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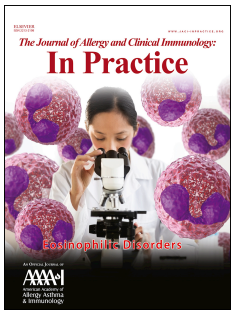

Exploring definitions and predictors of response to biologics for severe asthma

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Abstract:

Background: Biologic effectiveness is often assessed as 'response', a term which eludes consistent definition. Identifying those most likely to respond in real-life has proven challenging.

Objective: To explore definitions of biologic responders in adults with severe asthma and investigate patient characteristics associated with biologic response.

Methods: This was a longitudinal cohort study using data from 21 countries, which shared data with the International Severe Asthma Registry. Changes in 4 asthma outcome domains were assessed in the 1-year period pre- and post-biologic-initiation in patients with predefined level of pre-biologic impairment. Responder cut-offs were: ≥50% reduction in exacerbation rate, ≥50% reduction in long-term oral corticosteroid [LTOCS] daily dose, ≥1 category improvement in asthma control, and ≥100mL improvement in FEV_1. Responders were defined using single- and multiple-domains. The association between pre-biologic characteristics and post-biologic-initiation response were examined by multivariable analysis.

Results: 2,210 patients were included. Responder rate ranged from 80.7% (n=566/701) for exacerbation-response to 10.6% (n=9/85) for 4-domain-response. Many responders still exhibited significant impairment post-biologic-initiation: 46.7% (n=206/441) of asthma control-responders with uncontrolled asthma pre-biologic still had incompletely-controlled disease post-biologic-initiation. Predictors of response were outcome-dependent. Lung function-responders were more likely to have higher pre-biologic FeNO (OR:1.20 for every 25ppb increase), and shorter asthma duration (OR:0.81, for every 10-year increase in duration). Higher BEC and presence of T2-related comorbidities were positively associated with higher odds of meeting LTOCS-, control- and lung function-responder criteria.

Conclusion: Our findings underscore the multi-modal nature of 'response', show that many responders experience residual symptoms post-biologic-initiation, and that predictors of response vary according to outcome assessed.

Highlights box

What is already known about the topic?

Response to biologics is variable, partly due to inclusion of different outcomes in response definitions (e.g. exacerbations, long-term corticosteroid dose, symptom control, lung function). Identifying those most likely to respond in real-life has proven challenging.

What does this article add to our knowledge?

Response and their predictors vary according to outcome assessed. A greater pre-biologic impairment is associated with better response for all outcomes assessed. However shorter asthma duration is associated with better lung function response only.

How does the study impact current management guidelines?

Our findings suggest a more flexible interpretation to biologic response considering degree of pre-biologic impairment, and identification of characteristics (such as asthma duration) which can affect response to formulate a personalized likelihood of response.

Key words: anti-IgE; anti-IL5/5R; anti-IL4Rα; control; exacerbation; lung function; oral corticosteroid

Abbreviations

AD: atopic dermatitis

ADEPT: Anonymised Data Ethics Protocol and Transparency Committee

AR: allergic rhinitis

BEC: blood eosinophil count

BMI: body mass index

CI: confidence interval

CRS: chronic rhinosinusitis

EAACI: European Academy of Allergy and Clinical Immunology

FeNO: fractional exhaled nitric oxide

FEV_1: forced expiratory volume in one second

GINA: Global Initiative for Asthma

ISAR: International Severe Asthma Registry

LTOCS: long-term oral corticosteroids

NP: nasal polyposis

OCS: oral corticosteroids

OR: odds ratio

$ppFEV_1$: percent predicted forced expiratory volume in one second

RCT: randomized controlled trial

Introduction

Our understanding of asthma has changed over the last decades, from a syndrome characterized by episodic respiratory symptoms and variable airflow obstruction to a heterogenous disease with complex pathophysiology.[1–3] Asthma treatment development has mirrored this greater understanding, initially targeting symptoms (e.g., with bronchodilators), then the underlying inflammation associated with symptoms (e.g., with corticosteroids), until today, where we target the mediators and process(es) that drive inflammatory mechanisms (e.g. with biologic therapy).[2] But response to asthma treatment is heterogeneous. There is a need for novel ways to refine the assessment of treatment effect to help fine-tune treatment strategies.[4] Asthma outcomes, therefore, underwent a complementary evolution, from humble pre-to-post changes in outcomes (e.g. exacerbation reduction) to more ambitious multi-dimension outcomes (e.g. asthma control),[2,5,6] and eventually to response, which attempts to capture the complexity and heterogeneity of this disease.[2,7] However, there are some important gaps in the concept of biologic response in severe asthma: how should we define response? what is the burden of residual symptoms post-response? And how can we identify factors that predict response to biologics in real-life?

The concept of response to biologics has evolved from the demonstration of improvement in specific therapeutic objectives (e.g. exacerbations and oral corticosteroid [OCS] use) to the development of multi-component tools. These tools have measured response qualitatively according to level reached (e.g. non-response, response, super-response and remission) using various asthma outcomes, cut-offs and timings of assessment (e.g. 16-52 weeks post treatment), or quantitatively, measuring the extent to which a patient has improved compared to pre-biologic status,[7–16] and considering degree of pre-biologic impairment.[17]

Much effort has been made to standardize a response definition. A recent review has suggested a 4-domain definition including ≥50% reduction in exacerbation rate and long-term OCS (LTOCS) dose, improved asthma control, and increase in forced expiratory volume in one second (FEV_1) ≥100 mL.[7]

Perhaps unsurprisingly, due to variable response definitions applied, potential instability of response status, the heterogenous and variable nature of asthma itself, and the impact of pre-biologic symptom burden and comorbidities on response, reported response to biologics (defined using single domains) is also variable (58% to 86% in real-life studies).[12–14,16,18–21] Identifying pre-biologic variables that predict response and non-response is an important step in the implementation of precision medicine in asthma and will likely shorten patients' journey to response. However, response prediction in real-life has proven challenging, with predictors of response varying according to biologic used and outcome assessed, and further hampered by homogenous populations included in randomized controlled trials (RCTs).[12,22–24]

The European Academy of Allergy, Asthma and Immunology (EAACI) has highlighted the need to better define biologic response, and to identify factors related to treatment failure as key areas for research.[25] The International Severe Asthma Registry (ISAR; https://www.isaregistries.opcglobal.org/), containing data on over 16,000 patients from 26 countries (Aug 2023), offers a unique opportunity to fill in some of the gaps in our understanding of biologic response.[26] Our aims were to: explore biologic responder definitions in adult patients with severe asthma in real-life, quantify what residual

symptoms/limitations remain in responders, and investigate associated patient characteristics, which may be used to identify predictors of response to biologic therapy.

Methods

Study design and data source

This was a longitudinal, pre-to-post biologic cohort study including data from 21 countries (**Table E1, Table E2A-D**) sharing data with ISAR (https://isaregistries.org/)[26–28] from 05.01.2017 to 01.25.2023. Biologic class categorization was based on first biologic used. Change in four asthma outcomes was measured from pre-biologic-initiation (i.e. baseline) to as close as possible to 1-year post-biologic-initiation (**Table 1; Figure 1**). Ethics approval was obtained from the Anonymized Data Ethics Protocols and Transparency Committee (ADEPT0922).

Patients

Patients were ≥18 years old at biologic initiation and had severe asthma (i.e. receiving treatment at Global Initiative for Asthma (GINA) 2018 Step 5 or with uncontrolled asthma (i.e. severe symptoms or ≥2 exacerbations/year requiring OCS) at GINA Step 4).[28,29] Patients were also required to have at least one of the following: ≥2 exacerbations, percent predicted FEV_1 ($ppFEV_1$) <80% in the year preceding biologic initiation, LTOCS use, or have partly- or un-controlled asthma at biologic-initiation (i.e. impairment in each outcome included in responder definition). Other pre-requisites included treatment with anti-IgE, anti-IL5/5R, or anti-IL4Rα, available registry data prior to, or on, biologic initiation date for ≥1 study domains, and ≥24 weeks follow-up data). Those with a history of bronchial thermoplasty were excluded.

Variables

Patient demographic and pre-biologic asthma clinical characteristics collected included (amongst others) biomarker levels, age of asthma onset, asthma duration and presence of comorbidities (**Table 2** and **Table E1**).

Asthma outcome domains, timing of assessments and responder definitions

Asthma outcome domains used to define responders were: exacerbation rate, LTOCS daily dose, asthma control, and FEV_1.[17] Definitions and timing of pre-and post-biologic assessments are provided in **Table 1**. Responder domains and cut-offs (i.e. pre-to-post biologic change for each asthma outcome) were informed by previous severe asthma trials and an ISAR study research,[17] 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 assessed the magnitude of improvement according to starting point and outcome assessed. Domains and cut-offs were categorized *a priori* as: ≥50% reduction in exacerbation rate, ≥50% reduction in LTOCS daily dose, ≥1 category improvement in asthma control (assessed using either GINA control criteria, ACT or ACQ; **Table E3**), and ≥100 mL improvement in FEV_1 (further categorized as 100-199 mL, 200-400 mL, and ≥500 mL improvement). 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 control cut-offs and correlations[30,31] have been described and used by others.[16,32,33] Responder definitions included single- and multiple-domains (**Figure 1**), the latter included 2 domains (i.e. exacerbations and LTOCS), 3 domains (i.e. exacerbations and LTOCS plus asthma control or lung function) and all 4 domains.

Statistical analyses

R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) was used to conduct all statistical analyses.[34] The proportion of patients meeting criteria for each individual-and multiple-domain definition of responder (overall and by biologic class) were summarized using descriptive statistics. Exacerbation counts were annualized to account for variation in follow-up duration. For other domains, no action was taken. Distribution of follow-up time for each domain by biologic classes is provided in **Table E4.** Pre- and post-biologic status were also described as cross-tabulations for individual domain responders, stratified as responders and non-responders, and presented as stacked bar charts. The association between pre-biologic characteristics and response to biologic were examined by multivariable analysis, using binary logistic regression for exacerbations, LTOCS and control (binary outcome variable: responder yes/no) or ordinal logistic regression assuming proportional odds for lung function (ordinal outcome variable: non-responder/100-199/200-499/500+mL FEV_1 improvement) techniques. These analyses were adjusted for age, sex and the pre-biologic asthma-related outcome considered for response definition. Linear or log-linear assumption applied to continuous variables. Significance was tested through log-likelihood ratios. These analyses were restricted to single-domain responder definitions, due to limited numbers of patients eligible for multiple-domain responder analysis. Pre-biologic characteristics considered for multivariable regression models were those with a significant ($p<.05$) association for any domain in univariable analyses, informed by prior knowledge, and based on previous findings.[12,22–24,35] Models were fitted overall and for each class of biologics separately (but not anti-IL4Rα due to small sample size). To examine the potential effect modification of biologic class (anti-IgE versus anti-IL5/5R), a single model was fitted in these patients adding biologic class as an interaction term with pre-biologic variable of interest.

Results

Patients

As of 25th January 2023, 14,284 patients were enrolled in ISAR, 6,816 had initiated biologics and of these 3,717 had pre- and post-biologic-initiation data for ≥1 asthma outcome domain. In total 2,210 patients met inclusion criteria and were included in ≥1 analysis (**Figure 2, Table E2A-D)**; 665, 1,405 and 140 patients received anti-IgE, anti-IL5/R, and anti-IL4Rα, respectively. The USA (n=645; 29.2%), UK (n=427; 19.3%), and Italy (n=368; 16.7%) contributed the largest proportion of patients (**Table E5**).

Patient demographics and pre-biologic clinical characteristics

Patients were predominantly White (80.6%; n=1540/1911), had never smoked (66.0%; n=1142/1731), had a median asthma duration of 20 years, with a tendency towards more females (59.7%; n=1319/2210 (**Table 2A**). Median age and body mass index (BMI) were 55 years and 27.9 kg/m^2, respectively. Biomarkers indicative of T2-high disease (i.e., blood eosinophil count [BEC], fractional exhaled nitric oxide [FeNO) and IgE] were elevated; 94.7% (n=1750/1847) had an eosinophilic phenotype. Most patients (84.0%; n=895/1065) had a positive allergy aeroallergen test. The prevalences of potentially T2-related comorbidities were >50 % for allergic rhinitis (AR) and chronic rhinosinusitis (CRS) and 30% for NP (**Table 2A**). See **Table E5** for other comorbidities**.** Patients experienced a median of 2 exacerbations/year pre-biologic-initiation, 57.1% (n=1129/1978) were treated with LTOCS, 74.2% (n=1005/1355) had uncontrolled asthma, and 68.7% (n=1239/1804) had a ppFEV$_1$ <80% (**Table 2B)**. Patients, who subsequently initiated anti-IL5/5R tended to have more severe

disease, and those who subsequently initiated anti-IL4Rα, less severe disease (**Table 2B**).

Frequency of responders

The % of patients who met responder definitions ranged from 80.7% (n=566/701; 95% CI: 77.7-83.5%) for exacerbations to approximately 50% for the other single-domains (**Figure 3**). For lung function responders, 11.8% (n=122/1030), 21.9% (n=226/1030), and 19.8% (n=204/1030) had a ≥100 to <200mL, ≥200 to <500mL, and ≥500mL post-biologic-initiation FEV_1 improvement, respectively. The proportion of responders diminished with increasing number of domains included in the definition, ranging from 33.1% (n=80/242; 95% CI 27.4-39.2%) for 2-domains, approximately 15% for 3-domains and 10.6% (n=9/85; 95% CI 5.5-19.1%) for 4-domains (**Figure 3**). The proportion of responders by biologic class showed a similar pattern (**Table E4; Figure E1**). The prevalence of multi-domain response defined using all possible combinations of our 4 pre-defined domains is summarized in **Table E6**.

Post-biologic outcome in responders

Among exacerbation responders who had experienced 3+ exacerbations pre-biologic-initiation or ≥1 that required hospitalisation, 12.7% (n=52/409) still experienced ≥1 exacerbation which required hospitalization or had ≥3 exacerbations/year post-biologic-initiation (**Figure 4A; Table E7**). Overall, 53.2% (n=188/353) of patients treated with >10mg/day LTOCS pre-biologic-initiation were classified as responders, but 19.1% (n=36/188) still received >5mg/day post-biologic-initiation (**Figure 4B**) and 46.7% (n=206/441) of control-responders who had uncontrolled asthma pre-biologic, still had partly controlled disease post-biologic-initiation (**Figure 4C**). Between 33.3 to 82.0% of lung function responders still had a $ppFEV_1$ <80% post-biologic-initiation, dependent upon the magnitude of lung function

improvement achieved with biologic treatment (**Figure 4D**). Similar patterns were noted for anti-IgE, anti-IL5/5R, and anti-IL4Rα (**Table E7**).

Correlates of response to biologic

In general, the odds of being a responder for each domain increased with greater pre-biologic impairment in that domain (i.e. intra domain). Other pre-biologic characteristics which increased the odds of meeting responder criteria varied by domain (i.e. inter domain) (**Figure 5A-D; Table E8**).

Exacerbations responder

Pre-biologic characteristics tending to associate with greater odds of achieving exacerbation-responder status included: lower LTOCS daily dose (odds ratio (OR): 0.85; 95% confidence interval (CI): 0.77, 0.95, for every 5 mg/day increase in pre-biologic LTOCS daily dose); no pre-biologic prescription for theophylline (OR: 0.77; 95% CI: 0.52, 1.14 for theophylline users); absence of osteoporosis (OR: 0.60; [95% CI: 0.34, 1.08] for presence of osteoporosis); and a history of atopic dermatitis (AD; OR: 1.54; 95% CI: 0.73, 3.25) (**Figure 5A**). By contrast, higher pre-biologic BEC, IgE, or FeNO levels were not associated with greater odds of meeting the exacerbation-responder criterion (**Figures 5A**).

LTOCS responder

Patients with lower pre-biologic-initiation exacerbation rates tended towards greater likelihood of achieving a ≥50% reduction in LTOCS daily dose (**Figure 5B**). LTOCS-responders were also more likely to have higher pre-biologic-initiation BEC (OR 1.15; 95% CI 1.03, 1.27 for every pre-biologic concentration-doubling), but not IgE or FeNO; lower BMI (OR: 0.89, 95%

CI: 0.80, 0.98, for every 5-unit increase); no pre-biologic use of theophylline (OR: 0.66; 95% CI 0.46, 0.96 for theophylline users); a history of sleep apnea (OR 2.24; 95% CI: 1.58, 3.17), and T2-related comorbidity (**Figure 5B**).

Asthma control responder

Patients more likely to be asthma control-responders were those with better lung function, less exacerbations/year and lower LTOCS daily dose pre-biologic-initiation (**Figure 5C**). Higher pre-biologic-initiation BEC (but not IgE or FeNO) was also positively associated with greater odds of achieving control-responder status (OR: 1.32; 95% CI: 1.18, 1.48 for every concentration-doubling). Those with a lower BMI (OR: 0.72; 95% CI: 0.65, 0.80 for every 5-unit increase pre-biologic), no prescription for theophylline (OR: 0.51; 95% CI: 0.33, 0.78 for theophylline users); absence of sleep apnea (OR: 0.68; 95% CI: 0.46, 1.00 for those with sleep apnea), and a history of CRS, AR, or NP, also tended towards a greater likelihood of achieving a ≥1 category improvement in control status post-biologic-initiation (**Figure 5C**).

FEV_1 responders

Lung function-responders were also more likely to have a lower pre-biologic LTOCS daily dose (OR: 0.92 (95% CI: 0.84, 1.00) for every 5mg/day increase pre-biologic), and higher pre-biologic levels of BEC (OR: 1.31, 95% CI: 1.17, 1.47 for every concentration-doubling) and FeNO (OR: 1.20, 95% CI: 1.10, 1.31 for every 25 ppb increase) (**Figure 5D**). Asthma onset and duration predicted lung function-responders only, with those older at asthma onset and with shorter asthma duration more likely responding in FEV_1 post-biologic-initiation (**Figure 5D**). The odds of achieving lung function-responder status increased by 1.11 (95% CI: 1.06, 1.17) for every 5-years older at asthma onset and decreased by 0.81 (95% CI: 0.73, 0.90) for every

10-year increase in asthma duration**.** When age at asthma onset and asthma duration were included in a single model (removing age at biologic initiation from the model to avoid collinearity), the odds ratio for a 10-year increment in asthma duration remained stable (0.81, 95% CI: 0.70, 0.93), whereas the association with age at asthma onset was null (OR=1.00, 95% CI: 0.94, 1.06, for a 5-year increment).Patients with lower pre-biologic BMI, no prescription of theophylline, absence of osteoporosis and the presence of CRS, AR or NP also had a greater tendency to be FEV_1-responders (**Figure 5D**).

Biologic class comparison (anti-IgE and anti-IL5/5R)

Overall, the above trends were similar for anti-IgE and anti-IL5/5R **Table E8**), with the exception of BEC, where some ORs were significantly different (p for heterogeneity <0.05) between anti-IgE and anti-IL5/5R. For example, higher BEC was positively associated with exacerbation response for anti-IL5/5R (OR: 1.23; 95% CI 1.01, 1.49; p=0.035), but negatively associated with exacerbation response for anti-IgE (OR: 0.65; 95% CI 0.45, 0.94; p=0.022) (**Table E8**). Similarly, higher BEC was also associated with achieving responder criteria for control in patients treated with anti-IL5/5R (OR: 1.55; 95% CI 1.34, 1,80; p<0.001), but not in patients treated with anti-IgE (**Table E8**). Insufficient patient numbers precluded analyses for anti-IL4Rα.

Discussion

Our study shows that the concept of response is complex and dependent upon patients and outcomes assessed. Responder rates varied widely depending upon type and number of domains included in the definition, emphasizing the importance of interpreting biologic response data across studies with caution and the need for a unified theory of 'response'. Many patients, particularly those with more severe pre-biologic-initiation impairment, continued to experience clinically-relevant symptoms post-biologic-initiation even those categorized as responders, highlighting the need to provide realistic expectations to patients at the start of their journey along the response pathway. Multiple pre-biologic characteristics were associated with better biologic response. Lung function response was more likely in those with higher pre-biologic-initiation FeNO, lower LTOCS, shorter duration of asthma and older age at asthma onset. Other pre-biologic characteristics were common across all four responder domains (e.g. greater pre-biologic impairment in domain of interest) in common with previous research,[36–38] or for all responder domains except exacerbations (e.g. higher pre-biologic BEC, lower BMI, history of a T2-related comorbidity). Some characteristics increased the odds of responding in one domain but decreased the odds in another (**Figure 6**). These findings shed new light on the concept of 'response', reflecting its complexity and the interplay of multiple factors which govern it.

We found that biologic responder rates ranged from 44-81% for single domain definitions (highest for exacerbations, the primary target of biologic therapy) and 11-33% for multiple domain definitions. A previous ISAR study reported similar single-domain biologic responder rates, which also varied by domain and increased with greater pre-biologic impairment,

ranging from 70.2-90.0% for exacerbation rate, 46.3-52.3% for asthma control, 31.1-58.5% for LTOCS daily dose, and 35.8-50.6% for $ppFEV_1$ (albeit categorizing responder in absolute terms pre- and post-biologic and describing a biologic responder in terms of category improvements).[17] Interestingly, in that study, even patients with little or no impairment in lung function pre-biologic showed post-biologic improvement; with 28.5% of patients with $ppFEV_1$ ≥80% pre-treatment achieving a post-biologic-initiation improvement of ≥100 mL.[17] These wide responder ranges show that a substantial proportion of patients do not respond to biologic therapy (by our definitions), implying some degree of underlying disease activity, perhaps the presence of non-T2 asthma, already irreversibly damaged lungs (e.g. persistent airflow obstruction), and the need for even more effective or alternative therapies. Wide responder ranges also confirm that some patients respond in some domains but not in others and emphasizes the urgency of agreeing a common approach to assess response for use in RCTs and real-life clinical studies, and to inform asthma management guidelines. Two different multi-modal responder definitions have recently been published, the first defined good response using 3-domains (≥50% exacerbation and LTOCS reduction and control)[8] and the second defined responder using 4-domains (≥50% exacerbations and LTOCS reduction, improved control and >100 mL increase in FEV_1).[7] Both of these responder definitions have been captured in the current study, yielding responder rates to biologic therapy of 18.5% and 10.6%, respectively.

But is achieving response or being a responder the end of the story? The answer very much depends upon the level of pre-biologic impairment in each domain assessed and what is achievable for each patient based upon the level of that impairment. For example, 33.3% of

lung function-responders still had a ppFEV$_1$ <80% post-biologic even though their FEV$_1$ had already improved by ≥500 mL when treated with biologic. This residual impairment may be due to drug, treatment and social determinants (e.g. adherence and access) and/or due to heterogeneity of severe asthma, including the presence of an underlying pathophysiology not targeted by the existing biologics, T2 low asthma, and/or non-pulmonary comorbidities such as obesity.

Long-term non-reversible damage may also limit response in some patients, implying the need for earlier intervention for possibly optimum benefit. It's also important to consider that biologics represent only certain aspects of the treatable traits approach to management and may require supplementation with other therapies as appropriate. Alternatively, residual impairment may indicate the need to switch biologics and may prompt us to consider response as a journey on the way to the final destination (i.e. remission). In the current study we consider ppFEV$_1$<80% as residual impairment, but a definition using lower limit of normal could also be considered.

Interestingly, some predictors of better response to biologics were apparent only for the lung function-responder definition (e.g. higher FeNO, later asthma onset and shorter duration), associated with a 20%, 11%, and 19% increase in odds of achieving lung function-responder status, respectively. This is in agreement with others, who found a greater increase in post-biologic FEV$_1$ (relative to placebo) in those with high vs. low pre-biologic FeNO levels,[24] in those with late (≥40 yrs) vs. early (<40 yrs) onset asthma,[39] and in patients diagnosed after versus before 18 years of age.[38] A better FEV$_1$ response in patients with a high FeNO may

suggest that those with a poor lung function and elevated FeNO might be a future target population for earlier intervention, perhaps already at the time of the first exacerbation. A greater likelihood of responding to biologic therapy in younger patients with a shorter duration of asthma would be important considering that the speed of lung function decline is faster in younger adults (aged 18-39 years) experiencing exacerbations and persists even in patients on higher average daily dosages of inhaled corticosteroid.[40]

Other predictors of better response to biologics were apparent for all responder definitions except exacerbations (e.g. higher pre-biologic BEC), although higher BEC was associated with greater odds of exacerbation response for those treated with anti-IL5/5R group. GINA 2023 lists high BEC as a predictor of asthma response to anti-IgE as well as to anti-IL5/5R, anti-IL4R and anti-TSLP, for those with severe asthma and exacerbations in the last year,[2] and RCTs have found an association of higher BEC and greater exacerbation rate reduction for omalzumab.[36,41] Our results do not contradict that position, but rather represent a consequence of assessing the relationship between pre-biologic biomarker concentration and exacerbations in a different way (i.e. relative to pre-biologic status, not compared to control). Indeed, others have shown the same relatively flat association of BEC concentration with pre-to-post biologic associated exacerbation rate reduction, and not just for omalizumab.[42–44] Our results may also have been influenced by non-pathophysiologic factors in real life patients not observed in RCT populations.

In our study, the ability to identify responders based on their pre-biologic characteristics was complicated by the fact that while certain pre-biologic factors were associated with meeting

responder criterion in one domain, the opposite could be true for other domains. This effect was noted for all domains assessed. For example, those with greater pre-biologic exacerbation burden had increased odds of meeting the exacerbation responder criterion but were less likely to meet responder criteria for LTOCS and asthma control. Predicting response is, therefore, not simple, but in response in one domain was more likely in patients who were suffering from major impairment in that same domain, but who were not suffering from multi-domain impairment. Further research in this area is warranted to untangle the inter-relationships between pre-biologic characteristics and biologic response and to develop multivariable treatment benefit prediction tools.[45]

Limitations include those common to real-world studies, including regression to the mean phenomenon and missing data (more apparent for multiple domain analyses), intercountry variability in data quality, and the influence of unmeasured confounders (inherent for all observational studies). Being of a single-arm pre-to-post biologic design, we could not account for a potential placebo effect. Small sample sizes for each domain limited modelling despite the fact that our cohort was derived from the largest adult severe asthma registry in the world. This exploratory study also examined a large number of potential response predictors and multiple testing may have led to false-positive associations. Other limitations include the small anti-IL4Rα group, the fact that the association analysis was done for single domain responder definitions only, and use of absolute values for FEV_1 alone to assess lung function response; use of lower limit of normal for FEV_1 or FEV_1/FVC could be considered for future study. Use of three tools to assess asthma control (i.e. GINA, ACT and ACQ) could be considered a limitation, although these are all validated tools with good inter-test correlation,[30,31] 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. While inclusion of only those with a certain degree of pre-biologic impairment was considered necessary to observe response (i.e. those with no impairment cannot improve further), it may have limited generalizability of our findings. Future research could consider alternative definitions of lung function response in those with fixed airflow obstruction and those with $ppFEV_1 \geq 80\%$, assess LTOCS response for those with and without adrenal insufficiency (a condition that is currently not systematically recorded in ISAR),[28,46] and consider pre-biologic characteristics associated with non-response to biologics.

Study strengths were inclusion of a large, real-life and heterogenous severe asthma population receiving biologic therapy, with sufficient breadth to define responders using both single- and multi-domains (including lung function), across a range of pre-biologic impairment, both overall and by class.[26–28,46] We assessed likelihood of achieving responder status using a large number of pre-biologic variables routinely captured in everyday clinical practice. Research is ongoing within ISAR to identify biomarker combinations predictive of response, to explore remission definitions and prevalence in patients with severe asthma treated with biologics in real-life, and to identify pre-biologic characteristics associated with achieving it.[47,48] As this area of research continues to develop, it will be interesting to see whether we experience a paradigm shift from the journey (i.e. response) to the destination (i.e. remission).

Our findings have underscored the multi-modal nature of 'response'. Although many patients respond to biologic therapy, some respond better than others, and many responders still

experience significant symptoms/impairment post-biologic. Knowing which patient will respond in real-life is important to facilitate optimal biologic use, ensuring timely, appropriate, and cost-effective treatment. A move to the concept of personalized response, away from fixed definitions of relative improvement towards a more flexible approach, could also be considered. Such an approach should (i) align with patients' goals (i.e. include domains of interest), (ii) consider level of pre-biologic impairment, and (iii) identify the presence/absence of characteristics, which can affect response to formulate a personalized likelihood of response.

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Legend to Figures

Figure 1: Single and multiple domain responder definitions.

*compared to pre-biologic values

Abbreviations: FEV_1: forced expiratory volume in one second; LTOCS: long-term oral corticosteroid

Figure 2: Subject disposition

Abbreviations: Bd: bronchodilator; Bx: biologic; ISAR: International Severe Asthma Registry; LTOCS: long-term oral corticosteroid; $ppFEV_1$: percent predicted forced expiratory volume in one second

Figure 3: Proportion of single- and multi-domain responders to biologic therapy.

Panel A: 1.3% refers to % with ≥1 hospitalized exacerbations or 3+ in total post-biologic

Control assessed using GINA criteria,[2] asthma control test[5] or asthma control questionnaire[6]

Abbreviations: FEV_1: forced expiratory volume in one second; LTOCS: long-term oral corticosteroid.

Figure 4: Post-biologic status for responders for each responder definition

Exacerbation responder: ≥50% reduction versus pre-biologic; LTOCS daily dose responder: ≥50% reduction versus pre-biologic; Asthma control responder: ≥1 category improvement in control status versus pre-biologic; Lung function responder: ≥100 mL FEV_1 increase versus pre-biologic

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

Figure 5: Association between selected pre-biologic characteristics and response to biologic for each single-domain responder definition.

Odds ratios are adjusted for age and sex, as well as pre-biologic exacerbations (panel A), LTOCS dose (panel B), asthma control (panel C) or ppFEV_1 (panel D).

Exacerbation responder: ≥50% reduction versus pre-biologic; LTOCS daily dose responder: ≥50% reduction versus pre-biologic; Asthma control responder: ≥1 category improvement in control status versus pre-biologic; Lung function responder: ≥100 mL FEV_1 increase versus pre-biologic.

Abbreviations: AD: atopic dermatitis; AR: allergic rhinitis; BEC: blood eosinophil count; BMI: body mass index; CI: confidence interval; CRS: chronic rhinosinusitis; FeNO: fractional exhaled nitric oxide; GINA: Global Initiative for Asthma; LTOCS: long-term oral corticosteroids; NP: nasal polyps; OR: odds ratio; FEV_1: forced expiratory volume in one second

Figure 6: Summary of associations between selected pre-biologic characteristics and response to biologic for each single-domain responder definition.

*statistically significant ($p<0.05$) association

Exacerbation responder: ≥50% reduction versus pre-biologic; LTOCS daily dose responder: ≥50% reduction versus pre-biologic; Asthma control responder: ≥1 category improvement in control status versus pre-biologic; Lung function responder: ≥100 mL FEV_1 increase versus pre-biologic

Abbreviations: AD: atopic dermatitis; AR: allergic rhinitis; BEC: blood eosinophil count; BMI: body mass index; CRS: chronic rhinosinusitis; FeNO: fractional exhaled nitric oxide; LTOCS: long-term oral corticosteroid; NP: nasal polyps

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

Outcome	Definition	Pre-biologic	Post biologic	Single domain responder definitions
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)	≥50% exacerbation reduction vs pre-biologic
Asthma control*	• GINA control test,[2] OR • ACT Test[5] OR • ACQ[6]	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)	≥1 category improvement in control status vs pre-biologic

Daily LTOCS dose†	• Continuous OCS treatment for ≥3 months at point of biologic initiation (and usually > 1 year) expressed as prednisolone equivalent dose (mg)	At biologic initiation	Closest to 1-year post biologic (24 weeks minimum and 80 weeks maximum)	≥50% LTOCS daily dose reduction vs pre-biologic
Lung function‡	• FEV_1 • $ppFEV_1$	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)	≥100 mL FEV_1 increase vs pre-biologic

Abbreviations: ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; FEV_1: forced expiratory volume in one second; 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). In cases where results from more than 1 test were recorded, the prioritization was: 1) GINA test; 2) ACT; 3) ACQ

† 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 lung function parameters used if available, and pre-bronchodilator used otherwise, while ensuring that pre- and post-biologic measures were both either pre- or post-bronchodilator.

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

Characteristics	Total (N=2210)	Anti-IgE (N=665)	Anti-IL5/5R (N=1405)	Anti-IL4Rα (N=140)
Age at biologic initiation (attained years)				
Median (Q1, Q3)	55 (45, 63)	52 (41, 61)	56 (47, 64)	55 (45, 64)
Sex, N	2209	664	1405	140
Female, n (%)	1319 (59.7)	404 (60.8)	829 (59.0)	86 (61.4)
Race or Ethnicity, N	1911	588	1209	114
Black/African, n (%)	70 (3.7)	28 (4.8)	36 (3.0)	6 (5.3)
Mixed, n (%)	14 (0.7)	6 (1.0)	7 (0.6)	1 (0.9)
North East Asian, n (%)	83 (4.3)	18 (3.1)	56 (4.6)	9 (7.9)
Other, n (%)	140 (7.3)	43 (7.3)	87 (7.2)	10 (9.8)
South East Asian, n (%)	64 (3.3)	30 (5.1)	34 (2.8)	0 (0.0)
White, n (%)	1540 (80.6)	463 (78.7)	989 (81.8)	88 (77.2)
BMI (kg/m2), N	2064	591	1334	139
Median (Q1, Q3)	27.9 (24.2, 32.8)	28.4 (24.7, 33.7)	27.6 (24.0, 32.3)	28.1 (24.8, 33.5)
Smoking status at biologic initiation, N	1731	501	1116	114
Current smoker, n (%)	42 (2.4)	21 (4.2)	19 (1.7)	2 (1.8)
Ex-smoker, n (%)	547 (31.6)	143 (28.5)	361 (32.3)	43 (37.7)

Characteristics	Total (N=2210)	Anti-IgE (N=665)	Anti-IL5/5R (N=1405)	Anti-IL4Rα (N=140)
Never smoker, n (%)	1142 (66.0)	337 (67.3)	736 (65.9)	69 (60.5)
Age-of-asthma onset (years, continuous), N	1440	368	1022	50
Median (Q1, Q3)	30 (13, 45)	21 (7, 40)	32 (17, 46)	25 (9, 45)
Age-of-asthma onset (years, categorical), N	1461	373	1038	50
0-11 years, n (%)	337 (23.1)	130 (34.9)	192 (18.5)	15 (30.0)
12-40 years, n (%)	674 (46.1)	158 (42.4)	497 (47.9)	19 (38.0)
> 40 years, n (%)	450 (30.8)	85 (22.8)	349 (33.6)	16 (32.0)
Asthma duration (years, continuous), N	1440	368	1022	50
Median (Q1, Q3)	20 (9, 35)	23 (13, 37)	19 (9, 34)	27 (7, 42)
Asthma duration (years, categorical), N	1453	372	1031	50
<10 years, n (%)	367 (25.3)	70 (18.8)	283 (27.4)	14 (28.0)
≥10 years, n (%)	1086 (74.7)	302 (81.2)	748 (72.6)	36 (72.0)
Positive allergen test, N	1166	407	711	48
Yes, n (%)	895 (76.8)	386 (94.8)	476 (66.9)	33 (68.8)
Use of medication in the year preceding Bx initiation, N	1834	572	1128	134
LAMA, n (%)	72 (3.9)	25 (4.4)	40 (3.5)	7 (5.2)

Characteristics	Total (N=2210)	Anti-IgE (N=665)	Anti-IL5/5R (N=1405)	Anti-IL4Rα (N=140)
Theophylline, n (%)	203 (11.1)	65 (11.4)	134 (11.9)	4 (3.0)
LTRA, n (%)	833 (45.4)	290 (50.7)	473 (41.9)	70 (52.2)
Macrolide, n (%)	255 (13.9)	97 (17.0)	123 (10.9)	35 (26.1)
Pre-biologic highest BEC, N (10^9 cells/L), N	1507	411	1003	93
Median (Q1, Q3)	500 (230, 800)	300 (150, 600)	546 (300, 900)	300 (200, 600)
Pre-bx latest FeNO result (ppb), N	1134	265	792	77
Median (Q1, Q3)	36 (20, 70)	28 (14, 58)	40 (22, 73)	31 (17, 57)
Pre-bx latest blood IgE count (IU/mL), N	1462	461	916	85
Median (Q1, Q3)	167 (64, 450)	262 (121, 567)	133 (47, 381)	91 (27, 289)
History of allergic rhinitis, N	1479	504	845	130
Yes, n (%)	785 (53.1)	300 (59.5)	429 (50.8)	56 (43.1)
History of chronic rhinosinusitis, N	1853	553	1173	127
Yes, n (%)	975 (52.6)	250 (45.2)	663 (56.5)	62 (48.8)
History of nasal polyposis, N	1973	587	1256	130
Yes, n (%)	591 (30.0)	109 (18.6)	446 (35.5)	36 (27.7)

Characteristics	Total (N=2210)	Anti-IgE (N=665)	Anti-IL5/5R (N=1405)	Anti-IL4Rα (N=140)
History of osteoporosis, N	1800	584	1086	130
Yes, n (%)	335 (18.6)	115 (19.7)	196 (18.0)	24 (18.5)
Eosinophilic gradient*[49], N	1847	357	1405	85
Grade 0, n (%)	2 (0.1)	2 (0.6)	0 (0.0)	0 (0.0)
Grade 1, n (%)	25 (1.4)	22 (6.2)	0 (0.0)	3 (3.5)
Grade 2, n (%)	70 (3.8)	63 (17.6)	0 (0.0)	7 (8.2)
Grade 3, n (%)	1750 (94.7)	270 (75.6)	1405 (100.0)	75 (88.2)

Abbreviations: Bx: biologic; BEC: blood eosinophil concentration; FeNO: fractional exhaled nitric oxide; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; Q: inter-quartile

*Assessed using a multi-component eosinophil phenotype classification algorithm which uses BEC and other clinical parameters (i.e. adult onset, LTOCS use, FeNO levels, presence of NP and class of prescribed biologic) to categorize phenotype along an eosinophilic gradient.[49] Grade 0 (unlikely/non-eosinophilic); Grade 1 (least likely); Grade 2 (likely); Grade 3 (most likely). Note: patients receiving anti- IL5/5R were all categorized as 'Most likely' by the algorithm.

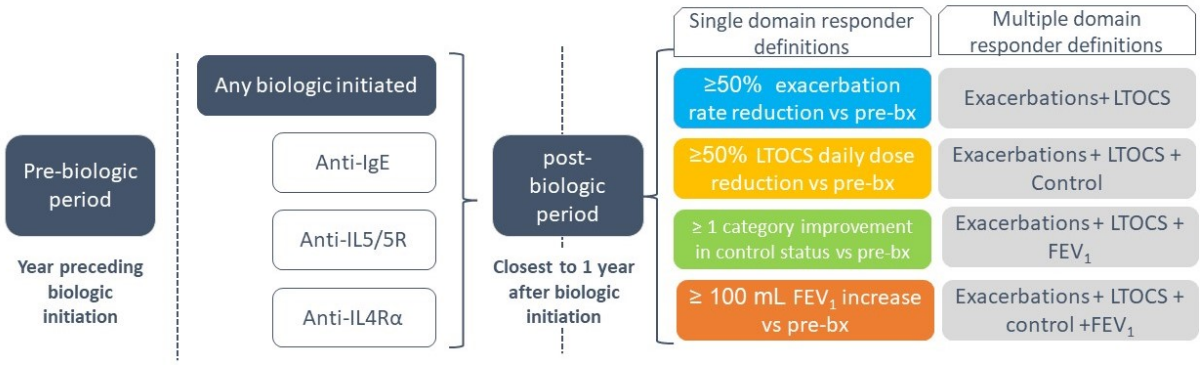
Table 2B: Pre-biologic asthma-related characteristics used in responder definitions

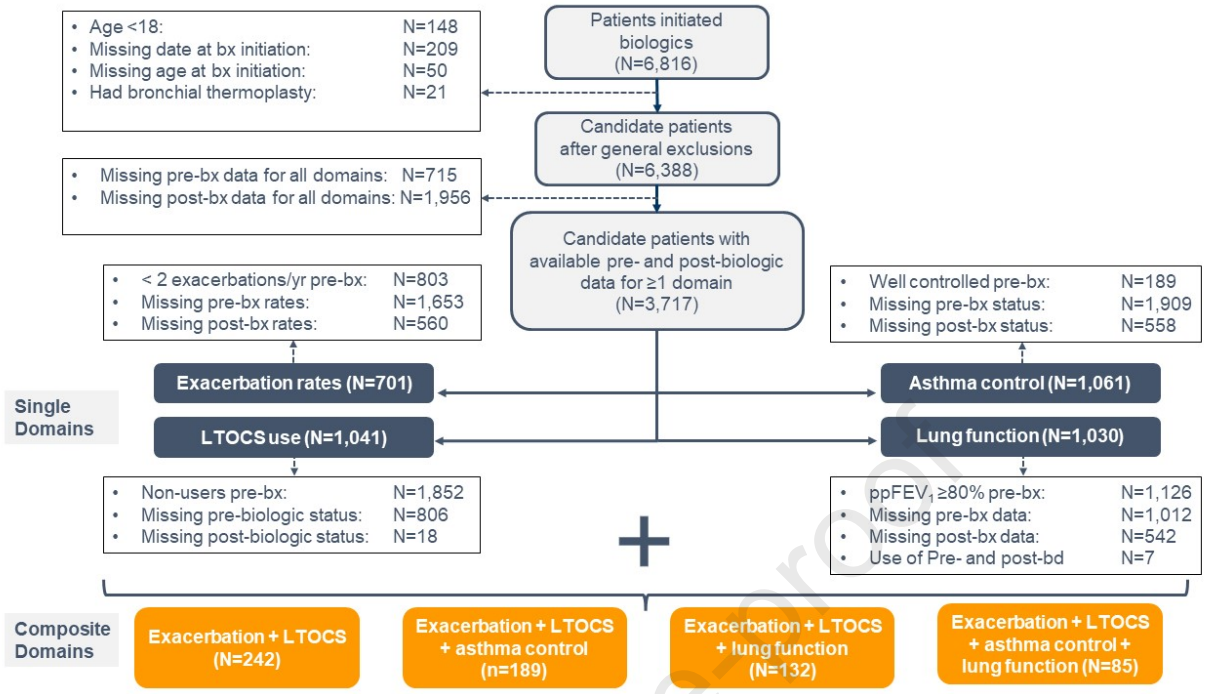
Characteristics	Total (N=2210)	Anti-IgE (N=665)	Anti-IL5/5R (N=1405)	Anti-IL4Rα (N=140)
Pre-biologic exacerbations*, N	1517	377	1054	86
Median (Q1, Q3)	2 (1, 4)	2 (1, 4)	3 (1, 5)	1 (0, 2)
Pre-biologic exacerbations*, N	1632	425	1095	112
0, n (%)	364 (22.3)	120 (28.2)	190 (17.4)	54 (48.2)
1 (not hospitalized), n (%)	228 (14.0)	75 (17.6)	134 (12.2)	19 (17.0)
2 (not hospitalized), n (%)	246 (15.1)	71 (16.7)	156 (14.2)	19 (17.0)
≥1 hospitalized or ≥3 in total, n (%)	794 (48.7)	159 (37.4)	615 (56.2)	20 (17.9)
Missing	458	186	263	9
Pre-biologic LTOCS daily dose (mg)*, N	1050	299	708	43
Median (Q1, Q3)	10 (5, 20)	10(5, 20)	10 (5, 20)	10 (5, 17.5)
Pre-biologic LTOCS*, N	1978	539	1333	106
Non-user, n (%)	849 (42.9)	232 (43.0)	554 (41.6)	63 (59.4)
≤5mg/day, n (%)	328 (16.6)	96 (17.8)	217 (16.3)	15 (14.2)
>5 to 10mg/day, n (%)	365 (18.5)	100 (18.6)	252 (18.9)	13 (12.3)
>10mg/day, n (%)	357 (18.0)	103 (19.1)	239 (17.9)	15 (14.2)
User but missing dose, n (%)	79 (4.0)	8 (1.5)	71 (5.3)	0 (0.0)
Pre-biologic asthma control†, N	1355	38	938	49
Well controlled, n (%)	96 (7.1)	34 (9.2)	59 (6.3)	3 (6.1)
Partly controlled, n (%)	254 (18.7)	66 (17.9)	174 (18.6)	14 (28.6)

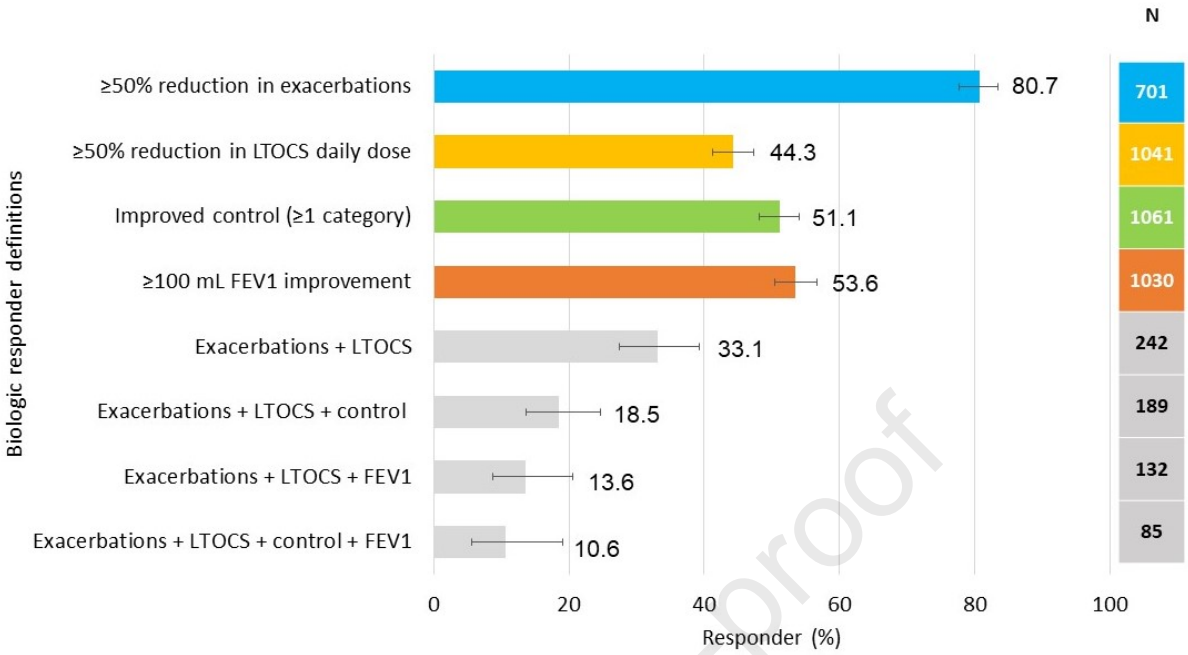
Characteristics	**Total (N=2210)**	**Anti-IgE (N=665)**	**Anti-IL5/5R (N=1405)**	**Anti-IL4Rα (N=140)**
Uncontrolled, n (%)	1005 (74.2)	268 (72.8)	705 (75.2)	32 (65.3)
Pre-biologic ppFEV$_1$† , N	1804	525	1155	124
Median (Q1, Q3)	70.4 (56.3, 85.2)	68.6 (55.8, 80.0)	71.5 (56.3, 87.2)	72.1 (60.7, 86.4)
Pre-biologic ppFEV$_1$ †, N	1804	525	1155	124
≥80%, n (%)	565 (31.3)	132 (25.1)	401 (34.7)	32 (25.8)
<80%, n (%)	1239 (68.7)	393 (74.9)	754 (65.3)	92 (74.2)

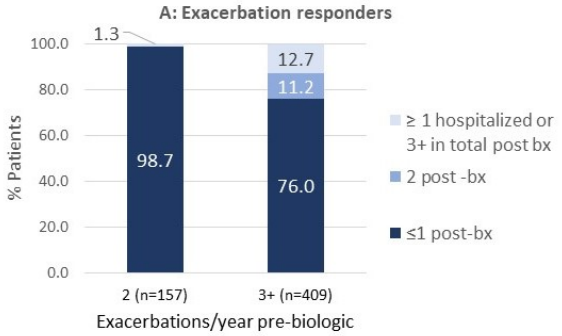
* In the year preceding biologic initiation; † in the year preceding and closest to biologic initiation

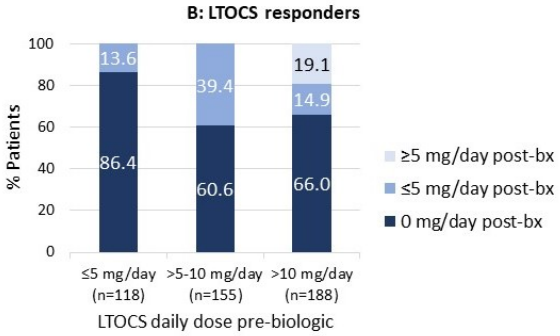
Abbreviations: ppFEV$_1$: percent predicted forced expiratory volume in one second; LTOCS: long-term oral corticosteroid

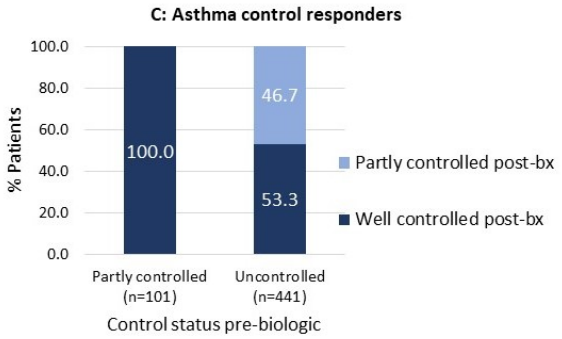


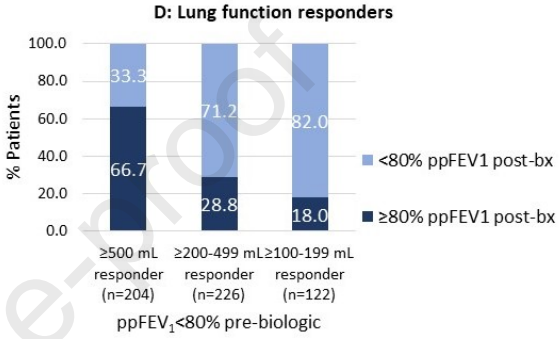


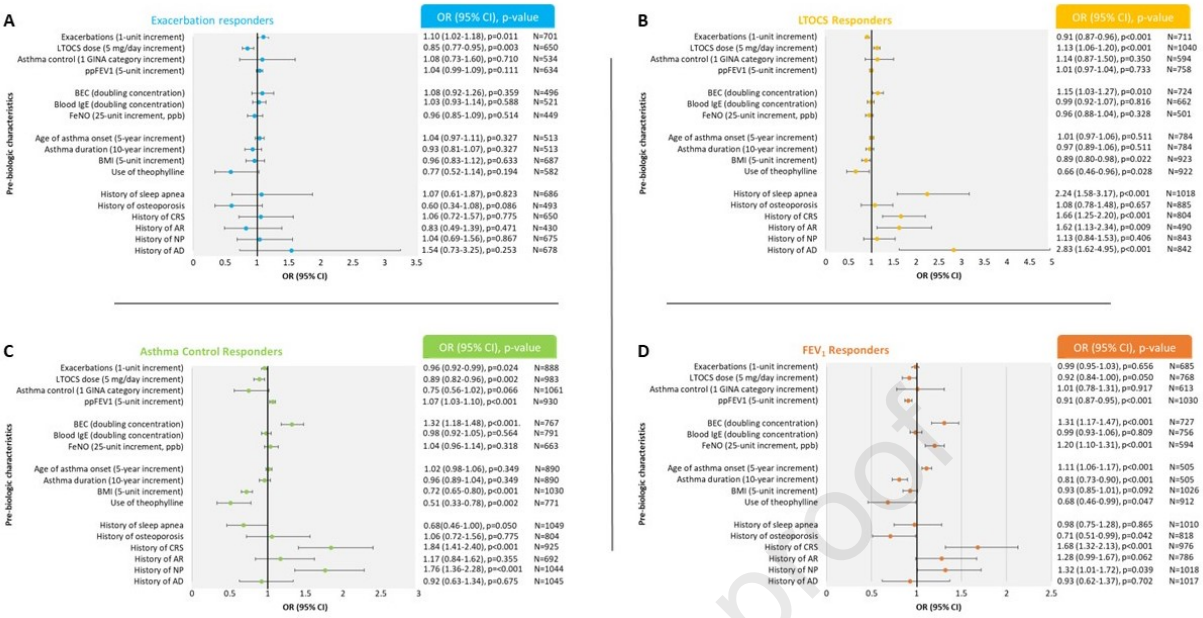












Pre-biologic characteristics	Trend or significant positive association with Exacerbation responders	Trend or significant positive association with LTOCS responder	Trend or significant positive association with Asthma control responder	Trend or significant positive association with Lung function responder
Responder domains	Higher exacerbation rate*	Lower exacerbation rate*	Lower exacerbation rate*	
	Lower LTOCS daily dose*	Higher LTOCS daily dose*	Lower LTOCS daily dose*	Lower LTOCS daily dose*
			Worse asthma control	
			Better lung function*	Worse lung function*
Biomarkers		Higher BEC*	Higher BEC*	Higher BEC*
				Higher FeNO*
Asthma metrics				Older asthma onset*
				Shorter asthma duration*
BMI		Lower BMI*	Lower BMI*	Lower BMI
Treatment	No theophylline	No theophylline*	No theophylline*	No theophylline*
		Sleep apnea*	No sleep apnea*	
	No osteoporosis			No osteoporosis*
Comorbidity profile		CRS*	CRS*	CRS*
		AR*	AR	AR
			NP*	NP*
	AD	AD*		

Online Supplement

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Study registration and ethics approval

The study was registered with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; EUPAS 104132), and designed, implemented, and reported in compliance with the EnCePP and with all applicable local and international laws and regulations.

Figure E1 Legend

Proportion of single- and multi-domain responders to biologic therapy, by biologic class

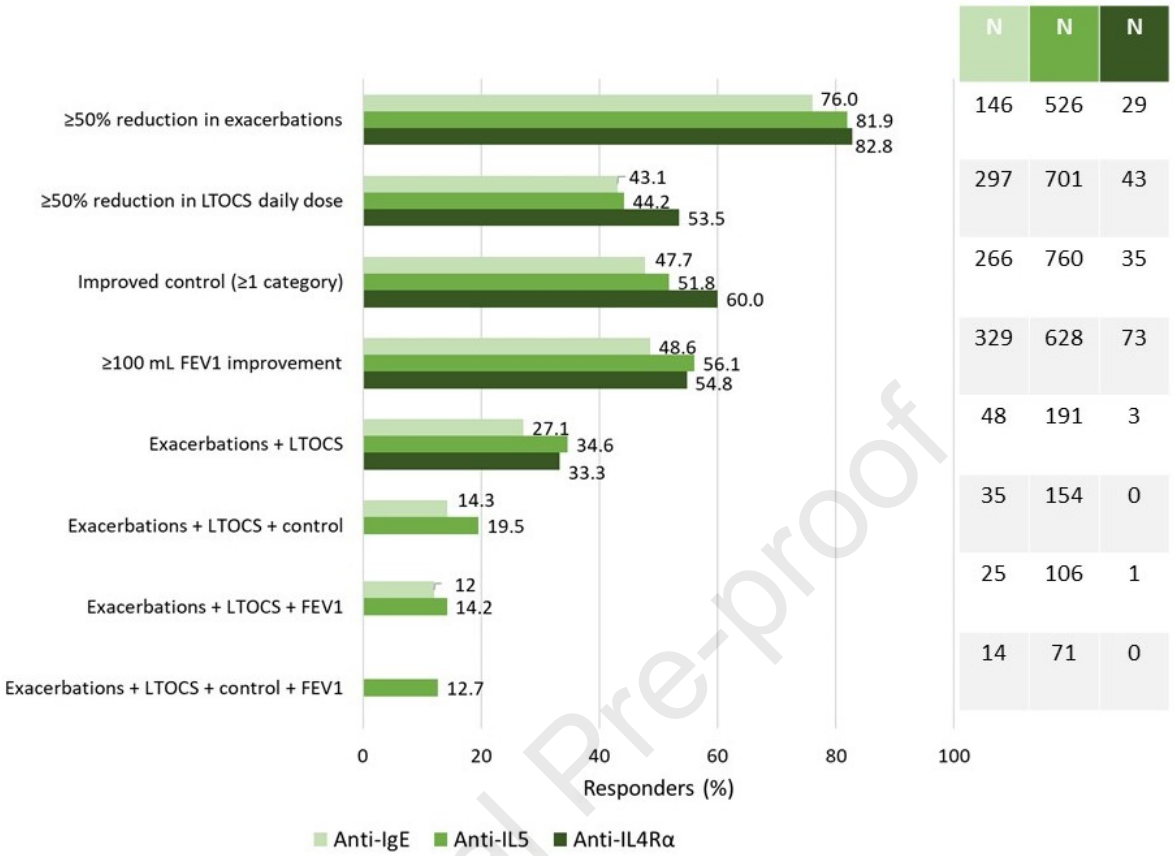

Table E1. Patient characteristic variables.

Label	Type	Value	Construct/comments
Meta data			
Calendar year at biologic initiation	Numerical	-	
Follow-up duration (weeks)	Numerical	-	
Patient characteristics variables			
Demographic characteristics[a]			
Age at biologic initiation (years)	Numerical	-	Attained age in complete years
Sex	Nominal	Female, male	
Race/Ethnicity	Nominal	White, South East Asian, North East Asian, Black/African, Mixed, Other, Unknown	
Country	Nominal	Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, India, Ireland, Italy, Japan, Kuwait, Mexico, Poland, Portugal, Saudi Arabia,	

		Singapore, South Korea, Spain, Taiwan, UAE, UK, USA	
BMI at biologic initiation (kg/m^2)	Numerical	-	Weight in kg/(height in m)^2
Smoking status at biologic initiation	Ordinal	Current smoker, ex-smoker, never smoker	
Asthma clinical features[b]			
Age of asthma onset (years)	Numerical	-	Attained age in complete years at which asthma was diagnosed or symptoms began
Age of asthma onset in categories (years)	Categorical	<10, ≥10	
Asthma duration	Numerical	-	Whole years between age of asthma onset and biologic initiation
BEC pre biologic (10^9 cells/L)	Numerical	-	Highest measure recorded up to biologic initiation date
Blood IgE count pre biologic (IU/mL)	Numerical	-	Closest measure to biologic to initiation date
FeNO test pre-biologic (ppb)	Numerical	-	Closest measure to biologic initiation date
Allergy test results pre-biologic	Binary	Positive, negative	From skin prick test or serum test for dust mite, grass mix, cat hair,

			mould mix, dog hair, aspergillus, weed mix, trees, food mix, animal mix, or other environmental allergens
Asthma-related medication at biologic initiation[b]			
LAMA in the year preceding biologic initiation	Binary	Yes, no	
Theophylline in the year preceding biologic initiation	Binary	Yes, no	
LTRA in the year preceding biologic initiation	Binary	Yes, no	
Macrolide antibiotic in the year preceding biologic initiation	Binary	Yes, no	
History of comorbidities at biologic initiation			
Allergic rhinitis[b]	Binary	Yes, no	
Chronic rhinosinusitis[b]	Binary	Yes, no	
Nasal polyps[c]	Binary	Yes, no	
Eczema/atopic dermatitis[b]	Binary	Yes, no	
Sleep apnea[c]	Binary	Yes, no	
Anxiety/depression[c]	Binary	Yes, no	

Osteoporosis[c]	Binary	Yes, no	
Diabetes[c]	Binary	Yes, no	
Chronic heart disease[c]	Binary	Yes, no	
Pneumonia[c]	Binary	Yes, no	
Peptic ulcer[c]	Binary	Yes, no	
Pulmonary embolism/ venous thromboembolism[c]	Binary	Yes, no	
Cataract[c]	Binary	Yes, no	
Chronic kidney disease[c]	Binary	Yes, no	
Glaucoma[c]	Binary	Yes, no	
Cerebrovascular accident[c]	Binary	Yes, no	

a. Core ISAR variables.

b. Core ISAR variables, although not necessarily available pre-biologic initiation if biologic initiation occurred before enrolment visit.

c. Effectiveness bolt-on variables, collected by a selection of participating countries.

Abbreviations: BEC: blood eosinophil count; BMI: body mass index; FeNO: fractional exhaled nitric oxide; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist

Table E2A: Number and proportion of patients excluded from the EXACERBATION 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 exacerbation data available	6. No pre-biologic exacerbation data available	7. Pre-biologic exacerbations <2/year	
Total (N=6816)	148 (2.2%)	209 (3.1%)	50 (0.7%)	21 (0.3%)	2516 (36.9%)	2368 (34.7%)	803 (11.8%)	701 (10.3%)
Argentina (N=61)	0 (0.0%)	19 (31.1%)	3 (4.9%)	0 (0.0%)	15 (24.6%)	17 (27.9%)	7 (11.5%)	0 (0.0%)
Australia (N=322)	2 (0.6%)	25 (7.8%)	4 (1.2%)	12 (3.7%)	86 (26.7%)	133 (41.3%)	33 (10.2%)	27 (8.4%)
Bulgaria (N=65)	0 (0.0%)	2 (3.1%)	0 (0.0%)	0 (0.0%)	48 (73.8%)	13 (20.0%)	1 (1.5%)	1 (1.5%)
Canada (N=266)	1 (0.4%)	21 (7.9%)	1 (0.4%)	0 (0.0%)	90 (33.8%)	102 (38.3%)	32 (12.0%)	19 (7.1%)
Colombia (N=166)	3 (1.8%)	26 (15.7%)	1 (0.6%)	0 (0.0%)	55 (33.1%)	41 (24.7%)	31 (18.7%)	9 (5.4%)

Denmark (N=334)	4 (1.2%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	78 (23.4%)	34 (10.2%)	93 (27.8%)	124 (37.1%)
Greece (N=92)	0 (0.0%)	5 (5.4%)	0 (0.0%)	0 (0.0%)	39 (42.4%)	16 (17.4%)	19 (20.7%)	13 (14.1%)
India (N=6)	0 (0.0%)	3 (50.0%)	0 (0.0%)	0 (0.0%)	2 (33.3%)	1 (16.7%)	0 (0.0%)	0 (0.0%)
Ireland (N=3)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	2 (66.7%)	0 (0.0%)	0 (0.0%)
Italy (N=1138)	16 (1.4%)	3 (0.3%)	0 (0.0%)	0 (0.0%)	478 (42.0%)	455 (40.0%)	96 (8.4%)	90 (7.9%)
Japan (N=146)	6 (4.1%)	6 (4.1%)	0 (0.0%)	0 (0.0%)	44 (30.1%)	68 (46.6%)	13 (8.9%)	9 (6.2%)
Kuwait (N=231)	6 (2.6%)	5 (2.2%)	3 (1.3%)	0 (0.0%)	131 (56.0%)	68 (29.1%)	4 (1.7%)	14 (6.0%)
Mexico (N=175)	6 (3.4%)	28 (16.0%)	6 (3.4%)	0 (0.0%)	69 (39.4%)	49 (28.0%)	17 (9.7%)	0 (0.0%)
Poland (N=274)	3 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	127 (46.3%)	135 (49.3%)	8 (2.9%)	1 (0.4%)
Portugal (N=95)	3 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	52 (57.7%)	33 (34.7%)	5 (5.3%)	2 (2.1%)
Saudi Arabia (N=112)	1 (0.9%)	34 (30.4%)	0 (0.0%)	1 (0.9%)	28 (25.0%)	22 (19.6%)	24 (21.4%)	2 (1.8%)
Singapore (N=25)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (36.0%)	15 (60.0%)	1 (4.0%)	0 (0.0%)

South Korea (N=35)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	13 (37.1%)	9 (25.7%)	9 (25.7%)	3 (8.6%)
Spain (N=582)	22 (3.8%)	10 (1.7%)	2 (0.3%)	1 (0.2%)	310 (53.3%)	196 (33.7%)	24 (4.1%)	17 (2.9%)
Taiwan (N=111)	1 (0.9%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	29 (26.1%)	52 (46.8%)	14 (12.6%)	11 (9.9%)
UAE (N=155)	2 (1.3%)	12 (7.7%)	0 (0.0%)	0 (0.0%)	74 (47.7%)	56 (36.1%)	10 (6.5%)	1 (0.6%)
UK (N=575)	1 (0.2%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	241 (41.9%)	6 (1.0%)	97 (16.9%)	228 (39.7%)
USA (N=1847)	71 (3.8%)	4 (0.2%)	29 (1.6%)	6 (0.3%)	497 (26.9%)	845 (45.7%)	265 (14.3%)	130 (7.0%)

Table E2B: Number and proportion of patients excluded from the LTOCS 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 LTOCS data available	6. No pre-biologic LTOCS data available	7. Non-LTOCS user pre-biologic	
Total (N=6816)	148 (2.2%)	209 (3.1%)	50 (0.7%)	21 (0.3%)	2121 (31.1%)	1390 (20.4%)	1836 (26.9%)	1041 (15.3%)
Argentina (N=61)	0 (0.0%)	19 (31.1%)	3 (4.9%)	0 (0.0%)	15 (24.6%)	11 (18.0%)	14 (23.0%)	0 (0.0%)
Australia (N=322)	2 (0.6%)	25 (7.8%)	4 (1.2%)	12 (3.7%)	86 (26.7%)	19 (5.9%)	121 (37.6%)	61 (18.9%)
Bulgaria (N=65)	0 (0.0%)	2 (3.1%)	0 (0.0%)	0 (0.0%)	48 (73.8%)	10 (15.4%)	6 (9.2%)	2 (3.1%)
Canada (N=266)	1 (0.4%)	21 (7.9%)	1 (0.4%)	0 (0.0%)	90 (33.8%)	21 (7.9%)	136 (51.1%)	43 (16.2%)
Colombia (N=166)	3 (1.8%)	26 (15.7%)	1 (0.6%)	0 (0.0%)	55 (33.1%)	22 (13.3%)	35 (21.1%)	25 (15.1%)

Denmark (N=334)	4 (1.2%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	78 (23.4%)	33 (9.9%)	195 (58.4%)	24 (7.2%)
Greece (N=92)	0 (0.0%)	5 (5.4%)	0 (0.0%)	0 (0.0%)	39 (42.4%)	15 (16.3%)	24 (26.1%)	15 (16.3%)
India (N=6)	0 (0.0%)	3 (50.0%)	0 (0.0%)	0 (0.0%)	2 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ireland (N=3)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0.0%)
Italy (N=1138)	16 (1.4%)	3 (0.3%)	0 (0.0%)	0 (0.0%)	478 (42.0%)	287 (25.2%)	235 (20.6%)	199 (17.5%)
Japan (N=146)	6 (4.1%)	6 (4.1%)	0 (0.0%)	0 (0.0%)	44 (30.1%)	26 (17.8%)	45 (30.8%)	21 (14.4%)
Kuwait (N=231)	6 (2.6%)	5 (2.2%)	3 (1.3%)	0 (0.0%)	131 (56.0%)	14 (6.0%)	189 (80.8%)	2 (0.9%)
Mexico (N=175)	6 (3.4%)	28 (16.0%)	6 (3.4%)	0 (0.0%)	69 (39.4%)	11 (6.3%)	60 (34.3%)	6 (3.4%)
Poland (N=274)	3 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	127 (46.3%)	38 (13.9%)	65 (23.7%)	54 (19.7%)
Portugal (N=95)	3 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	52 (54.7%)	19 (20.0%)	14 (14.7%)	8 (8.4%)
Saudi Arabia (N=112)	1 (0.9%)	34 (30.4%)	0 (0.0%)	1 (0.9%)	28 (25.0%)	6 (5.4%)	37 (33.0%)	7 (6.2%)
Singapore (N=25)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (36.0%)	5 (20.0%)	9 (36.0%)	5 (20.0%)

South Korea (N=35)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	13 (37.1%)	6 (17.1%)	7 (20.0%)	8 (22.9%)
Spain (N=582)	22 (3.8%)	10 (1.7%)	2 (0.3%)	1 (0.2%)	310 (53.3%)	114 (19.6%)	77 (13.2%)	0 (0.0%)
Taiwan (N=111)	1 (0.9%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	29 (26.1%)	10 (9.0%)	49 (44.4%)	23 (20.7%)
UAE (N=155)	2 (1.3%)	12 (7.7%)	0 (0.0%)	0 (0.0%)	74 (47.7%)	13 (8.4%)	52 (33.5%)	1 (0.6%)
UK (N=575)	1 (0.2%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	241 (41.9%)	0 (0.0%)	170 (29.6%)	314 (54.6%)
USA (N=1847)	71 (3.8%)	4 (0.2%)	29 (1.6%)	6 (0.3%)	497 (26.9%)	709 (38.4%)	295 (16.0%)	223 (12.1%)

Table E2C: Number and proportion of patients excluded from the ASTHMA CONTROL 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 asthma control data available	6. No pre-biologic asthma control data available	7. Well control pre-biologic	
Total (N=6816)	148 (2.2%)	209 (3.1%)	50 (0.7%)	21 (0.3%)	2514 (36.9%)	2624 (38.5%)	189 (2.8%)	1061 (15.6%)
Argentina (N=61)	0 (0.0%)	19 (31.1%)	3 (4.9%)	0 (0.0%)	14 (23.0%)	19 (31.1%)	0 (0.0%)	6 (9.8%)
Australia (N=322)	2 (0.6%)	25 (7.8%)	4 (1.2%)	12 (3.7%)	80 (24.8%)	73 (22.7%)	3 (0.9%)	123 (38.2%)
Bulgaria (N=65)	0 (0.0%)	2 (3.1%)	0 (0.0%)	0 (0.0%)	45 (69.2%)	14 (21.5%)	0 (0.0%)	4 (6.2%)
Canada (N=266)	1 (0.4%)	21 (7.9%)	1 (0.4%)	0 (0.0%)	69 (25.9%)	127 (47.7%)	16 (6.0%)	31 (11.7%)
Colombia (N=166)	3 (1.8%)	26 (15.7%)	1 (0.6%)	0 (0.0%)	53 (31.9%)	73 (44.0%)	0 (0.0%)	10 (6.0%)

Denmark (N=334)	4 (1.2%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	68 (20.4%)	108 (32.3%)	24 (7.2%)	129 (38.6%)
Greece (N=92)	0 (0.0%)	5 (5.4%)	0 (0.0%)	0 (0.0%)	42 (45.7%)	14 (15.2%)	4 (4.3%)	27 (29.3%)
India (N=6)	0 (0.0%)	3 (50.0%)	0 (0.0%)	0 (0.0%)	3 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ireland (N=3)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (33.3%)	2 (66.7%)	0 (0.0%)	0 (0.0%)
Italy (N=1138)	16 (1.4%)	3 (0.3%)	0 (0.0%)	0 (0.0%)	423 (37.2%)	390 (34.3%)	51 (4.5%)	255 (22.4%)
Japan (N=146)	6 (4.1%)	6 (4.1%)	0 (0.0%)	0 (0.0%)	42 (28.8%)	76 (52.1%)	1 (0.7%)	15 (10.3%)
Kuwait (N=231)	6 (2.6%)	5 (2.2%)	3 (1.3%)	0 (0.0%)	122 (52.1%)	72 (30.8%)	1 (0.4%)	22 (9.4%)
Mexico (N=175)	6 (3.4%)	28 (16.0%)	6 (3.4%)	0 (0.0%)	95 (54.3%)	36 (20.6%)	0 (0.0%)	4 (2.3%)
Poland (N=274)	3 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	100 (36.5%)	170 (62.0%)	1 (0.4%)	0 (0.0%)
Portugal (N=95)	3 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	52 (54.7%)	34 (35.8%)	0 (0.0%)	6 (6.3%)
Saudi Arabia (N=112)	1 (0.9%)	34 (30.4%)	0 (0.0%)	1 (0.9%)	35 (31.2%)	24 (21.4%)	2 (1.8%)	15 (13.4%)
Singapore (N=25)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (32.0%)	14 (56.0%)	2 (8.0%)	1 (4.0%)

South Korea (N=35)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	13 (37.1%)	13 (37.1%)	0 (0.0%)	8 (22.9%)
Spain (N=582)	22 (3.8%)	10 (1.7%)	2 (0.3%)	1 (0.2%)	312 (53.6%)	199 (34.2%)	10 (1.7%)	26 (4.5%)
Taiwan (N=111)	1 (0.9%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	24 (21.6%)	56 (50.4%)	1 (0.9%)	25 (22.5%)
UAE (N=155)	2 (1.3%)	12 (7.7%)	0 (0.0%)	0 (0.0%)	75 (48.4%)	56 (36.1%)	7 (4.5%)	3 (1.9%)
UK (N=575)	1 (0.2%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	224 (39.0%)	20 (3.5%)	37 (6.4%)	291 (3.2%)
USA (N=1847)	71 (3.8%)	4 (0.2%)	29 (1.6%)	6 (0.3%)	614 (33.2%)	1034 (56.0%)	29 (1.6%)	60 (%)

Table E2D: Number and proportion of patients excluded from the LUNG FUNCTION 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 $ppFEV_1$ data available	6. No pre-biologic $ppFEV_1$ data available	7. Pre-biologic $ppFEV_1$ >=80%	
Total (N=6816)	148 (2.2%)	209 (3.1%)	50 (0.7%)	21 (0.3%)	2498 (36.6%)	1727 (25.3%)	1126 (16.5%)	1030 (15.1%)
Argentina (N=61)	0 (0.0%)	19 (31.1%)	3 (4.9%)	0 (0.0%)	16 (26.3%)	17 (27.9%)	2 (3.3%)	4 (6.6%)
Australia (N=322)	2 (0.6%)	25 (7.8%)	4 (1.2%)	12 (3.7%)	99 (30.7%)	111 (34.5%)	27 (8.4%)	42 (13.0%)
Bulgaria (N=65)	0 (0.0%)	2 (3.1%)	0 (0.0%)	0 (0.0%)	45 (69.2%)	14 (21.5%)	0 (0.0%)	4 (6.2%)
Canada (N=266)	1 (0.4%)	21 (7.9%)	1 (0.4%)	0 (0.0%)	76 (28.6%)	89 (33.5%)	64 (24.1%)	11 (4.1%)

Colombia (N=166)	3 (1.8%)	26 (15.7%)	1 (0.6%)	0 (0.0%)	53 (31.9%)	71 (42.8%)	7 (4.2%)	5 (3.0%)
Denmark (N=334)	4 (1.2%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	63 (18.9%)	38 (11.4%)	105 (31.4%)	123 (36.8%)
Greece (N=92)	0 (0.0%)	5 (5.4%)	0 (0.0%)	0 (0.0%)	37 (40.2%)	32 (34.8%)	12 (13.0%)	6 (6.5%)
India (N=6)	0 (0.0%)	3 (50.0%)	0 (0.0%)	0 (0.0%)	2 (33.3%)	1 (16.7%)	0 (0.0%)	0 (0.0%)
Ireland (N=3)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	2 (66.7%)	0 (0.0%)	0 (0.0%)
Italy (N=1138)	16 (1.4%)	3 (0.3%)	0 (0.0%)	0 (0.0%)	440 (38.7%)	457 (40.2%)	121 (10.6%)	98 (8.6%)
Japan (N=146)	6 (4.1%)	6 (4.1%)	0 (0.0%)	0 (0.0%)	43 (29.5%)	73 (50.0%)	13 (8.9%)	5 (3.4%)
Kuwait (N=231)	6 (2.6%)	5 (2.2%)	3 (1.3%)	0 (0.0%)	88 (37.6%)	74 (31.6%)	41 (17.5%)	14 (6.0%)
Mexico (N=175)	6 (3.4%)	28 (16.0%)	6 (3.4%)	0 (0.0%)	75 (42.9%)	38 (21.7%)	20 (11.4%)	2 (1.1%)
Poland (N=274)	3 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	133 (48.5%)	109 (39.8%)	23 (8.4%)	6 (2.2%)
Portugal (N=95)	3 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	55 (57.9%)	35 (36.8%)	0 (0.0%)	2 (2.1%)
Saudi Arabia (N=112)	1 (0.9%)	34 (30.4%)	0 (0.0%)	1 (0.9%)	32 (28.6%)	39 (34.8%)	3 (2.7%)	2 (1.8%)

Singapore (N=25)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (36.0%)	15 (60.0%)	1 (4.0%)	0 (0.0%)
South Korea (N=35)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	15 (42.9%)	9 (25.7%)	4 (11.4%)	6 (17.1%)
Spain (N=582)	22 (3.8%)	10 (1.7%)	2 (0.3%)	1 (0.2%)	308 (52.9%)	202 (34.7%)	22 (3.4%)	15 (2.6%)
Taiwan (N=111)	1 (0.9%)	4 (3.6%)	0 (0.0%)	0 (0.0%)	25 (22.5%)	56 (50.4%)	18 (16.2%)	7 (6.3%)
UAE (N=155)	2 (1.3%)	12 (7.7%)	0 (0.0%)	0 (0.0%)	78 (50.3%)	58 (37.4%)	4 (2.6%)	1 (0.6%)
UK (N=575)	1 (0.2%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	181 (31.5%)	18 (3.1%)	165 (28.7%)	208 (36.2%)
USA (N=1847)	71 (3.8%)	4 (0.2%)	29 (1.6%)	6 (0.3%)	624 (33.8%)	169 (9.1%)	474 (25.7%)	469 (25.4%)

Table E3: asthma control test used by each country

Country	N	Proportions of patients by asthma control assessment tool used
Argentina, Bulgaria, Canada, Colombia, Greece, Japan, Kuwait, Mexico, Portugal, Saudi Arabia, Singapore, South Korea, Taiwan, UAE	177	GINA: 100%
Australia	123	ACQ: 100%
Denmark	129	ACQ: 89.1% ACT: 10.9%
Italy	255	GINA: 78.8% ACQ: 21.2%
Spain	26	ACT: 100%
UK	291	ACQ: 100%
USA	60	ACT: 100%
TOTAL	1061	GINA: 35.6% ACQ: 54.9% ACT: 9.4%

Abbreviations: ACQ: Asthma Control Questionnaire;[1] ACT: Asthma Control Test;[2] GINA: Global Initiative for Asthma[3]

Table E4: Proportion of responders for single and multiple domains, overall and by biologic class

Characteristics	Total (N=2210)	Anti-IgE (N=665)	Anti-IL5/5R (N=1405)	Anti-IL4Rα (N=140)
Exacerbations response (≥50% reduction), N	701	146	526	29
Responders, n (%)	566 (80.7)	111 (76.0)	431 (81.9)	24 (82.8)
Non-responders, n (%)	135 (19.3)	35 (24.0)	95 (18.1)	5 (17.2)
Follow-up duration for exacerbations (wks)				
Median	52.1	52.1	52.7	52.1
Q1, Q3	52.1, 59.4	52.1, 60.7	52.1, 60.0	52.1, 52.1
Range	48.0 - 80.0	48.4 - 79.9	48.0 - 80.0	48.1 - 58.1
LTOCS response (≥50% reduction in daily doses), N	1041	297	701	43
Responders, n (%)	461 (44.3)	128 (43.1)	30 (44.2)	23 (53.5)
Non-responders, n (%)	580 (55.7)	169 (56.9)	391 (55.8)	20 (46.5)
Follow-up duration for LTOCS (weeks)				
Median	52.1	52.1	52.1	52.1
Q1, Q3	52.1, 52.3	52.1, 52.3	52.1, 52.1	52.1, 52.3
Range	24.0 - 79.9	24.1 - 79.9	24.0 - 77.9	28.4 - 52.3
Asthma control* response (≥1 category improvement), N	1061	266	760	35
Responders, n (%)	542 (51.1)	127 (47.7)	394 (51.8)	21 (60.0)
Non-responders, n (%)	519 (48.9)	139 (52.3)	366 (48.2)	14 (40.0)
Follow-up duration for asthma control (weeks)				
Median	52.0	51.2	52.0	53.0
Q1, Q3	46.0, 58.1	44.0, 58.0	47.0, 58.0	37.6, 58.6
Range	24.0 - 80.0	25.0 - 79.9	24.0 - 80.0	28.1 - 77.7
Lung function response (increase in FEV_1), N	1030	329	628	73

Responders >=500mL, n (%)	204 (19.8)	50 (15.2)	137 (21.8)	17 (23.3)
Responders >=200 to <500mL, n (%)	226 (21.9)	67 (20.4)	145 (23.1)	14 (19.2)
Responders >=100 to <200mL, n (5)	122 (11.8)	43 (13.1)	70 (11.1)	9 (12.3)
Non-responders, n (%)	478 (46.4)	169 (51.4)	276 (43.9)	33 (45.2)
Follow-up duration for lung function (weeks)				
Median	51.9	51.9	52.0	45.9
Q1, Q3	45.0, 58.3	44.9, 58.6	46.1, 57.9	37.3, 59.1
Range	24.0 - 80.0	24.0 - 79.7	24.0 - 80.0	24.6 - 79.0
Response in exacerbations and LTOCS, N	242	48	191	3
Responders in both domains, n (%)	80 (33.1)	13 (27.1)	66 (34.6)	1 (33.3)
Non-responders in 1 domain, n (%)	125 (51.7)	25 (52.1)	98 (51.3)	2 (66.7)
Non-responders in both domains, n (%)	37 (15.3)	10 (20.8)	27 (14.1)	0 (0.0)
Response in exacerbations, LTOCS, and asthma control*, N	189	35	154	0
Responders in all 3 domains, n (%)	35 (18.5)	5 (14.3)	30 (19.5)	-
Non-responders in 1 or 2 domains, n (%)	129 (68.3)	24 (68.6)	105 (68.2)	-
Non-responders in all 3 domains, n (%)	25 (13.2)	6 (17.1)	19 (12.3)	-
Response in exacerbations, LTOCS, and lung function (>=100mL FEV_1 increase), N	132	25	106	1
Responders in all 3 domains, n (%)	18 (13.6)	3 (12.0)	15 (14.2)	0 (0.0)
Non-responders in 1 or 2 domains, n (%)	101 (76.5)	18 (72.0)	82 (77.4)	1 (100.0)
Non-responders in all 3 domains, n (%)	13 (9.8)	4 (16.0)	9 (8.5)	0 (0.0)
Response in exacerbations, LTOCS, asthma control*, and lung function (≥100mL FEV_1 increase), N	85	14	71	0
Responders in all 4 domains, n (%)	9 (10.6)	0 (0.0)	9 (12.7)	-
Non-responders in 1 to 3 domains, n (%)	67 (78.8)	11 (78.6)	56 (78.9)	-
Non-responders in all 4 domains, n (%)	9 (10.6)	3 (21.4)	6 (8.5)	-

*Asthma control assessed using Asthma Control Questionnaire,[1] Asthma Control Test,[2] or GINA control test[3] (see Table E3)

Abbreviations: FEV_1: forced expiratory volume in one second; LTOCS: long-term oral corticosteroid; Q: quartile

Table E5: Patient data contributed by country and comorbidity prevalence overall and by biologic class

Characteristics	Anti-IgE (N=665)	Anti-IL5/5R (N=1405)	Anti-IL4Rα (N=140)	Total (N=2210)
History of allergic rhinitis, N	504	845	130	1479
Yes, n (%)	300 (59.5)	429 (50.8)	56 (43.1)	785 (53.1)
History of chronic rhinosinusitis, N	553	1173	127	1853
Yes, n (%)	250 (45.2)	663 (56.5)	62 (48.8)	975 (52.6)
History of nasal polyposis, N	587	1256	130	1973
Yes, n (%)	109 (18.6)	446 (35.5)	36 (27.7)	591 (30.0)
History of osteoporosis, N	584	1086	130	1800
Yes, n (%)	115 (19.7)	196 (18.0)	24 (18.5)	335 (18.6)
History of sleep apnea, N	650	1375	134	2159
Yes, n (%)	146 (22.5)	196 (14.3)	42 (31.3)	384 (17.8)
History of anxiety/depression, N	582	1163	124	1869
Yes, n (%)	111 (19.1)	165 (14.2)	24 (19.4)	300 (16.1)
History of pneumonia, N	478	771	129	1378
Yes, n (%)	55 (11.5)	105 (13.6)	25 (19.4)	185 (13.4)
History of eczema/atopic dermatitis, N	586	1255	131	1972
Yes, n (%)	69 (11.8)	108 (8.6)	21 (16.0)	198 (10.0)
History of diabetes, N	655	1377	139	2171
Yes, n (%)	86 (13.1)	108 (7.8)	19 (13.7)	213 (9.8)
History of cataract, N	537	850	134	1521
Yes, n (%)	19 (3.5)	57 (6.7)	3 (2.2)	79 (5.2)

Characteristics	Anti-IgE (N=665)	Anti-IL5/5R (N=1405)	Anti-IL4Rα (N=140)	Total (N=2210)
History of heart failure and/or myocardial infarction, N	497	738	120	1355
Yes, n (%)	19 (3.8)	41 (5.6)	2 (1.7)	62 (4.6)
History of peptic ulcer, N	494	738	132	1364
Yes, n (%)	23 (4.7)	28 (3.8)	4 (3.0)	55 (4.0)
History of chronic kidney disease, N	456	665	116	1237
Yes, n (%)	15 (3.3)	24 (3.6)	2 (1.7)	41 (3.3)
History of glaucoma, N	533	836	137	1506
Yes, n (%)	10 (1.9)	15 (1.8)	1 (0.7)	26 (1.7)
History of pulmonary embolism/venous thromboembolism, N	599	1118	137	1854
Yes, n (%)	13 (2.2)	16 (1.4)	6 (4.4)	35 (1.9)
History of cerebrovascular accident, N	523	778	135	1436
Yes, n (%)	5 (1.0)	2 (0.3)	3 (2.2)	10 (0.7)
Country, N	665	1405	140	2210
Argentina, n (%)	0 (0.0)	1 (0.1)	7 (5.0)	8 (0.4)
Australia, n (%)	44 (6.6)	99 (7.0)	4 (2.9)	147 (6.7)
Bulgaria, n (%)	4 (0.6)	2 (0.1)	0 (0.0)	6 (0.3)
Canada, n (%)	13 (2.0)	60 (4.3)	4 (2.9)	77 (3.5)
Colombia, n (%)	15 (2.3)	12 (0.9)	7 (5.0)	34 (1.5)
Denmark, n (%)	32 (4.8)	163 (11.6)	2 (1.4)	197 (8.9)

Characteristics	Anti-IgE (N=665)	Anti-IL5/5R (N=1405)	Anti-IL4Rα (N=140)	Total (N=2210)
Greece, n (%)	15 (2.3)	19 (1.4)	0 (0.0)	34 (1.5)
Italy, n (%)	97 (14.6)	271 (19.3)	0 (0.0)	368 (16.7)
Japan, n (%)	7 (1.1)	25 (1.8)	9 (6.4)	41 (1.9)
Kuwait, n (%)	17 (2.6)	7 (0.5)	1 (0.7)	25 (1.1)
Mexico, n (%)	7 (1.1)	2 (0.1)	1 (0.7)	10 (0.5)
Poland, n (%)	26 (3.9)	34 (2.4)	0 (0.0)	60 (2.7)
Portugal, n (%)	2 (0.3)	10 (0.7)	0 (0.0)	12 (0.5)
Saudi Arabia, n (%)	6 (0.9)	15 (1.1)	0 (0.0)	21 (1.0)
Singapore, n (%)	1 (0.2)	4 (0.3)	0 (0.0)	5 (0.2)
South Korea, n (%)	7 (1.1)	7 (0.5)	1 (0.7)	15 (0.7)
Spain, n (%)	5 (0.8)	28 (2.0)	0 (0.0)	33 (1.5)
Taiwan, n (%)	17 (2.6)	21 (1.5)	1 (0.7)	39 (1.8)
UAE, n (%)	2 (0.3)	0 (0.0)	4 (2.9)	6 (0.3)
UK, n (%)	79 (11.9)	347 (24.7)	1 (0.7)	427 (19.3)
USA, n (%)	269 (40.5)	278 (19.8)	98 (70.0)	645 (29.2)

Table E6: Summary of proportion of responders for multiple domains using all possible combinations of pre-defined domains

Response definition	Domains included	Prevalence post-biologic
1	Exacerbations + LTOCS	33.1% (n=80/242)
2	Exacerbations + LTOCS + control*	18.5% (n=35/189)
3	Exacerbations + LTOCS + FEV_1	13.6% (n=18/132)
4	Exacerbations + LTOCS + control* + FEV_1	10.6% (n=9/85)
5	Exacerbations + control*	42.7% (n=198/459)
6	Exacerbations + FEV_1	39.9% (n=138/346)
7	Exacerbations + control* + FEV_1	20.7% (n=50/241)
8	LTOCS + control*	25.5% (n=108/423)
9	LTOCS + FEV_1	23.6% (n=78/331)
10	LTOCS + control* + FEV_1	14.1% (n=29/205)
11	Control* + FEV_1	28.9% (n=142/491)

*Asthma control assessed using Asthma Control Questionnaire,[1] Asthma Control Test,[2] or GINA control test[3] (see Table E3)

FEV_1: forced expiratory volume in one second; LTOCS: long-term oral corticosteroid

Table E7: pre- to post-biologic trajectories for each domain, in responders and non-responders separately, overall and by biologic class

Response definition	Pre-biologic status	Post-biologic status				
Overall						
≥50% reduction in exacerbations						
	Exacerbations	0	1 (no hosp.)	2 (no hosp.)	≥1 w/ hosp. or 3+ total	Total
Responders	2	120	35	0	2	157
	3+	212	99	46	52	409
	Total	332	134	46	54	566
Non-responders	2	0	0	25	14	49
	3+	0	0	13	83	96
	Total	0	0	38	97	135
≥50% reduction in LTOCS						
	LTOCS	Non-user	≤5mg/day	>5 to 10 mg/day	>10 mg/day	Total
Responders	≤5mg/day	102	16	0	0	118
	>5 to 10 mg/day	94	61	0	0	155
	>10 mg/day	124	28	31	5	188
	Total	320	105	31	5	461
Non-responders	≤5mg/day	0	190	12	8	210
	>5 to 10 mg/day	0	11	175	19	205
	>10 mg/day	0	0	9	156	165
	Total	0	201	196	183	580

≥1 GINA category improvement in asthma control*						
	Asthma control	Well controlled	Partly controlled	Uncontrolled	Total	
Responders	Partly controlled	101	0	0	101	
	Uncontrolled	235	206	0	441	
	Total	336	206	0	542	
Non-responders	Partly controlled	0	67	50	117	
	Uncontrolled	0	0	402	402	
	Total	0	67	452	519	
Increase in FEV_1						
	$ppFEV_1$	≥80%	<80%	Total		
≥500 mL increase responders	<80% (total)	136	68	204		
≥200-499 mL increase responders	<80% (total)	65	161	226		
≥100-199 mL increase responders	<80% (total)	22	100	122		
Non-responders	<80% (total)	5	473	478		
Anti-IgE						
≥50% reduction in exacerbations						
	Exacerbations	0	1 (no hosp.)	2 (no hosp.)	≥1 w/ hosp. or 3+ total	Total
Responders	2	36	8	0	0	44
	3+	29	20	5	13	67
	Total	65	28	5	13	111

Non-responders	2	0	0	7	5	12
	3+	0	0	6	17	23
	Total	0	0	13	22	35
≥50% reduction in LTOCS						
	LTOCS	Non-user	≤5mg/day	>5 to 10 mg/day	>10 mg/day	Total
Responders	≤5mg/day	33	0	0	0	33
	>5 to 10 mg/day	32	7	0	0	39
	>10 mg/day	38	5	12	1	56
	Total	103	12	12	1	128
Non-responders	≤5mg/day	0	57	3	3	63
	>5 to 10 mg/day	0	5	51	4	60
	>10 mg/day	0	0	2	44	46
	Total	0	62	56	51	169
≥1 GINA category improvement in asthma control*						
	Asthma control	Well controlled	Partly controlled	Uncontrolled	Total	
Responders	Partly controlled	21	0	0	21	
	Uncontrolled	45	61	0	106	
	Total	66	61	0	127	
Non-responders	Partly controlled	0	16	20	36	
	Uncontrolled	0	0	103	103	
	Total	0	16	123	139	
Increase in FEV_1						

	ppFEV$_1$	≥80%	<80%	Total		
≥500 mL increase responders	<80% (total)	37	13	50		
≥200-499 mL increase responders	<80% (total)	22	45	67		
≥100-199 mL increase responders	<80% (total)	4	39	43		
Non-responders	<80% (total)	2	167	169		
Anti-IL5/5R						
≥50% reduction in exacerbations						
	Exacerbations	0	1 (no hosp.)	2 (no hosp.)	≥1 w/ hosp. or 3+ total	Total
Responders	2	74	23	0	2	99
	3+	177	77	39	39	332
	Total	251	100	39	41	431
Non-responders	2	0	0	17	9	26
	3+	0	0	7	62	69
	Total	0	0	24	71	95
≥50% reduction in LTOCS						
	LTOCS	Non-user	≤5mg/day	>5 to 10 mg/day	>10 mg/day	Total
Responders	≤5mg/day	64	16	0	0	80
	>5 to 10 mg/day	56	53	0	0	109
	>10 mg/day	77	21	19	4	121
	Total	197	90	19	4	310

Non-responders	≤5mg/day	0	125	8	4	137
	>5 to 10 mg/day	0	6	118	15	139
	>10 mg/day	0	0	7	108	115
	Total	0	131	133	127	391
≥1 GINA category improvement in asthma control*						
	Asthma control	Well controlled	Partly controlled	Uncontrolled	Total	
Responders	Partly controlled	75	0	0	75	
	Uncontrolled	180	139	0	319	
	Total	255	139	0	394	
Non-responders	Partly controlled	0	47	29	76	
	Uncontrolled	0	0	290	290	
	Total	0	47	319	366	
Increase in FEV_1						
	$ppFEV_1$	≥80%	<80%	Total		
≥500 mL increase responders	<80% (total)	87	50	137		
≥200-499 mL increase responders	<80% (total)	37	108	145		
≥100-199 mL increase responders	<80% (total)	17	53	70		
Non-responders	<80% (total)	3	273	276		
Anti-IL4Rα						
≥50% reduction in exacerbations						

	Exacerbations	0	1 (no hosp.)	2 (no hosp.)	≥1 w/ hosp. or 3+ total	Total
Responders	2	10	4	0	0	14
	3+	6	2	2	0	10
	Total	16	6	2	0	24
Non-responders	2	0	0	0	0	0
	3+	0	0	0	4	4
	Total	0	0	1	4	5
≥50% reduction in LTOCS						
	LTOCS	Non-user	≤5mg/day	>5 to 10 mg/day	>10 mg/day	Total
Responders	≤5mg/day	5	0	0	0	5
	>5 to 10 mg/day	6	1	0	0	7
	>10 mg/day	9	2	0	0	11
	Total	20	3	0	0	23
Non-responders	≤5mg/day	0	8	1	1	10
	>5 to 10 mg/day	0	0	6	0	6
	>10 mg/day	0	0	0	4	4
	Total	0	8	7	5	20
≥1 GINA category improvement in asthma control*						
	Asthma control	Well controlled	Partly controlled	Uncontrolled	Total	
Responders	Partly controlled	5	0	0	5	
	Uncontrolled	10	6	0	16	
	Total	15	6	0	21	
Non-responders	Partly controlled	0	4	1	5	
	Uncontrolled	0	0	9	9	
	Total	0	4	10	14	

Increase in FEV_1						
	$ppFEV_1$	≥80%	<80%	Total		
≥500 mL increase responders	<80% (total)	12	5	17		
≥200-499 mL increase responders	<80% (total)	6	8	14		
≥100-199 mL increase responders	<80% (total)	1	8	9		
Non-responders	<80% (total)	0	33	33		

*Asthma control assessed using Asthma Control Questionnaire,[1] Asthma Control Test,[2] or GINA control test[3] (see Table E3)

Abbreviations: FEV_1: forced expiratory volume in one second; GINA: Global Initiative for Asthma; LTOCS: long-term oral corticosteroid; $ppFEV_1$: percent predicted forced expiratory volume in one second

Table E8: Association between selected pre-biologic factors and single domain response, adjusted for age at biologic initiation, sex and pre-biologic asthma-related outcome considered for response assessment

Pre-biologic factors	Responder domains			
	Exacerbations N OR (95% CI) p-value	**LTOCS** N OR (95% CI) p-value	**Asthma control** N OR (95% CI) p-value	**Lung function** N OR (95% CI) p-value
All biologic classes				
Exacerbations (1-unit increment)	701 1.10 (1.02-1.18) 0.011	711 0.91 (0.87-0.96) <0.001	888 0.96 (0.92-0.99) 0.024	685 0.99 (0.95-1.03) 0.656
LTOCS dose (5-mg/day increment)	650 0.85 (0.77-0.95) 0.003	1040 1.13 (1.06-1.20) <0.001	983 0.89 (0.82-0.96) 0.002	768 0.92 (0.84-1.00) 0.050
Asthma control* (1-GINA category increment)	534 1.08 (0.73-1.6) 0.710	594 1.14 (0.87-1.50) 0.350	1061 0.75 (0.56-1.02) 0.066	613 1.01 (0.78-1.31) 0.917
ppFEV$_1$ (5-unit increment)	634 1.04 (0.99-1.09) 0.111	758 1.01 (0.97-1.04) 0.733	930 1.07 (1.03-1.10) <0.001	1030 0.91 (0.87-0.95) <0.001
BEC (doubling in concentration)	496 1.08 (0.92-1.26) 0.359	724 1.15 (1.03-1.27) 0.010	767 1.32 (1.18-1.48) <0.001	727 1.31 (1.17-1.47) <0.001
Blood IgE level (doubling in concentration)	521 1.03 (0.93-1.14)	662 0.99 (0.92-1.07)	791 0.98 (0.92-1.05)	756 0.99 (0.93-1.06)

Pre-biologic factors	Responder domains			
	Exacerbations N OR (95% CI) p-value	**LTOCS** N OR (95% CI) p-value	**Asthma control** N OR (95% CI) p-value	**Lung function** N OR (95% CI) p-value
	0.588	0.816	0.564	0.809
FeNO (25-unit increment, ppb)	449 0.96 (0.85-1.09) 0.514	501 0.96 (0.88-1.04) 0.328	663 1.04 (0.96-1.14) 0.318	594 1.20 (1.10-1.31) <0.001
Age-of-asthma onset (5-year increment)	513 1.04 (0.97-1.11) 0.327	784 1.01 (0.97-1.06) 0.511	890 1.02 (0.98-1.06) 0.349	505 1.11 (1.06-1.17) <0.001
Asthma duration (10-year increment)	513 0.93 (0.81-1.07) 0.327	784 0.97 (0.89-1.06) 0.511	890 0.96 (0.89-1.04) 0.349	505 0.81 (0.73-0.90) <0.001
BMI (5-unit increment)	687 0.96 (0.83-1.12) 0.633	923 0.89 (0.80-0.98) 0.022	1030 0.72 (0.65-0.80) <0.001	1026 0.93 (0.85-1.01) 0.092
Smoking status (ever vs. never)	628 0.97 (0.62-1.51) 0.890	727 1.27 (0.92-1.75) 0.142	895 0.94 (0.70-1.25) 0.676	902 0.98 (0.76-1.27) 0.901
Use of LTRA (yes vs. no)	582 0.77 (0.52-1.14) 0.194	922 0.84 (0.64-1.09) 0.189	771 0.84 (0.63-1.13) 0.242	912 1.11 (0.87-1.42) 0.396
Use of theophylline (yes vs. no)	592 0.59 (0.34-1.03) 0.062	922 0.66 (0.46-0.96) 0.028	771 0.51 (0.33-0.78) 0.002	912 0.68 (0.46-0.99) 0.047

Pre-biologic factors	Responder domains			
	Exacerbations N OR (95% CI) p-value	**LTOCS** N OR (95% CI) p-value	**Asthma control** N OR (95% CI) p-value	**Lung function** N OR (95% CI) p-value
History of allergic rhinitis (yes vs. no)	430 0.83 (0.49-1.39) 0.471	490 1.62 (1.13-2.34) 0.009	692 1.17 (0.84-1.62) 0.355	786 1.28 (0.99-1.67) 0.062
History of chronic rhinosinusitis (yes vs. no)	650 1.06 (0.72-1.57) 0.775	804 1.66 (1.25-2.20) <0.001	925 1.84 (1.41-2.40) <0.001	976 1.68 (1.32-2.13) <0.001
History of nasal polyposis (yes vs. no)	675 1.04 (0.69-1.56) 0.867	843 1.13 (0.84-1.53) 0.406	1044 1.76 (1.36-2.28) <0.001	1018 1.32 (1.01-1.72) 0.039
History of eczema/atopic dermatitis (yes vs. no)	678 1.54 (0.73-3.25) 0.253	842 2.83 (1.62-4.95) <0.001	1045 0.92 (0.63-1.34) 0.675	1017 0.93 (0.62-1.37) 0.702
T2-related comorbidity score (1-point increment; 0 to 4 score system)	399 0.96 (0.76-1.20) 0.691	445 1.09 (0.91-1.30) 0.335	562 1.18 (1.02-1.37) 0.030	738 1.25 (1.10-1.43) 0.001
History of osteoporosis (yes vs. no)	493 0.60 (0.34-1.08) 0.086	885 1.08 (0.78-1.48) 0.657	804 1.06 (0.72-1.56) 0.775	818 0.71 (0.51-0.99) 0.042
History of sleep apnea (yes vs. no)	686 1.07 (0.61-1.87) 0.823	1018 2.24 (1.58-3.17) <0.001	1049 0.68 (0.46-1.00) 0.050	1010 0.98 (0.75-1.28) 0.865

Pre-biologic factors	Responder domains			
	Exacerbations N OR (95% CI) p-value	**LTOCS** N OR (95% CI) p-value	**Asthma control** N OR (95% CI) p-value	**Lung function** N OR (95% CI) p-value
History of chronic kidney disease (yes vs. no)	274 0.67 (0.13-3.49) 0.638	547 1.58 (0.55-4.53) 0.400	435 0.52 (0.10-2.75) 0.444	553 0.74 (0.35-1.51) 0.412
History of glaucoma (yes vs. no)	322 Model did not converge	652 0.52 (0.19-1.47) 0.219	592 0.91 (0.29-2.85) 0.877	679 0.97 (0.28-2.99) 0.955
Anti-IgE				
Exacerbations (1-unit increment)	146 1.15 (0.97-1.36) 0.109	181 0.85 (0.75-0.95) 0.006	204 1.00 (0.93-1.08) 0.964	163 1.01 (0.92-1.10) 0.811
LTOCS dose (5-mg/day increment)	141 0.92 (0.74-1.14) 0.427	296 1.10 (1.00-1.22) 0.051	248 0.80 (0.66-0.97) 0.022	203 0.91 (0.77-1.08) 0.302
Asthma control* (1-GINA category increment)	107 1.20 (0.57-2.51) 0.634	151 0.91 (0.54-1.54) 0.728	266 0.55 (0.30-1.01) 0.054	163 1.16 (0.71-1.89) 0.549
$ppFEV_1$ (5-unit increment)	124 1.02 (0.93-1.12) 0.718	200 0.99 (0.93-1.05) 0.662	219 1.05 (0.98-1.12) 0.161	326 0.91 (0.84-0.99) 0.021
BEC (doubling in concentration)	102 0.65 (0.45-0.94) 0.022	169 1.10 (0.88-1.37) 0.420	190 1.02 (0.83-1.26) 0.822	213 1.37 (1.11-1.69) 0.003

Pre-biologic factors	Responder domains			
	Exacerbations N OR (95% CI) p-value	**LTOCS** N OR (95% CI) p-value	**Asthma control** N OR (95% CI) p-value	**Lung function** N OR (95% CI) p-value
Blood IgE level (doubling in concentration)	126 0.96 (0.77-1.21) 0.744	190 1.00 (0.85-1.18) 0.973	216 1.04 (0.89-1.23) 0.605	255 0.98 (0.86-1.12) 0.753
FeNO (25-unit increment, ppb)	77 0.91 (0.62-1.34) 0.638	109 1.10 (0.90-1.36) 0.351	122 1.05 (0.81-1.36) 0.711	150 1.31 (1.09-1.59) 0.004
Age-of-asthma onset (5-year increment)	101 1.12 (0.94-1.32) 0.198	199 1.08 (0.99-1.17) 0.097	200 1.09 (1.00-1.19) 0.052	98 1.10 (0.98-1.24) 0.115
Asthma duration (10-year increment)	101 0.80 (0.57-1.12) 0.198	199 0.86 (0.73-1.03) 0.097	200 0.84 (0.71-1.00) 0.052	98 0.83 (0.65-1.05) 0.115
BMI (5-unit increment)	140 0.81 (0.60-1.10) 0.179	235 0.84 (0.69-1.03) 0.095	249 0.69 (0.56-0.86) 0.001	329 0.95 (0.82-1.09) 0.461
Smoking status (ever vs. never)	126 0.66 (0.27-1.65) 0.376	195 1.26 (0.69-2.29) 0.448	218 0.75 (0.41-1.37) 0.353	284 0.83 (0.51-1.35) 0.460
Use of LTRA (yes vs. no)	125 1.11 (0.48-2.58) 0.800	259 0.94 (0.57-1.55) 0.812	198 1.18 (0.65-2.13) 0.584	307 1.11 (0.73-1.70) 0.627
Use of theophylline (yes vs. no)	125 0.66 (0.18-2.44)	259 0.86 (0.45-1.64)	198 0.45 (0.18-1.12)	307 0.66 (0.32-1.31)

Pre-biologic factors	Responder domains			
	Exacerbations N OR (95% CI) p-value	**LTOCS** N OR (95% CI) p-value	**Asthma control** N OR (95% CI) p-value	**Lung function** N OR (95% CI) p-value
	0.534	0.644	0.086	0.245
History of allergic rhinitis (yes vs. no)	104 0.62 (0.22-1.74) 0.367	169 1.43 (0.76-2.68) 0.270	210 0.98 (0.53-1.85) 0.962	293 1.52 (0.98-2.38) 0.062
History of chronic rhinosinusitis (yes vs. no)	136 1.30 (0.58-2.94) 0.524	219 1.25 (0.72-2.17) 0.422	227 1.35 (0.77-2.35) 0.294	319 1.24 (0.81-1.88) 0.325
History of nasal polyposis (yes vs. no)	140 1.27 (0.49-3.30) 0.626	231 1.24 (0.65-2.38) 0.513	260 1.09 (0.62-1.93) 0.767	327 1.03 (0.56-1.86) 0.926
History of eczema/atopic dermatitis (yes vs. no)	140 2.57 (0.53-12.53) 0.242	230 1.89 (0.79-4.51) 0.151	259 1.34 (0.63-2.85) 0.448	327 0.92 (0.48-1.72) 0.792
T2-related comorbidity score (1-point increment; 0 to 4 score system)	101 0.90 (0.57-1.42) 0.638	156 1.01 (0.75-1.36) 0.944	176 1.10 (0.82-1.48) 0.535	285 1.18 (0.94-1.48) 0.159
History of osteoporosis (yes vs. no)	121 0.25 (0.08-0.79) 0.018	261 0.63 (0.35-1.13) 0.123	230 1.03 (0.50-2.11) 0.943	287 0.47 (0.26-0.85) 0.015
History of sleep apnea (yes vs. no)	145 1.61 (0.49-5.30) 0.432	290 1.51 (0.84-2.71) 0.168	263 0.66 (0.33-1.29) 0.223	317 0.93 (0.59-1.45) 0.752

Pre-biologic factors	Responder domains			
	Exacerbations N OR (95% CI) p-value	**LTOCS** N OR (95% CI) p-value	**Asthma control** N OR (95% CI) p-value	**Lung function** N OR (95% CI) p-value
History of chronic kidney disease (yes vs. no)	Model did not converge	189 3.98 (0.43-37.13) 0.225	151 Model did not converge	236 0.42 (0.11-1.31) 0.158
History of glaucoma (yes vs. no)	Model did not converge	220 0.19 (0.02-1.72) 0.140	196 0.89 (0.13-5.95) 0.905	270 3.19 (0.54-19.30) 0.186
Anti-IL5/5R				
Exacerbations (1-unit increment)	526 1.10 (1.01-1.19) 0.027	500 0.93 (0.88-0.98) 0.006	657 0.95 (0.90-0.99) 0.015	488 0.97 (0.92-1.02) 0.246
LTOCS dose (5-mg/day increment)	480 0.84 (0.74-0.95) 0.006	701 1.13 (1.05-1.22) 0.002	701 0.91 (0.84-0.99) 0.036	525 0.92 (0.83-1.02) 0.095
Asthma control* (1-GINA category increment)	422 1.07 (0.67-1.73) 0.773	432 1.22 (0.88-1.69) 0.244	760 0.85 (0.60-1.22) 0.389	432 0.97 (0.69-1.34) 0.838
$ppFEV_1$ (5-unit increment)	486 1.05 (1.00-1.11) 0.063	526 1.01 (0.98-1.05) 0.449	679 1.08 (1.04-1.12) <0.001	628 0.90 (0.86-0.95) <0.001
BEC (doubling in concentration)	372 1.23 (1.01-1.49) 0.035	525 1.18 (1.04-1.33) 0.010	551 1.55 (1.34-1.80) <0.001	465 1.31 (1.13-1.52) <0.001

Pre-biologic factors	Responder domains			
	Exacerbations N OR (95% CI) p-value	**LTOCS** N OR (95% CI) p-value	**Asthma control** N OR (95% CI) p-value	**Lung function** N OR (95% CI) p-value
Blood IgE level (doubling in concentration)	378 1.05 (0.94-1.22) 0.294	441 0.99 (0.91-1.08) 0.873	551 0.99 (0.91-1.08) 0.863	458 1.05 (0.94-1.11) 0.633
FeNO (25-unit increment, ppb)	358 0.95 (0.83-1.09) 0.500	364 0.91 (0.82-1.01) 0.064	521 1.05 (0.95-1.15) 0.330	404 1.14 (1.03-1.27) 0.014
Age-of-asthma onset (5-year increment)	404 1.01 (0.93-1.10) 0.770	568 0.99 (0.93-1.04) 0.594	662 0.99 (0.94-1.04) 0.748	393 1.11 (1.05-1.18) <0.001
Asthma duration (10-year increment)	404 0.98 (0.83-1.15) 0.770	568 1.03 (0.92-1.15) 0.594	662 1.02 (0.92-1.12) 0.748	393 0.81 (0.72-0.91) <0.001
BMI (5-unit increment)	518 1.00 (0.83-1.21) 0.999	646 0.92 (0.82-1.05) 0.220	747 0.70 (0.62-0.79) <0.001	624 0.91 (0.81-1.03) 0.138
Smoking status (ever vs. never)	474 1.01 (0.60-1.71) 0.967	498 1.30 (0.88-1.94) 0.190	659 1.04 (0.75-1.46) 0.799	553 1.12 (0.81-1.54) 0.510
Use of LTRA (yes vs. no)	439 0.66 (0.41-1.05) 0.079	621 0.85 (0.61-1.18) 0.321	543 0.74 (0.52-1.05) 0.093	534 1.16 (0.84-1.60) 0.357
Use of theophylline (yes vs. no)	439 0.61 (0.33-1.15)	621 0.59 (0.38-0.94)	543 0.52 (0.32-0.86)	534 0.70 (0.44-1.10)

Pre-biologic factors	**Responder domains**			
	Exacerbations N OR (95% CI) p-value	**LTOCS** N OR (95% CI) p-value	**Asthma control** N OR (95% CI) p-value	**Lung function** N OR (95% CI) p-value
	0.126	0.026	0.010	0.124
History of allergic rhinitis (yes vs. no)	299 0.88 (0.47-1.66) 0.695	284 1.90 (1.17-3.09) 0.010	448 1.36 (0.91-2.03) 0.137	422 1.41 (0.99-2.02) 0.058
History of chronic rhinosinusitis (yes vs. no)	487 1.06 (0.66-1.69) 0.818	549 2.12 (1.49-3.01) <0.001	667 2.22 (1.62-3.04) <0.001	585 1.73 (1.28-2.36) <0.001
History of nasal polyposis (yes vs. no)	508 0.93 (0.58-1.49) 0.760	575 1.17 (0.83-1.66) 0.369	750 2.08 (1.54-2.81) <0.001	619 1.17 (0.85-1.61) 0.320
History of eczema/atopic dermatitis (yes vs. no)	511 1.82 (0.69-4.81) 0.227	575 4.13 (1.88-9.07) <0.001	751 0.79 (0.50-1.26) 0.325	618 1.06 (0.59-1.90) 0.839
T2-related comorbidity score (1-point increment; 0 to 4 score system)	271 0.97 (0.73-1.28) 0.831	253 1.24 (0.98-1.58) 0.076	357 1.27 (1.05-1.52) 0.013	382 1.24 (1.04-1.47) 0.016
History of osteoporosis (yes vs. no)	344 0.96 (0.46-2.03) 0.922	587 1.40 (0.94-2.10) 0.101	542 1.11 (0.69-1.79) 0.665	465 0.79 (0.51-1.22) 0.291
History of sleep apnea (yes vs. no)	513 1.06 (0.53-2.14) 0.865	686 3.09 (1.93-4.97) <0.001	753 0.63 (0.38-1.04) 0.070	623 1.16 (0.80-1.68) 0.439

Pre-biologic factors	Responder domains			
	Exacerbations N OR (95% CI) p-value	**LTOCS** N OR (95% CI) p-value	**Asthma control** N OR (95% CI) p-value	**Lung function** N OR (95% CI) p-value
History of chronic kidney disease (yes vs. no)	162 0.68 (0.12-3.76) 0.655	325 1.02 (0.28-3.66) 0.978	256 Model did not converge	257 1.14 (0.39-3.32) 0.806
History of glaucoma (yes vs. no)	202 Model did not converge	389 0.64 (0.17-2.44) 0.516	366 1.36 (0.26-7.1) 0.713	339 0.18 (0.01-1.20) 0.127

*Asthma control assessed using Asthma Control Questionnaire,[1] Asthma Control Test,[2] or GINA control test[3] (see Table E3)

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

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