Exploring definitions and predictors of severe asthma clinical remission post-biologic in adults

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Running title: definitions and predictors of asthma remission

Word count: 3488

Funding Statement

This study was conducted by the Observational and Pragmatic Research Institute (OPRI) Pte Ltd and was partially funded by Optimum Patient Care Global and AstraZeneca Ltd. No funding was received by the Observational & Pragmatic Research Institute Pte Ltd (OPRI) for its contribution.

Article description: 1.27 therapy

Author contributions

Conceptualization and design: all authors

Formal analysis: GS, LB, DP

Data interpretation: all authors

Supervision: VC and DP

Manuscript preparation and review: all authors

142 This article has an online data supplement, which is accessible from this issue's table of
143 content online at www.atsjournals.org"

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At a glance commentary

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Scientific knowledge on the subject:

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

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What this study adds to the field:

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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.

Conflict of Interest Statements

Luis Perez-de-Llano reports grants, personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from GSK, grants, personal fees and non-financial support from TEVA, personal fees and non-financial support from Chiesi, grants, personal fees and non-financial support from Sanofi, personal fees from MSD, personal fees from TECHDOW PHARMA, grants, personal fees and non-financial support from FAES, personal fees from Leo-Pharma, grants and personal fees from GEBRO, personal fees from GILEAD, outside the submitted work.

Ghislaine Scelo is a consultant for Observational and Pragmatic Research Institute (OPRI). OPRI conducted this study in collaboration with Optimum Patient Care and AstraZeneca.

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institution received remuneration; and has a current research grant funded by GlaxoSmithKline.

Mona Al-Ahmad has received advisory board and speaker fees from AstraZeneca, Sanofi, Novartis, and GlaxoSmithKline and received a grant from Kuwait Foundation for the Advancement of Sciences (KFAS).

Riyad Al-Lehebi has given lectures at meetings supported by AstraZeneca, Boehringer Ingelheim, Novartis, GlaxoSmithKline, and Sanofi, and participated in advisory board fees from GlaxoSmithKline, AstraZeneca, Novartis, Abbott.

Alan Altraja has received lecture fees from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, GSK, MSD, Norameda, Novartis, Orion, Sanofi, and Zentiva; sponsorships from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, GlaxoSmithKline, MSD, Norameda, Novartis, and Sanofi; and has participated in advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi, and Teva.

Celine Bergeron has received advisory board and speaker fees from ValeoPharma, Sanofi-Aventis, GSK, Astra-Zeneca, Grifols; has participated in clinical trials (paid to University) sponsored by Sanoti-Aventis, GSK, Astra-Zaneca, BioHaven, Regeneron.

Leif Bjermer received during the last three years consulting/lecture fees from Acucort, AstraZeneca, Birc, Chiesi, GSK, Phargentis and Sanofi.

Anne S Bjerrum has received lecture fees from Astra Zeneca, Sanofi, GSK and Novartis

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John Busby has received research grants from AstraZeneca and personnel fees from NuvoAir, outside the submitted work.

G. Walter Canonica has received research grants, as well as lecture or advisory board fees from A. Menarini, Alk-Albello, Allergy Therapeutics, Anallergo, AstraZeneca, MedImmune, Boehringer Ingelheim, Chiesi Farmaceutici, Circassia, Danone, Faes, Genentech, Guidotti Malesci, GlaxoSmithKline, Hal Allergy, Merck, MSD, Mundipharma, Novartis, Orion, Sanofi Aventis, Sanofi, Genzyme/Regeneron, Stallergenes, UCB Pharma, Uriach Pharma, Teva, Thermo Fisher, and Valeas.

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Liam G. Heaney has received grant funding, participated in advisory boards and given lectures at meetings supported by Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Hoffmann la Roche, GlaxoSmithKline, Novartis, Theravance, Evelo Biosciences, Sanofi, and Teva; he has received grants from MedImmune, Novartis UK, Roche/ Genentech Inc, and GlaxoSmithKline, Amgen, Genentech/Hoffman la Roche, AstraZeneca, MedImmune, GlaxoSmithKline, Aerocrine, and Vitalograph; he has received sponsorship for attending international scientific meetings from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, and Napp Pharmaceuticals; he has also taken part in asthma clinical trials sponsored by AstraZeneca, Boehringer Ingelheim, Hoffmann la Roche, and GlaxoSmithKline for which his institution received remuneration; he is the Academic Lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma which involves industrial partnerships with a number of pharmaceutical companies including Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffmann la Roche, and Janssen.

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Takashi Iwanaga received lecture fees from Kyorin, GlaxoSmithKline, Novartis, Boehringer Ingelheim, AstraZeneca and Sanofi.

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Mariko Siyue Koh reports grant support from AstraZeneca, and honoraria for lectures and advisory board meetings paid to her hospital (Singapore General Hospital) from GlaxoSmithKline, AstraZeneca, Novartis, Sanofi, and Boehringer Ingelheim, outside the submitted work.

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Désirée Larenas Linnemann reports personal fees from ALK-Abelló, AstraZeneca national and global, Bayer, Chiesi, Grunenthal, Grin, GSK national and global, Viatris, Menarini, MSD, Novartis, Pfizer, Sanofi, Siegfried, UCB, Carnot, grants from Abbvie, Bayer, Lilly, Sanofi, AstraZeneca, Pfizer, Novartis, Circassia, UCB, GSK, outside the submitted work.

Lauri Lehtimäki has received personal fees from ALK, AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, Novartis, Orion Pharma and Sanofi.

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Todor A. Popov declares relevant research support from Novartis and Chiesi Pharma.

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Pujan Patel has received advisory board and speaker fees from AstraZeneca, GlaxoSmithKline, Novartis and Sanofi/Regeneron.

Chin Kook Rhee received consulting/lecture fees from MSD, AstraZeneca, GSK, Novartis, Takeda, Mundipharma, Boehringer Ingelheim, Teva, Sanofi, and Bayer.

Diana Cano Rosales has received speaker fees from AstraZeneca, Boehringer Ingelheim, and Sanofi and has acted as an investigator for trials sponsored by AstraZeneca, Sanofi and GSK.

Mohsen Sadatsafavi has received honoraria from AstraZeneca, Boehringer Ingelheim, TEVA, and GSK for purposes unrelated to the content of this manuscript and has received research funding from AstraZeneca and Boehringer Ingelheim directly into his research account from AstraZeneca for unrelated projects.

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Ming-Ju Tsai has received sponsorship to attend or speak at conferences, honoraria for lecturing or attending advisory boards, and research grants from the following companies: AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Pfizer, Shionogi and Orient EuroPharma.

Charlotte Ulrik reports personal fees for talks, participation in advisory boards etc. from AstraZeneca, GlaxoSmithKline, Teva, Boehringer Ingelheim, Orion Pharma, Sanofi Genzyme, TFF Pharmaceuticals, Covis Pharma, Berlin-Chemie, Takeda, Chiesi, and Pfizer, outside the submitted work.

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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 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

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 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.

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

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, 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* 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

485 considered remission definition, age, and sex. Pre-biologic asthma-related outcomes,
486 biomarkers, asthma duration, and BMI were analyzed as continuous variables.'. The models
487 were fitted overall and for each biologic class (not anti-IL4Rα due to small sample size). To test
488 for difference between anti-IgE and anti-IL5/5R patients, a single model was fitted in these
489 patients adding biologic class as an interaction term with the variables of interest.

490

Results

Patients

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%) 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) (**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)**.

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

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–

609 16) The prevalence of 4-domain biologic associated remission (including lung function)
610 ranged from 14.5 to 43.0%, (20.3% in the current study),(13, 15–18, 20–22) varying according
611 to lung function criterion applied, patient cohort, and biologic. Examples of previously used
612 lung function remission criteria include FEV_1>80% predicted (as in the present study),(22) an
613 objective assessment of normal lung function,(2) and an FEV_1 above the lower limit of normal
614 or no more than 100 mL less than baseline.(13) We consider inclusion of a high lung function
615 hurdle an important component of clinical remission as it is representative of lung function
616 optimization,(6) and may encourage earlier intervention with targeted treatment prior to
617 irreversible lung damage. We also acknowledge the difficulty in achieving it in patients who
618 frequently exhibit limited reversibility,(35–37), the lack of consensus in defining lung function
619 optimization/stabilization,(38) and the ongoing debate on whether a lung function domain,
620 used in sentinel remission papers (39) and national guidelines(10) should be included as a
621 remission criterion. Of note, a reduced FEV_1 can be due to other non-asthma factors and,
622 therefore, be unrelated to the presence of remission.
623
624 Although severe asthma remission is achievable in some patients when treated with a biologic
625 in real-life, other patients receiving the same treatment failed to achieve it.(13, 22) This is
626 likely due to a complex interplay of factors, including the heterogeneity of asthma itself, the
627 timing of biologic intervention and assessment of remission, the presence of non-reversible
628 airflow obstruction and the negative impact of comorbidities on asthma control.(40)
629 Understanding why certain patients with severe asthma treated with biologics fail to achieve
630 remission is arguably just as important as predicting those who do achieve it. This represents
631 an important unmet need which requires consideration of the pathway to remission and
632 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).

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 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 t34 ezepelumab 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 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.

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

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).

Acknowledgements

We thank Drs David Jackson and Diahn-Warng Perng for their contribution to study design and result interpretation as part of the FULL BEAM working group; Drs Kenneth Chapman, Susanne Hansen, Konstantinos Kostikas, and Jorge Maspero as members of the Full BEAM working group and for review of early drafts of this article; Drs Arnaud Bourdin, Deirdre Long, Nicolas Roche, Carlos Andres Celis Preciado and Ivan Solarte Rodrigues for review of the article outline, Aaron Beastall for data interpretation and analyses, and Prof William Henley for statistical advice. We also thank Dr Ruth B Murray (Medscript NZ Ltd) for assistance with drafting and editing this manuscript. Finally, a big thank you to our International Severe Asthma Registry collaborators (see online suppl).

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Figure legends

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

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

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

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

Footnotes

Figure 1: 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: Abbreviations: $ppFEV_1$: percent predicted forced expiratory volume in one second; LTOCS: long-term oral corticosteroid.

Figure 3: Abbreviations: $ppFEV_1$: percent predicted forced expiratory volume in one second; LTOCS: long-term oral corticosteroid.

Figure 4: 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.

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)

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.

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).

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)

	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

	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

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)

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)

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