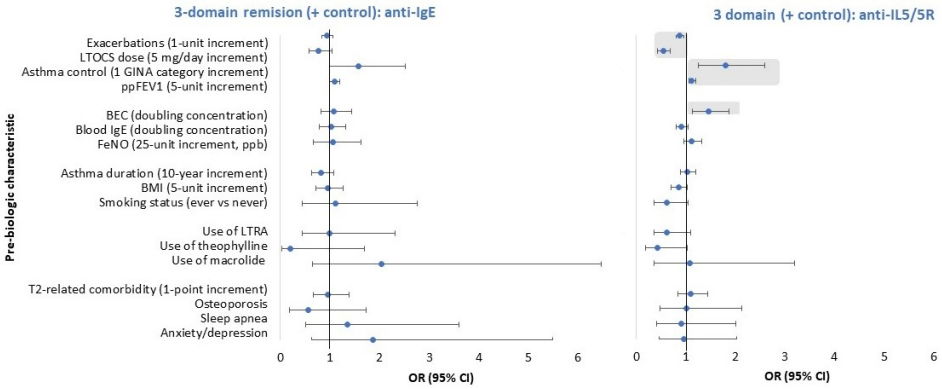

Figure E7: Association between selected pre-biologic characteristics and 3-domain remission (i.e. 0 exacerbation + no LTOCS + well or partly-well controlled asthma) by biologic class in in patients with severe asthma.

207x90mm (144 x 144 DPI)

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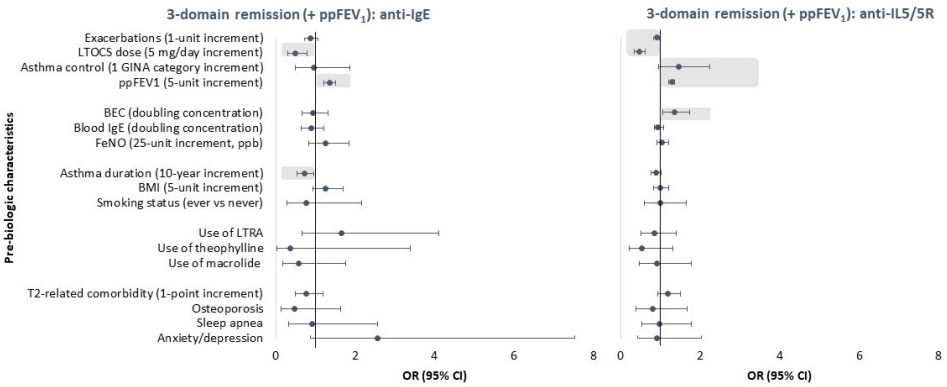

Figure E8: Association between selected pre-biologic characteristics and 3-domain remission (i.e. 0 exacerbations + no LTOCS + ppFEV1 ≥80%) by biologic class in in patients with severe asthma.

210x91mm (144 x 144 DPI)

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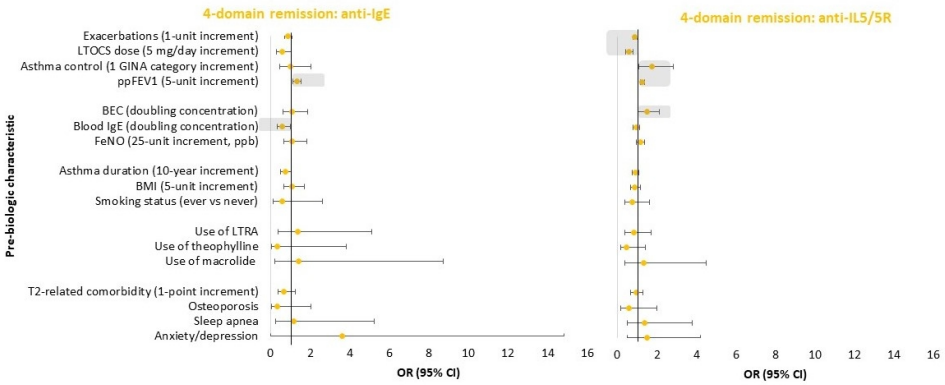

Figure E9: Association between selected pre-biologic characteristics and 4-domain remission (i.e.0 exacerbations + no LTOCS + well or partly controlled asthma + ppFEV1 ≥80%) by biologic class in in patients with severe asthma.

214x92mm (144 x 144 DPI)

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