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Impact of pre-biologic impairment on meeting domain-specific biologic responder definitions in patients with severe asthma

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ABSTRACT

Background: There is little agreement on clinically useful criteria for identifying real-world responders to biologic treatments for asthma.

Objective: To investigate the impact of pre-biologic impairment on meeting domain-specific biologic responder definitions in adults with severe asthma.

Methods: This was a longitudinal, cohort study across 22 countries participating in the International Severe Asthma Registry (https://isaregistries.org/) between May 2017 and January 2023. Change in 4 asthma domains (exacerbation rate, asthma control, long-term oral corticosteroid [LTOCS] dose, and lung function) was assessed from biologic initiation to 1 year post-treatment (minimum 24 weeks). Pre- to post-biologic changes for responders and nonresponders were described along a categorical gradient for each domain derived from pre-biologic distributions (exacerbation rate: 0 to 6+/y; asthma control: well controlled to uncontrolled; LTOCS: 0 to >30 mg/d; percent-predicted forced expiratory volume in 1 second [ppFEV$_1$]: <50% to ≥80%).

Results: Percentage of biologic responders (ie, those with a category improvement pre- to post-biologic) varied by domain and increased with greater pre-biologic impairment, increasing from 70.2% to 90.0% for exacerbation rate, 46.3% to 52.3% for asthma control, 31.1% to 58.5% for LTOCS daily dose, and 35.8% to 50.6% for ppFEV$_1$. The proportion of patients having improvement post-biologic tended to be greater for anti–IL-5/5R compared with for anti-IgE for exacerbation, asthma control, and ppFEV$_1$ domains, irrespective of pre-biologic impairment.

Conclusion: Our results provide realistic outcome-specific post-biologic expectations for both physicians and patients, will be foundational to inform future work on a multidimensional approach to define and assess biologic responders and response, and may enhance appropriate patient selection for biologic therapies.

Trial Registration: The ISAR database has ethical approval from the Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (ADEPT0218) and is registered with the European Union Electronic Register of Post-Authorization studies (ENCEPP/DSPP/23720). The study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) Code of Conduct (EUPAS38288) and with all applicable local and international laws and regulation, and registered with ENCEPP (https://www.encepp.eu/encepp/viewResource.htm?id=38289). Governance was provided by ADEPT (registration number: ADEPT1220).

Introduction

Identifying responders and nonresponders among patients with asthma treated with biologics is not easy, as response incorporates a combination of "clinical signals" that might not be the same in every patient.[1,2] Response is a word frequently used (and overused) when describing post-biologic treatment effect(s). However, a universal definition is yet to be formulated,[3,4] essentially resulting in subjective assessment of this term. Clinical trialists, for example, have traditionally used minimal clinically important difference to define the smallest relevant within-person change.[4] Others have defined "partial responders," "super responders," and "nonresponders."[2,5] Quantitative and qualitative tools have been devised to measure response[4,6-8] but using different outcomes and cutoffs. The National Institute for Health and Care Excellence has historically recognized an exacerbation rate reduction of at least 50% or a clinically meaningful reduced dose of long-term oral corticosteroid (LTOCS) as an adequate response, assessed up to 12 months after biologic therapy initiation. The Global Initiative for Asthma (GINA) acknowledges that there are no well-defined criteria for a good response but recommends consideration of exacerbations, symptom control, lung function, medical adverse effects, treatment intensity (including oral corticosteroid [OCS] dose), and patient satisfaction.[3] Indeed, patients tend to view "positive response" to biologic therapy in a slightly different light, citing reduction in exacerbation severity and quicker recovery time after exacerbations, fewer difficulties with social interaction, greater ability to participate in life, increased energy, and reduced impact on mental health as important factors.[9]

A few real-world studies have attempted to define responders based on post-biologic improvements in a variety of clinical and functional (ie, quality of life) end points,[10-15] with reduction in exacerbations and OCS dose and improvement in asthma control being the most common criteria. In these studies, the proportion of patients with a response ranged from 52% to 88%, depending on response definition and biologic assessed, and time of response assessment ranged from 12 weeks to 1 year.[10-15] For example, using data from the Danish Severe Asthma Register, Soendergaard et al[15] defined complete response as resolution of the parameter setting the indication (ie, recurrent exacerbations and/or use of OCS) after 12 months of treatment. Others identified differential responsiveness to benralizumab in different severe eosinophilic subphenotypes ranging from 52% to 80%, with response defined as elimination of exacerbations.[14] Eger et al[2] adopted a slightly different approach, defining super, partial, and nonresponse in terms of symptoms remaining after treatment.

These studies highlighted that despite the emergence of common domains of treatment response, there is little agreement on optimal criteria for identifying responders in real life or on how to measure pre- to post-biologic transitions. In terms of domains to include in a response definition, we need to consider whether response is more difficult to achieve in some domains than in others, which domains should be included in a composite definition, what cutoffs should be applied to define response for each domain (rather than arbitrarily choosing cutoffs from randomized controlled trials [RCTs]), and what is the time scale to assess response (eg, short-term vs long-term response)? The impact of pre-biologic disease impairment on response also requires further thought: how likely is it to achieve response along a gradient of pre-biologic impairment, how do responders transition to post-biologic improvement, and what level of response is achievable in patients with significant pre-biologic impairment? This last question requires inclusion of patients who did not meet traditional requirements for entry into RCTs (eg, those with percent-predicted forced expiratory volume in 1 second [$ppFEV_1$] ≥ 80% or with an annual exacerbation rate ≤ 1).

As a first step to achieve consensus on a universal response definition, clinically relevant markers of treatment response that are unequivocally applicable to all biologics must first be chosen, and pre- to post-biologic transitions (considering pre-biologic impairment) must be characterized, quantified, and compared across biologic classes. The International Severe Asthma Registry (ISAR; https://www.isaregistries.opcglobal.org/) contains data on more than 17,000 patients from 25 countries, offering a unique opportunity to fill in some of the gaps in our understanding of biologic response in patients with severe asthma.[16] It includes a heterogeneous severe asthma population with a variety of pre-biologic impairment (different from RCT populations) that can aid in visualizing the spectrum of response and collects a wide range of asthma outcomes frequently assessed in real-life clinical practice (and most often included in response definitions). ISAR has sufficient pre- and post-biologic outcome data to gauge the scale of response for the most common biologic classes prescribed (ie, anti-IgE [omalizumab]; anti–interleukin [IL]-5/5 receptor [5R] [benralizumab, mepolizumab, and reslizumab], and anti–IL-4Rα [dupilumab]).[17-19] The aim of this study was to investigate the dynamics of response to biologic therapy across both clinical and functional asthma outcome domains and the extent to which these are met in patients receiving biologic therapy in real life. This aim was achieved by assessing the impact of pre-biologic disease severity on meeting domain-specific biologic responder definitions, along a spectrum of pre-biologic impairment for each domain, and by biologic class in patients with severe asthma.

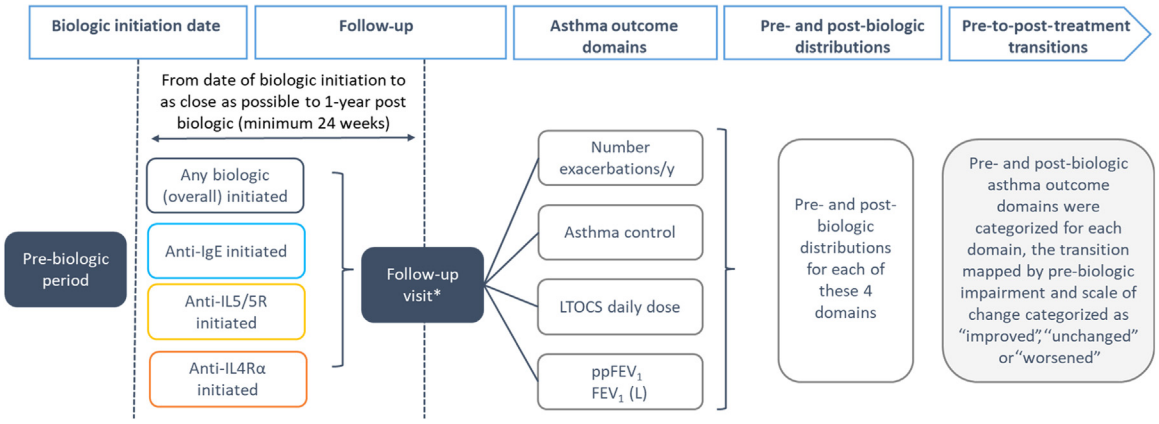


Figure 1. Study design. Asterisk denotes Maximum follow-up time for asthma control, LTOCS, and lung function: 80 weeks. FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroid; $ppFEV_1$, percent-predicted forced expiratory volume in 1 second. See Table 1 for definitions and categorizations of outcomes.

Table 1
Asthma Outcome Domain Definitions and Categories

Outcome	Definition	Pre-biologic categorization[a]	Post-biologic categorization[a]	Pre- to post-biologic change
Exacerbation	• Asthma-related hospital attendance/admission; and/or • Asthma-related ED attendance; and/or • Acute OCS course ≥3 d[b]	• High: 6+/y • Moderate: 2-5/y • Low: 1/y • Zero: 0/y	• High: 6+/y • Moderate: 2-5/y • Low: 1/y • Zero: 0/y	**Improved (responder)** Moved to a lower (better) category post-biologic **Unchanged**
Asthma control	• GINA control test,[3] • ACT test,[21] or • ACQ[22]	• Uncontrolled • Partly controlled • Well controlled	• Uncontrolled • Partly controlled • Well controlled	Remained at the same category post-biologic **Worsened (nonresponder)** Moved to higher (worse) category post-biologic
Daily LTOCS dose[b]	• Daily dose (mg) and includes prescriptions that have a longer duration (>3 mo).	• Very high: >30 mg • High: >10-30 mg • Moderate: >5-10 mg • Low: >0-5 mg • Zero: 0 mg	• Very high: >30 mg • High: >10-30 mg • Moderate: >5-10 mg • Low: >0-5 mg • Zero: 0 mg	
Lung function	• ppFEV$_1$ • Change in absolute FEV$_1$	• <50% • 50%-64% • 65%-79% • ≥80%	• <50% • Decrease ≥ 100 mL • 50%-64% • No change • 65%-79% • Increase 100-199 mL • ≥80% • Increase 200-499 mL • Increase ≥ 500 mL	

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; ED, emergency department; FEV$_1$, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; LTOCS, long-term oral corticosteroid; OCS, oral corticosteroid; ppFEV1, percent-predicted forced expiratory volume in 1 second.
[a]Domain values were categorized pre- and post-biologic, based on pre-biologic distributions for each outcome.
[b]The dose closest to biologic initiation was used. Post-biologic dose was that closest to 1-year post-biologic initiation.[c]Calculated using Quanjer's summary equations of reference ventilatory flow values.[23]

Methods

Study Design and Data Source

This was a longitudinal cohort study using registry data from ISAR (https://isaregistries.org/), consisting of pre-biologic (first biologic, assuming historic biologic courses were included in ISAR) and post-biologic (follow-up) periods (Fig 1). Registry details have been described elsewhere.[18] We included data from 22 countries (Argentina, Australia, Bulgaria, Canada, Colombia, Denmark, Greece, Ireland, Italy, Japan, Kuwait, Mexico, Poland, Portugal, Republic of Korea, Saudi Arabia, Singapore, Spain, Taiwan, United Arab Emirates, United Kingdom, and United States) that shared data with ISAR up to January 25, 2023. Pre- to post-biologic change in 4 asthma domains was assessed from the date of biologic initiation to as close as possible to 1 year post-biologic initiation, with a minimum follow-up duration of 24 weeks and a maximum of 80 weeks. Pre- to post-biologic transitions were described along a categorial gradient for each domain (Fig 1; Table 1). The study was designed, implemented, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (EMA 2014; EUPAS38288) and with all applicable local and international laws and regulations. The ISAR database has ethical approval from the Anonymized Data Ethics Protocols and Transparency Committee and this protocol (ADEPT1220).

Patients

Patients were required to be aged above or equal to 18 years at biologic initiation and have severe asthma (ie, receiving treatment at GINA 2018 step 5 or with uncontrolled asthma at GINA step 4).[20] They were also required to be treated with anti-IgE, anti−IL-5/5R, or anti−IL-4Rα therapy, have available registry data before or on biologic initiation date, and have follow-up data (as close to 1 year as possible). Timing of pre- and post-biologic outcome measurements is summarized in Table 2. Patients with a history of bronchial thermoplasty or with inadequate background data at the date of biologic initiation were excluded.

Variables

Collected pre-biologic demographic characteristics and clinical characteristics are found in Table 3 and included among others, sex (male/female), age of asthma onset and duration, body mass index, smoking status and co-morbidity history, including pre-biologic biomarker levels (ie, blood eosinophil count [BEC], fractional exhaled nitric oxide [FeNO], and total IgE), exacerbation rate, control status, LTOCS use, and dose and lung function. An exacerbation was defined as an asthma-related hospital attendance/admission and/or an asthma-related emergency room attendance, and/or an OCS course of more than or equal to 3 days. Asthma control was categorized as well, partly, or uncontrolled according to GINA 2023 criteria,[3] Asthma Control Test,[21] or Asthma Control Questionnaire.[22]

Asthma Outcome Domains and Categorizations

The asthma domains assessed were exacerbation rate, asthma control, LTOCS daily dose, and ppFEV$_1$ (Table 1). For FEV$_1$, we used post-bronchodilator measures if available, and pre-bronchodilator

Table 2
Timing of Pre- and Post-Biologic Asthma Outcome Domain Measurements

Outcome	Pre-biologic	Post-biologic
Exacerbation rate	1 y pre-biologic (or 48 wk minimum)	Annualized post-biologic (number of events assessed for a minimum of 24 wk and a maximum of 80 wk post-biologic)
Asthma control[a]	At biologic initiation (or assessment closest to biologic initiation up to a maximum of 1 y pre-biologic)	Closest to 1-y post-biologic (24 wk minimum and 80 wk maximum)
Daily LTOCS dose	At biologic initiation	Closest to 1-y post-biologic (24 wk minimum and 80 wk maximum)
% Predicted and absolute FEV$_1$[b]	At biologic initiation (or assessment closest to biologic initiation up to a maximum of 1 y pre-biologic)	Closest to 1-y post-biologic (24 wk minimum and 80 wk maximum)

Abbreviations: FEV$_1$, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroid.
[a]Assessed by Global Initiative for Asthma control criteria, Asthma Control Test, or Asthma Control Questionnaire.
[b]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.

Table 3
Patient Pre-Biologic Characteristics

Characteristic	Overall biologic (n = 3409)	Anti-IgE (n = 1266)	Anti–IL-5/5R (n = 1889)	Anti–IL-4Rα (n = 254)	*P* values[a]		
					Anti-IgE vs IL-5/5R	Anti–IL-5/5R vs anti–IL-4Rα	Anti- IgE vs anti–IL-4Rα
Sex	N = 3407	N = 1265	N = 1888	N = 254	.021	.555	.516
Female, n (%)	2110 (61.9%)	814 (64.3)	1138 (60.3)	158 (62.2)			
Age at biologic initiation					<.001	<.001	.131
Mean (SD)	52.5 (14.0)	49.5 (14.0)	54.7 (13.4)	50.9 (14.0)			
Median (Q1-Q3)	54 (44-63)	50 (40-59)	56 (46-65)	52 (41-62)			
Ethnicity	N = 3234	N = 1222	N = 1766	N = 246	.253	<.001	<.001
White, n (%)	2386 (73.8)	892 (73.0)	1333 (75.5)	161 (65.4)			
Asian, n (%)	224 (6.9)	84 (6.9)	121 (6.9)	19 (7.7)			
African, n (%)	83 (2.6)	32 (2.6)	44 (2.5)	7 (2.8)			
Mixed, n (%)	67 (2.1)	54 (4.4)	7 (0.4)	6 (2.4)			
Other, n (%)	228 (7.1)	83 (6.8)	125 (7.1)	20 (8.1)			
Unknown, n (%)	246 (7.6)	77 (6.3)	136 (7.7)	33 (13.4)			
BMI, kg/m^2	N = 3178	N = 1152	N = 1775	N = 251	<.001	<.001	.531
Mean (SD)	29.2 (6.8)	29.8 (7.0)	28.6 (6.4)	30.1 (7.5)			
Median (Q1-Q3)	28.1 (24.5-32.8)	28.8 (25.1-33.7)	27.5 (24.0-32.0)	29.0 (24.9-34.2)			
Smoking status	N = 2476	N = 890	N = 1398	N = 188	.004	.517	.028
Current, n (%)	64 (2.6)	32 (3.6)	27 (1.9)	5 (2.7)			
Ex-smoker, n (%)	724 (29.2)	213 (23.9)	448 (32.0)	63 (33.5)			
Never smoked, n (%)	1688 (68.2)	645 (72.5)	923 (66.0)	120 (63.8)			
Age of onset, y	N = 2201	N = 785	N = 1317	N = 99	<.001	.032	.257
Mean (SD)	29.5 (18.6)	25.6 (18.1)	32.0 (18.5)	27.8 (18.9)			
Median (Q1-Q3)	30 (13-43)	24 (9-38)	33 (14-46)	26 (10-43)			
Asthma duration, y	N = 2201	N = 785	N = 1317	N = 99	.163	.650	.885
Mean (SD)	22.8 (16.5)	23.4 (16.1)	22.4 (16.7)	23.2 (16.1)			
Median (Q1-Q3)	19 (9-34)	20 (11-34)	18 (9-34)	22 (7-34)			
Pre-bx exacerbation rate	N = 2036	N = 646	N = 1261	N = 129	.002	<.001	<.001
Mean rate/y (SD)	3.0 (3.2)	2.8 (3.2)	3.3 (3.3)	1.2 (1.4)			
Median (Q1-Q3)	2 (1-4)	2 (1-4)	2 (1-5)	1 (0-2)			
Asthma control[b]	N = 1767	N = 622	N = 1074	N = 71	.369	.003	.001
Well-controlled, n (%)	182 (10.3)	70 (11.3)	100 (9.3)	12 (16.9)			
Partly controlled, n (%)	302 (17.1)	85 (13.7)	198 (18.4)	19 (26.8)			
Uncontrolled, n (%)	1283 (72.6)	467 (75.1)	776 (72.3)	40 (56.3)			
Pre-bx LTOCS use	N = 2991	N = 1038	N = 1760	N = 193	<.001	<.001	.041
Yes, n (%)	1145 (38.3)	312 (30.1)	789 (44.8)	44 (22.8)			
Pre-bx LTOCS daily dose in users, mg	N = 1053	N = 299	N = 710	N = 44	.235	.255	.151
Mean (SD)	13.0 (11.0)	13.7 (12.4)	12.8 (10.6)	11.0 (6.6)			
Median (Q1-Q3)	10 (5-20)	10 (5-20)	10 (5-20)	10 (5-16)			
Pre-biologic ppFEV$_1$	N = 2486	N = 901	N = 1399	N = 186	.207	.337	.789
Mean (SD)	74.8 (22.4)	75.4 (22.2)	74.2 (22.5)	75.9 (22.2)			
Median (Q1-Q3)	74.4 (59.4-90.0)	74.4 (59.9-89.6)	74.1 (58.6-90.0)	75.6 (62.3-90.8)			
Pre-bx highest BEC cells/μL	N = 2238	N = 774	N = 1306	N = 158	<.001	<.001	.903
Mean (SD)	599.0 (560.5)	469.0 (471.0)	692.4 (609.3)	464.2 (351.7)			
Median (Q1-Q3)	460 (230-788)	300 (200-600)	530 (300-890)	395 (200-645)			
Pre-bx latest blood IgE, IU/mL	N = 2135	N = 857	N = 1140	N = 138	.010	.027	.233
Mean (SD)	413.2 (660.1)	448.0 (561.0)	374.3 (679.2)	517.6 (976.8)			
Median (Q1-Q3)	183 (72-486)	248 (113-576)	143 (50-384)	120 (32-484)			
Pre-bx latest FeNO, ppb	N = 1508	N = 412	N = 972	N = 124	<.001	<.001	.895
Mean (SD)	50.0 (47.1)	40.5 (42.4)	55.3 (49.6)	39.9 (34.5)			
Median (Q1-Q3)	34 (18-65)	26 (14-49)	39 (21-73)	28 (16-53)			
History of allergic rhinitis	N = 2683	N = 990	N = 1487	N = 206	<.001	.199	<.001
Yes, n (%)	1205 (44.9)	559 (56.5)	559 (37.6)	87 (42.2)			
History of CRS	N = 2627	N = 962	N = 1463	N = 202	<.001	.262	.016
Yes, n (%)	1363 (51.9)	420 (43.7)	836 (57.1)	107 (53.0)			
History of nasal polyposis	N = 2763	N = 999	N = 1558	N = 206	<.001	.443	<.001
Yes, n (%)	807 (29.2)	191 (19.1)	549 (35.2)	67 (32.5)			
History of eczema/AD	N = 2759	N = 999	N = 1554	N = 206	.075	<.001	.011
Yes, n (%)	297 (10.8)	115 (11.5)	145 (9.3)	37 (18.0)			
Eosinophilic gradient[25]	N = 2692	N = 661	N = 1889	N = 142	<.001	<.001	.025
Grade 0, n (%)	5 (0.2)	5 (0.8)	0 (0.0)	0 (0.0)			
Grade 1, n (%)	60 (2.2)	52 (7.9)	0 (0.0)	8 (5.6)			
Grade 2, n (%)	117 (4.3)	103 (15.6)	0 (0.0)	14 (9.9)			
Grade 3, n (%)	2510 (93.2)	501 (75.8)	1889 (100.0)[c]	120 (84.5)			

Abbreviations: AD, atopic dermatitis; ACT, Asthma Control Test; BEC, blood eosinophil count; BMI, body mass index; bx, biologic; CRS, chronic rhinosinusitis; FeNO, fractional exhaled nitric oxide; FEV$_1$, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; LTOCS, long-term oral corticosteroid; ppFEV1, percent-predicted forced expiratory volume in 1 second.
NOTE. Grade 0: unlikely/non-eosinophilic; Grade 1: least likely; Grade 2: likely; and Grade 3: most likely.
[a]Wilcoxon rank sum test for continuous variables; χ^2 test for categorical variables.
[b]Assessed by GINA criteria,[3] ACT,[22] or ACT.[21]
[c]All patients initiating anti–IL-5/5R are categorized as grade 3.[25]

measures otherwise, while ensuring that pre- and post-biologic measures were both either pre- or post-bronchodilator. In the subpopulation of patients included in the lung function analysis (N = 1728), post-bronchodilator measurements were used for 54.2% of the patients. Moreover, $PpFEV_1$ was calculated using Quanjer's summary equations of reference ventilatory flow values.[23]

Because response to biologic therapy is dependent on level of pre-biologic impairment, domain values were categorized pre- and post-biologic treatment, based on pre-biologic distributions for each asthma outcome assessed. The scale of pre- to post-biologic change was also categorized as "improved," "unchanged," or "worsened" (Table 1). Those who improved were termed "responders" and those who worsened were termed "nonresponders." This approach permitted stratification of the pre- to post-biologic change according to degree of pre-biologic impairment and a clear visualization of both sides of any transition.

Statistical Analyses

The statistical analysis plan was predefined. R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) was used to conduct all statistical analyses.[24] All outcomes were summarized descriptively. The eosinophil phenotype gradient algorithm, previously published by Heaney et al,[24] was used to categorize patients along a continuum of eosinophil involvement from grade 1 (least likely eosinophilic) to grade 3 (most likely eosinophilic) (eFig 1).[25] Pre- and post-biologic results were presented as distributions for each asthma outcome domain, transitions of pre- to post-biologic change by pre-biologic impairment using river plots and scale of any change described in tabular format, overall and by biologic class.

Results

Patients

As of January 25, 2023, 14,284 patients were enrolled in ISAR. A total of 6816 had initiated biologics, of whom 3409 met all inclusion criteria and had pre- and post-biologic data for at least 1 domain (Fig 2). The median post-biologic follow-up durations ranged from 47.1 to 52.1 weeks, depending on the domain and biologic class (eTable 1).

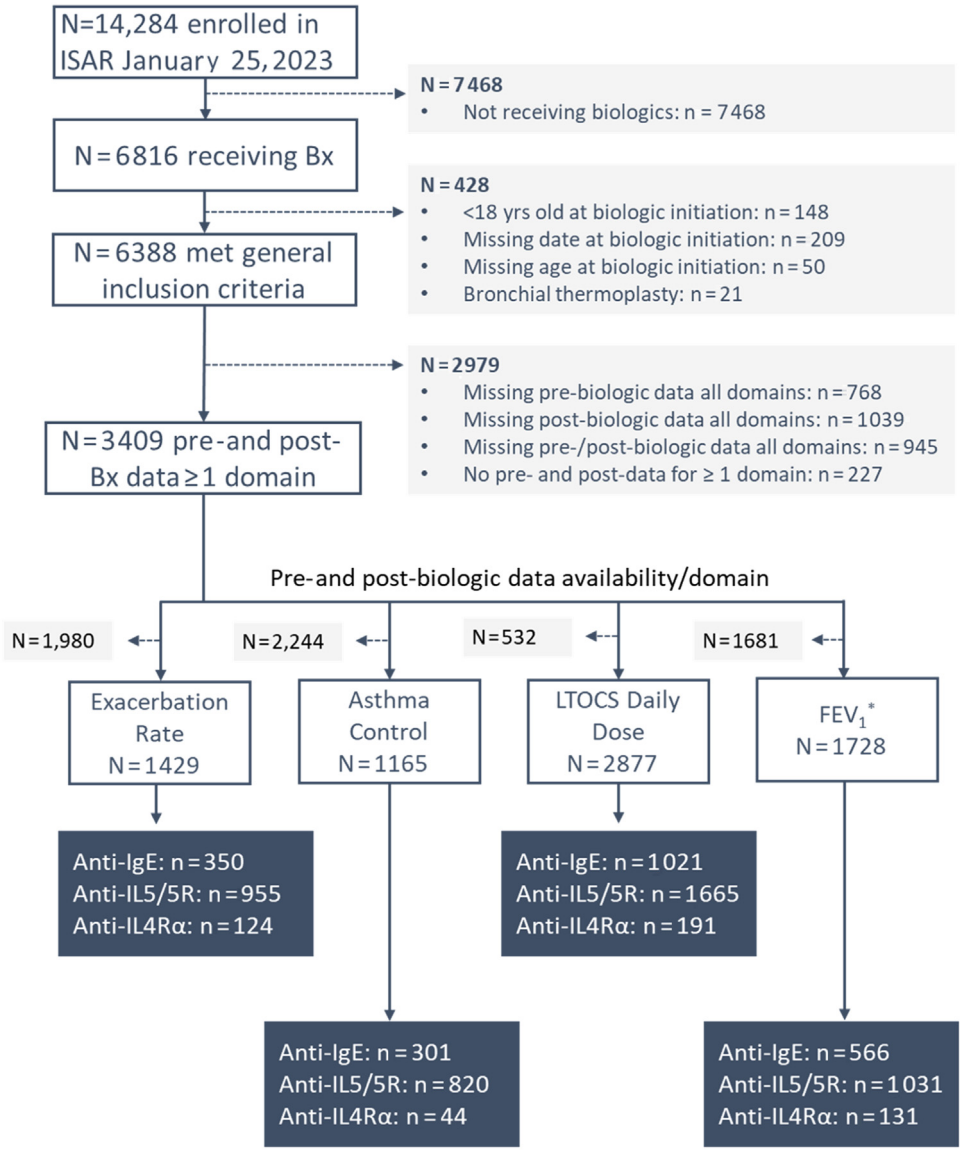


Figure 2. Subject disposition. Asterisk denotes both percent predicted and absolute. Bx, biologic; FEV_1, forced expiratory volume in 1 second; ISAR, International Severe Asthma Registry; LTOCS, long-term oral corticosteroid.

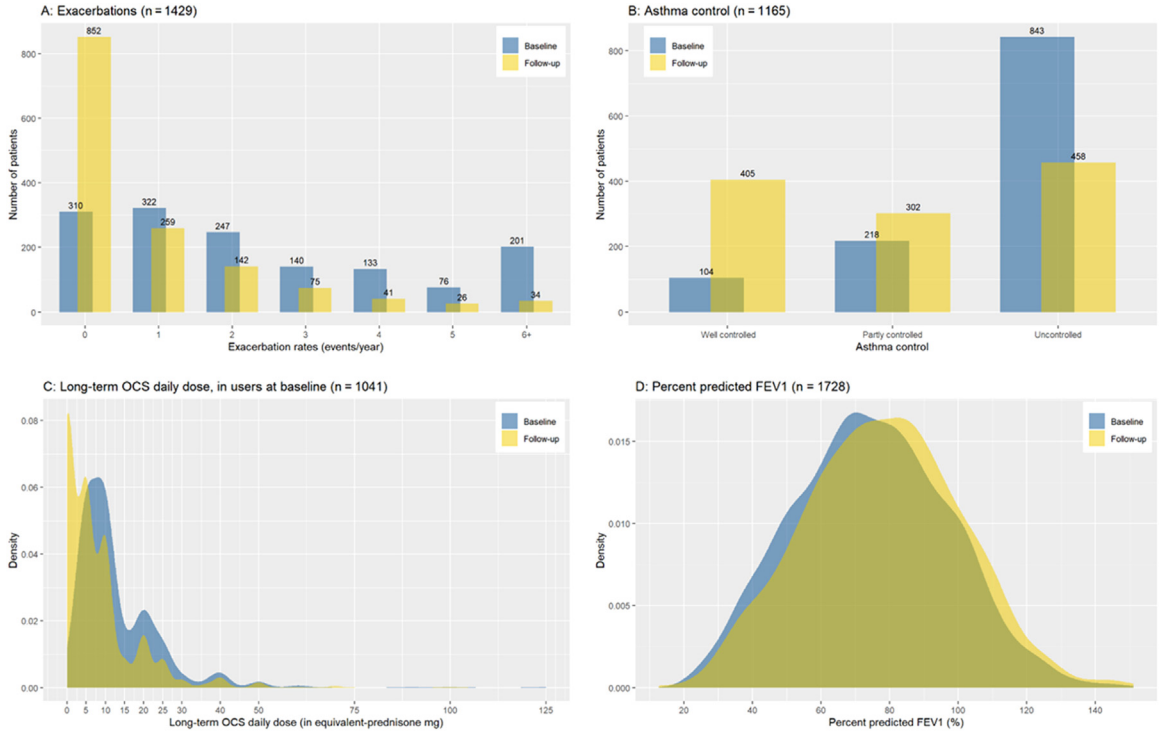


Figure 3. Distribution of asthma outcome domains pre- and approximately 1-year post-biologic therapy in adults with severe asthma. LTOCS distribution is restricted to users with available dose pre-biologic and who also have dose available at follow-up. See Table 1 for outcome definitions. *P* values for pre- and post-biologic distribution comparisons: (A) <.001 (McNemar nominal symmetry test); (B) <.001 (McNemar nominal symmetry test); (C) <.001 (Wilcoxon signed rank test); (D) <.001 (paired *t* test). FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroid.

Pre-Biologic Clinical Characteristics

Before biologic initiation, patients had experienced 3.0 exacerbations per year on average, and 72.6% (n = 1283 of 1767) of them had uncontrolled disease (Table 3). Overall, 38.3% (n = 1145 of 2991) of the patients had received LTOCS at a mean daily dose of 13.0 (SD, 11.0) mg, and the mean $ppFEV_1$ was 74.8%. Median levels of BEC, IgE, and FeNO were elevated at 460 (IQR, 230–788) cells/μL, 183 (72–486) IU/mL, and 34 (18–65) ppb, respectively (Table 3). More than 90% of the patients had an eosinophilic phenotype (eFig 1).[25] Those patients first treated with anti–IL-4Rα (predominantly from the United States) had less severe disease pre-biologic based on exacerbation rates, asthma control, and LTOCS use, and those first treated with anti–IL-5/5R had the most severe disease pre-biologic with regard to exacerbation rates and LTOCS (Table 3). Patients receiving anti–IL-5/5R therapies were also older than other patients, had later asthma onset, and had higher BEC and FeNO levels. Median IgE levels tended to be higher in the anti-IgE group, and these patients also tended to have a higher prevalence of allergic rhinitis and lower prevalence of chronic rhinosinusitis and nasal polyposis compared with those of patients receiving the other biologic classes.

Distribution of Clinical and Functional End Points Pre- and Post-Biologic Treatment

Statistically significant improvements were observed from pre- to post-biologic treatment for all asthma outcome domains assessed (Fig 3): 55.8% (n = 797 of 1429) of patients experienced more than or equal to 2 exacerbations per year pre-biologic compared with 22.3% (n = 318 of 1429) post-biologic (Fig 3A); 72.4% (n = 843 of 1165) of patients had uncontrolled asthma pre-biologic compared with 39.3% (n = 458 of 1165) post-biologic (Fig 3B); 30.7% (n = 320 of 1041) of LTOCS users pre-biologic no longer used LTOCS post-biologic (Fig 3C); and 40.4% (n = 698 of 1728) of patients had $ppFEV_1$ more than or equal to 80% pre-biologic compared with 46.8% (n = 809 of 1728) post-biologic (Fig 3D). A similar pattern was noted for each outcome domain by biologic class (eFig 2A-D). For lung function, the average improvement seemed to be greater in patients initiating anti–IL-5/5R or anti–IL-4Rα (+4.3 and +4.6 $ppFEV_1$, respectively) compared with that of patients who initiated anti-IgE (+1.7 $ppFEV_1$) (eFig 2D). Results were similar when restricting the study population to patients with available post-bronchodilator measures (eFig 3A and B).

Pre- to Post-Biologic Transitions Stratified by Pre-Biologic Impairment

Biologics Overall

Overall, the percentage of patients classified as responders to biologic therapy (classified as those with a category improvement pre- to post-biologic therapy) varied by outcome domain and increased with greater pre-biologic impairment, ranging from 70.2% to 90.0% for exacerbation rate (eFig 4A), 46.3% to 52.3% for asthma control (eFig 4B), 31.1% to 58.5% for LTOCS daily dose (eFig 4C), and 35.8% to 50.6% for $ppFEV_1$, depending on pre-biologic impairment in each outcome domain (eFig 4D; eTable 2). Looking at transitions in terms of absolute FEV_1, 28.4% of patients with a more than or equal to 80% $ppFEV_1$ pre-biologic had an FEV_1 improvement of 100 mL or greater (5.3% improved by 500+ mL) (eFig 4E). In contrast, a small proportion of patients had a worsening in each outcome domain (ie, nonresponders who moved to a poorer outcome category post-biologic), predominantly those with less pre-biologic impairment, ranging from 2.0% to 23.5% for exacerbation rate, 22.9% to 33.7% for asthma control, 1.7% to 6.1% for LTOCS daily dose, and 11.4% to 20.1% for $ppFEV_1$ (eFig 4A-D; eTable 2). Of the patients who experienced a worsening of exacerbation rate post-biologic, 26.6% had reduced their LTOCS daily dose. Outcome domains remained unchanged pre- to post-biologic for the remainder of patients, with the highest proportions noted in those with no impairment pre-biologic and the

lowest proportions noted in those with most severe pre-biologic impairment. For example, 76.5% (n = 237 of 310) of the patients with 0 exacerbations pre-biologic remained exacerbation free post-biologic; however, only 10.0% (n = 20 of 201) of the patients who experienced 6+ exacerbations pre-biologic also experienced 6+ exacerbations post-biologic (eFig 4A; eTable 2). The proportions with unchanged asthma outcome status post-biologic diminished with increasing pre-biologic impairment for the other outcome domains, ranging from 66.3% to 47.7% for asthma control (eFig 4B), 97.1% to 41.5% for LTOCS daily dose (eFig 4C), and 83.2% to 53.8% for ppFEV$_1$ (eFig 4D).

By Biologic Class

Pre- to post-biologic transitions were next evaluated by biologic class because patients in the anti–IL-5/5R therapy group had greater pre-biologic impairment. The proportion of patients having improvement post-biologic tended to be greater for those treated with anti–IL-5/R therapy compared with that of those treated with anti-IgE therapy for the exacerbation, asthma control, and ppFEV$_1$ outcome domains, irrespective of pre-biologic domain category (Fig 4A-D; eTable 2). The proportion of patients who experienced improvement seemed to be greater in the anti–IL-4Rα therapy group compared with in the other biologic classes; however, patient numbers were small by pre-biologic impairment stratification (Table 3).

Focusing on those patients with the greatest pre-biologic impairment for each outcome domain, the proportion of patients who had improvement in the anti-IgE, anti–IL-5/5R, and anti–IL-4Rα therapy groups, respectively, were 85.7% (n = 30 of 35), 90.9% (n = 149 of 164), and 100.0% (n = 2 of 2; with both patients treated with anti–IL-4Rα therapy moving from 6+ to 2-5 exacerbations/y) for exacerbations (Fig 4A); 50.7% (n = 106 of 209), 52.4% (n = 319 of 609), and 64.0% (n = 16 of 25) for asthma control (Fig 4B); 61.9% (n = 13 of 21) and 56.3% (n = 18 of 32) (no patients with anti–IL-4Rα were treated with >30 mg/d pre-biologic) for LTOCS dose (Fig 4C); and 42.5% (n = 31 of 73), 47.1% (n = 81 of 172), and 53.3% (n = 8 of 15) for ppFEV$_1$ (Fig 4D). A trend in favor of anti–IL-5/5R therapy over anti-IgE therapy was apparent for patients at the lower end of the severity spectrum pre-biologic for the exacerbation and asthma control domains. For example, for those patients with 1 exacerbation per year pre-biologic, exacerbations were eliminated post-biologic for 72.6% (n = 135 of 186) of patients treated with an anti–IL-5/5R therapy compared with 59.6% (n = 53 of 89) of patients treated with anti-IgE therapy (Fig 4A). Similarly, in terms of asthma symptoms, for those with partly controlled asthma pre-biologic, a transition to well-controlled disease was achieved by 49.7% (n = 75 of 151) and 36.8% (n = 21 of 57) of the patients treated with anti–IL-5/5R therapy and anti-IgE therapy, respectively (Fig 4B). All pre- to post-biologic outcome domain transitions by biologic class are available in the online supplement (eTable 2A-,D;eFig 5).

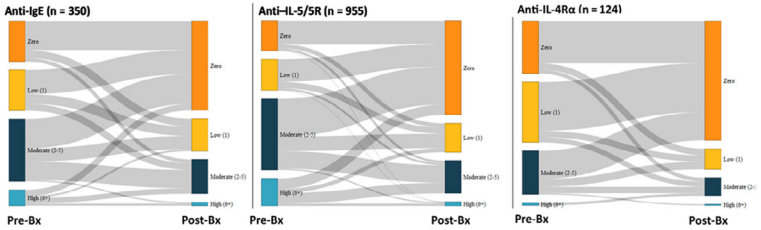
Discussion

Assessing response to biologic therapy is not an exact science, considering that various outcomes of response do not always evolve in the same direction, post-biologic effect is dependent on numerous pre-biologic factors, and response itself remains difficult to predict.[26,27] We found that pre- to post-biologic effect varied according to asthma outcome assessed and the degree of pre-biologic impairment; those with greater disease burden pre-biologic therapy tended to have a greater magnitude of effect for each domain assessed. A spectrum of responders and nonresponders within each domain relative to pre-biologic impairment was also identified; this was necessary to inform future work on response and predictors of response and remission. Moreover, we found that even those with low pre-biologic impairment, who would be actively excluded from RCTs investigating the efficacy of biologics, exhibited clinically meaningful post-biologic improvement, which was particularly marked for lung function. Our results provide realistic outcome-specific post-biologic expectations for both physicians and patients, will be foundational to inform future work on a multidimensional approach to define and assess biologics responders and response, and may enhance appropriate patient selection for biologic therapies. Work remains, even within large databases such as ISAR, to ensure all patients with severe asthma have sufficient pre- and post-biologic data recorded in each of the 4 outcome domains necessary to assess response, to encourage lung function assessment as an important determinant to assess response, and to instigate quality improvements to standardize data collection using responder threshold set.

To arrive at a universal definition of response, we contended that it is first necessary to know how different individual outcomes change with biologic therapy, before creating a composite measure of response, what is the range of potential improvement and non-improvement in these outcomes, and what is the scale of any improvement post-treatment, relative to pre-biologic status. Indeed, an expert consensus roadmap for severe eosinophilic asthma has also stressed the importance of conducting a “careful characterization of the symptom profile to have objective measures to follow when response is evaluated.”[1] Our methodologic approach to the response question was, therefore, different from that of previous work in this area.[4] We mapped pre- to post-biologic transitions, in each of 4 key asthma outcome domains frequently used in every day clinical practice, and applied this approach across a large and heterogeneous severe asthma population with a wide range of pre-biologic impairment in each domain assessed. This approach permitted an assessment of scale of change in terms of category change per outcome rather than according to predefined cutoffs. Inclusion of such a broad population such as that contained within ISAR therefore facilitated characterization of a spectrum of responders, permitted a more granular assessment of responder pathways across multiple domains and starting points, and allowed us to evaluate the extent and magnitude of improvement rather than define proportions of responders according to predefined cutoffs.

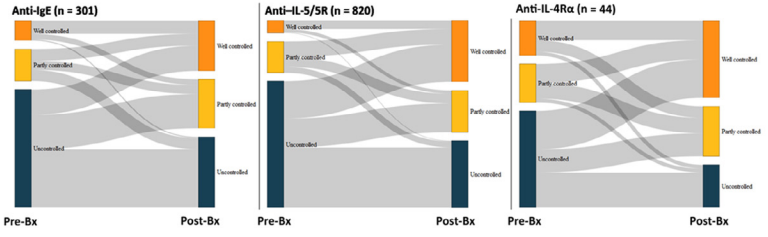
In common with other real-life studies, we found that both outcome domain type and pre-biologic status influenced change in outcomes post-biologic.[10,28-31] The outcome domain associated with pre- to post-biologic improvement in most patients was exacerbation rate (up to 90% of those with 6+ exacerbations in the year pre-biologic improved post-biologic). This domain has previously been weighted most heavily by expert consensus during recent development of the FEV$_1$, exacerbations, OCS, and symptoms score response evaluation tool.[6] The exacerbation responder rate noted in our study was perhaps unsurprising because it is an inclusion criterion for biologic efficacy and effectiveness studies and a prerequisite for biologic prescription in most countries.[32] However, what was surprising was the high responder rate (70.3%) noted even for those patients who experienced 1 exacerbation in the previous year—food for thought when considering the degree of pre-biologic impairment needed to trigger biologic use. Some differential effects on exacerbation responder rate were noted by biologic class, with a trend of more patients treated with an anti–IL-5/5R therapy improving in the exacerbation domain than patients treated with anti-IgE therapy, irrespective of the degree of pre-biologic impairment. This is in agreement with previous research from ISAR in patients eligible for both biologic classes, in which treatment with anti–IL-5/5R therapy reduced the mean number of exacerbations in the previous 12 months by 47.1% compared with 38.7% for anti-IgE therapy.[33] The responder rates for patients treated with anti–IL-4Rα therapy for the exacerbation domain seemed higher than for patients treated with an anti–IL-5/5R therapy, but should be interpreted with caution because of small sample size and the fact that the patients with anti–IL-4Rα had less severe asthma at baseline.

A



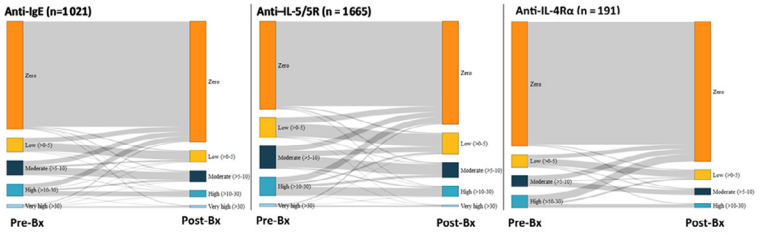
Exacerbation rate pre-bx	Post-biologic status, % of patients								
	Anti-IgE			Anti–IL-5/5R			Anti–IL-4Rα		
	Worsened	Unchanged	Improved	Worsened	Unchanged	Improved	Worsened	Unchanged	Improved
Zero 0/yr	28.1% (25/89)	71.9% (64/89)	NA	22.2% (40/180)	77.8% (140/180)	NA	19.5% (8/41)	80.5% (33/41)	NA
Low 1/yr	16.9% (15/89)	23.6% (21/89)	59.6% (53/89)	7.5% (14/186)	19.9% (37/186)	72.6% (135/186)	8.5% (4/47)	10.6% (5/47)	80.9% (38/47)
Moderate 2-5/yr	2.2% (3/137)	29.2% (40/137)	68.6% (94/137)	1.9% (8/425)	24.7% (105/425)	73.4% (312/425)	2.9% (1/34)	14.7% (5/34)	82.4% (28/34)
High 6+/yr	NA	14.3% (5/35)	85.7% (30/35)	NA	9.1% (15/164)	90.9% (149/164)	NA	0% (0/2)	100.0% (2/2)
All	13.7% (43/315)	37.1% (130/350)	67.8% (177/261)	7.8% (62/791)	31.1% (297/955)	76.9% (596/775)	10.7% (13/122)	34.7% (43/124)	81.9% (68/83)

B



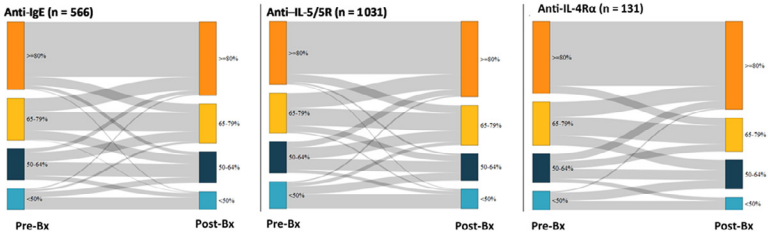
Asthma control* Pre-bx	Post-biologic status, % of patients								
	Anti-IgE			Anti–IL-5/5R			Anti–IL-4Rα		
	Worsened	Unchanged	Improved	Worsened	Unchanged	Improved	Worsened	Unchanged	Improved
Well	34.3% (12/35)	65.7% (23/35)	NA	31.7% (19/60)	68.3% (41/60)	NA	44.4% (4/9)	55.6% (5/9)	NA
Partly	35.1% (20/57)	28.1% (16/57)	36.8% (21/57)	19.2% (29/151)	31.1% (47/151)	49.7% (75/151)	10.0% (1/10)	40.0% (4/10)	50.0% (5/10)
Uncontrolled	NA	49.3% (103/209)	50.7% (106/209)	NA	47.6% (290/609)	52.4% (319/609)	NA	36.0% (9/25)	64.0% (16/25)
All	34.8% (32/92)	47.2% (142/301)	47.7% (127/266)	22.7% (48/211)	46.1% (378/820)	51.8% (394/790)	26.3% (5/19)	40.9% (18/44)	60.0% (21/35)

C



LTOCS daily dose (mg) pre-Bx	Post-biologic status, % of patients								
	Anti-IgE			Anti–IL-5/5R			Anti–IL-4Rα		
	Worsened	Unchanged	Improved	Worsened	Unchanged	Improved	Worsened	Unchanged	Improved
Zero 0 mg	2.6% (19/724)	97.4% (705/724)	NA	3.3% (32/964)	96.7% (932/964)	NA	1.4% (2/148)	98.6% (146/148)	NA
Low >0-5 mg	6.2% (6/96)	59.4% (57/96)	34.4% (33/96)	5.5% (12/217)	65.0% (141/217)	29.5% (64/217)	13.3% (2/15)	53.3% (8/15)	33.3% (5/15)
Moderate >5-10 mg	4.0% (4/99)	51.5% (51/99)	44.4% (44/99)	6.0% (125/248)	47.6% (118/248)	46.4% (115/248)	0% (0/13)	46.2% (6/13)	53.8% (7/13)
High >10-30 mg	2.5% (2/81)	39.5% (32/81)	55.6% (45/81)	1.5% (3/204)	44.6% (91/204)	53.9% (110/204)	0% (0/15)	26.7% (4/15)	73.3% (11/15)
Very high >30 mg	NA	38.1% (8/21)	61.9% (13/21)	NA	43.8% (14/32)	56.3% (18/32)	NA	- (0/0)	- (0/0)
All	3.1% (31/1000)	83.6% (853/1021)	45.5% (135/297)	3.8% (62/1633)	77.8% (1296/1665)	43.8% (307/701)	2.1% (4/191)	85.9% (164/191)	53.5% (23/43)

D



ppFEV$_1$ pre-bx	Post-biologic status, % of patients								
	Anti-IgE			Anti–IL-5/5R			Anti–IL-4Rα		
	Worsened	Unchanged	Improved	Worsened	Unchanged	Improved	Worsened	Unchanged	Improved
≥80%	19.0% (45/237)	81.0% (192/237)	NA	16.4% (66/403)	83.6% (337/403)	NA	10.3% (6/58)	89.7% (52/58)	NA
65-79%	22.1% (33/147)	44.9% (66/147)	32.7% (48/147)	18.4% (47/256)	43.8% (112/256)	37.9% (97/256)	22.9% (8/35)	42.9% (15/35)	34.3% (12/35)
50-64%	13.8% (15/109)	43.1% (47/109)	43.1% (47/109)	10.0% (20/200)	35.5% (71/200)	54.5% (109/200)	13.0% (3/23)	34.8% (8/23)	52.2% (12/23)
<50%	NA	57.5% (42/73)	42.5% (31/73)	NA	52.9% (91/172)	47.1% (81/172)	NA	46.7% (7/15)	53.30% (8/15)
All	18.9% (93/493)	61.3% (347/566)	38.3% (126/329)	15.5% (133/859)	59.3% (611/1031)	45.7% (287/628)	14.7% (17/116)	62.6% (82/131)	43.8% (32/73)

Figure 4. Proportion of patients transitioning from pre- (left) to approximately 1-year post-biologic (right) along a categorical gradient for each asthma outcome domain by biologic class. (A) exacerbation rate per year; (B) asthma control status (Asterisk denotes assessed using GINA criteria,[3] Asthma Control Test,[21] or Asthma Control Questionnaire.[22]); (C) LTOCS (mg); (D) ppFEV$_1$. See Table 2 for domain definitions and timing of assessments and eTable 2 for % patients and (N) numbers for each transition. Improved, moved to lower (better) category post-biologic; unchanged, remained at the same category post-biologic; worsened, moved to higher (poorer) category post-biologic (Table 1). Bx, biologic; GINA, Global Initiative for Asthma; LTOCS, long-term oral corticosteroid daily dose; NA, not applicable; ppFEV$_1$, percent-predicted forced expiratory volume in 1 second.

Overall, asthma control had the narrowest responder rate range (47.0%–52.2%) in our study and was relatively independent of pre-biologic status, probably because it has the fewest change options, and it may be influenced by other factors, such as comorbidities. Moreover, LTOCS daily dose exhibited a slightly different pre- to post-biologic transition pattern, revealing a myriad of transitions across the low, moderate, high, and very high categories, which may reflect the influence of patient and physician behavior and effectiveness of treatment.[34-36] Notably, much of the post-biologic year in the current study was before the study period of a previous study (PONENTE), which revealed that LTOCS could be more aggressively tapered.[37] Finally, ppFEV$_1$ was the outcome domain associated with pre- to post-biologic improvement in the smallest proportion of patients (36.1%-46.6% for all biologics combined). However, similar to the exacerbation rate domain, patients with relatively little or no impairment in lung function pre-biologic had post-biologic improvement in this domain; 28.8% of patients with ppFEV$_1$ more than or equal to 80% pre-biologic had a post-biologic improvement of 100+ mL, suggesting the benefit of biologic treatment before lung function becomes impaired. In common with the asthma control domain, the ppFEV$_1$ outcome domain was relatively independent of pre-biologic status and had considerable gradation within it comparable to the LTOCS domain; however, the ppFEV$_1$ domain was sensitive to change. Recent research has found that some patients take objective lung function measures into account to better understand their treatment response, valuing the ability to compare pre- and post-biologic values.[9] Taken together, these characteristics indicate that ppFEV$_1$ may be particularly sensitive to assessing response and should be considered in a composite definition.

In common with other studies,[2,12,14] a minority of patients worsened post-biologic (compared with pre-biologic status) and were considered nonresponders, with the nonresponder rate generally decreasing with increasing pre-biologic impairment. Currently, only the Global Evaluation of Treatment Effectiveness tool has defined nonresponse,[38] whereas the FEV$_1$, exacerbations, OCS, and symptoms score response evaluation tool has no established cutoff for nonresponders.[6] We found that the nonresponder rate was extremely low for the exacerbation and LTOCS domains and was similar across biologic classes, mirroring the corticosteroid-sparing and exacerbation-reduction properties of biologics in real-life studies.[39] The nonresponder rate was also relatively independent of pre-biologic status for the LTOCS domain, tending to be the highest in those treated with 0 to less than 5 mg pre-biologic. Reasons for nonresponse in asthma outcome domain post-biologic treatment are multifactorial, including differences in mechanism of action, biologic doses, and dose intervals, heterogeneity of asthma phenotype, influence of comorbidities (eg, presence of nasal polyps), and other factors such as age, obesity, and smoking history.[4,27] Although there is currently no definitive explanation for this variation in response, Hyland et al[27] have recently postulated an adaptive network theory to help explain it, moving away from a linear causal sequence of an anti-inflammatory pathway toward a model in which the target molecule is part of a causal network of other inflammatory markers that have reciprocal causal relations, together determining the response of target molecules to biologics.

In addition to responders and nonresponders, our study also predefined an “unchanged” category, representing those patients for whom asthma outcomes remained unchanged pre- to post-biologic. Whether this is an appropriate categorization remains open to debate. Perhaps those with “unchanged” status may be better categorized as “responders” or as “nonresponders” depending on the degree of pre-biologic impairment. For example, patients who experienced 0 exacerbations per year pre-biologic and who were also exacerbation free post-biologic (particularly in an environment of concomitant LTOCS withdrawal or dose reduction post-biologic) could be considered responders. However, patients whose exacerbation rate remains at 6+ per year, for example, should be considered as nonresponders. This issue requires further study and debate, highlights the complexity of defining response and nonresponse to biologic therapy in severe asthma, and suggests both the importance of patient perception on response and the need to use a patient-reported outcome measure when defining response.

Limitations of our study included those common to real-world studies, including recall bias and missing data. Our study population included a relatively small number of patients treated with anti–IL-4Rα therapy, and these patients tended to have a lower degree of pre-biologic impairment. In addition, the large proportions of responders observed in the most impaired categories may have been due to not only biologic effect but also a consequence of regression to the mean. Furthermore, previous ISAR research in a matched patient cohort has revealed that although continued high OCS exposure or switch to biologics was both associated with improvement in severe asthma outcomes, patients who switched to biologics experienced even greater improvements than those of patients who continued with long-term or frequent rescue OCS.[40] Inclusion of a patient-reported outcome domain would also have been useful to explore the concept of response from the patient perspective, and use of an alternative exacerbation domain (eg, CompEx)[41] warrants future study. Finally, further research on lung function improvement might benefit from applying the more recent spirometric prediction equations.[42]

Strengths of this study included inclusion of a large, real-life, and heterogeneous severe asthma population receiving biologic therapy with sufficient depth and granularity to assess pre- to post-biologic transitions for multiple domains along a wide range of pre-biologic impairment, overall and by biologic class. Categorization of post-biologic outcomes was not chosen arbitrarily, but informed by analysis of pre-biologic distributions for each asthma outcome domain and each biologic class. Further research to explore multidomain definitions of response and remission and understand factors that predict them is ongoing.

In conclusion, our findings have identified a spectrum of responders to biologic therapy by asthma outcome domain and pre-biologic impairment, mapped how responders transition to post-biologic improvement, and provided information on the likelihood and scale of post-biologic effect(s) in a real-life severe asthma cohort, including patients typically not enrolled in clinical trials or considered eligible for biologic therapy. Our study represents the first steps in generating a unified theory or algorithm of biologic response, providing valuable information about which asthma outcomes to include and cutoffs to use, bringing us one step closer to accurate response prediction.

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Supplementary Data

eTable 1
Post Biologic Follow-Up Duration for Each Domain

Domain	Total	Anti-IgE	Anti–IL-5/5R	Anti–IL-4Rα
Exacerbations (wk)	N = 1429	N = 350	N = 955	N = 124
Mean (SD)	53.0 (9.4)	53.2 (9.7)	53.4 (9.5)	49.0 (7.2)
Median (Q1-Q3)	52.1 (51.9-55.0)	52.1 (52.1-55.0)	52.1 (51.6-56.0)	52.1 (51.6-52.1)
Asthma control (wk)	N = 1165	N = 301	N = 820	N = 44
Mean (SD)	51.7 (11.8)	51.0 (12.4)	52.0 (11.5)	49.8 (13.9)
Median (Q1-Q3)	52.0 (45.9-58.1)	51.6 (44.0-58.1)	52.0 (47.0-58.0)	51.3 (35.1-57.8)
LTOCS (wk)	N = 2877	N = 1021	N = 1665	N = 191
Mean (SD)	50.4 (7.4)	50.7 (6.2)	50.4 (8.1)	48.4 (7.3)
Median (Q1-Q3)	52.1 (52.1-52.1)	52.1 (52.1-52.1)	52.1 (52.1-52.1)	52.1 (48.0-52.3)
% Predicted FEV_1 (wk)	N = 1728	N = 566	N = 1031	N = 131
Mean (SD)	51.2 (12.0)	51.2 (11.8)	51.5 (11.8)	48.8 (14.4)
Median (Q1-Q3)	51.9 (44.3-58.4)	51.7 (44.0-58.8)	52.0 (45.4-58.0)	47.1 (37.1-58.9)

Abbreviations: FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroid; Q1-Q3, inter- (first to third) quartile range.

eTable 2A
Distribution of Post-Biologic Exacerbation Rate Categories by Pre-Biologic Exacerbation Rate Categories, Overall and by Biologic Classes

Post-biologic annualized exacerbation rate/y	Zero	Low (1)	Moderate (2-5)	High (6+)	Total
		All biologics			
N	310	322	596	201	1429
Zero, n (%)	237 (76.45)	226 (70.19)	313 (52.52)	76 (37.81)	852 (59.62)
Low (1), n (%)	47 (15.16)	63 (19.57)	121 (20.30)	28 (13.93)	259 (18.12)
Moderate (2-5), n (%)	25 (8.06)	32 (9.94)	150 (25.17)	77 (38.31)	284 (19.87)
High (6+), n (%)	1 (0.32)	1 (0.31)	12 (2.01)	20 (9.95)	34 (2.38)
		Anti-IgE			
N	89	89	137	35	350
Zero, n (%)	64 (71.91)	53 (59.55)	65 (47.45)	14 (40.00)	196 (56.00)
Low (1), n (%)	17 (19.10)	21 (23.60)	29 (21.17)	4 (11.43)	71 (20.29)
Moderate (2-5), n (%)	8 (8.99)	15 (16.85)	40 (29.20)	12 (34.29)	75 (21.43)
High (6+), n (%)	0 (0.00)	0 (0.00%)	3 (2.19)	5 (14.29)	8 (2.29)
		Anti–IL-5/5R			
N	180	186	425	164	955
Zero, n (%)	140 (77.78)	135 (72.58)	226 (53.18)	62 (37.80)	563 (58.95)
Low (1), n (%)	25 (13.89)	37 (19.89)	86 (20.24)	24 (14.63)	172 (18.01)
Moderate (2-5), n (%)	14 (7.78)	13 (6.99)	105 (24.71)	63 (38.41)	195 (20.42)
High (6+), n (%)	1 (0.56)	1 (0.54)	8 (1.88)	15 (9.15)	25 (2.62)
		Anti–IL-4Rα			
N	41	47	34	2	124
Zero, n (%)	33 (80.49)	38 (80.85)	22 (64.71)	0 (0.00)	93 (75.00)
Low (1), n (%)	5 (12.20)	5 (10.64)	6 (17.65)	0 (0.00)	16 (12.90)
Moderate (2-5), n (%)	3 (7.32)	4 (8.51)	5 (14.71)	2 (100.00)	14 (11.29)
High (6+), n (%)	0 (0.00)	0 (0.00)	1 (2.94)	0 (0.00)	1 (0.81)

eTable 2B
Distribution of Post-Biologic Asthma Control[a] Categories by Pre-Biologic Asthma Control Categories, Overall and by Biologic Classes

Post-biologic asthma control	Well controlled	Partly controlled	Uncontrolled	Total
All biologics				
N	104	218	843	1165
Well controlled, n (%)	69 (66.35)	101 (46.33)	235 (27.88)	405 (34.76)
Partly controlled, n (%)	29 (27.88)	67 (30.73)	206 (24.44)	302 (25.92)
Uncontrolled, n (%)	6 (5.77)	50 (22.94)	402 (47.69)	458 (39.31)
Anti-IgE				
N	35	57	209	301
Well controlled, n (%)	23 (65.71)	21 (36.84)	45 (21.53)	89 (20.57)
Partly controlled, n (%)	10 (28.57)	16 (28.07)	61 (29.19)	87 (28.90)
Uncontrolled, n (%)	2 (5.71)	20 (35.09)	103 (49.28)	125 (41.53)
Anti–IL-5/5R				
N	60	151	609	820
Well controlled, n (%)	41 (68.33)	75 (49.67)	180 (29.56)	296 (36.10)
Partly controlled, n (%)	16 (26.67)	47 (31.13)	139 (22.82)	202 (24.63)
Uncontrolled, n (%)	3 (5.00)	29 (19.21)	290 (47.62)	322 (39.27)
Anti–IL-4Rα				
N	9	10	25	44
Well controlled, n (%)	5 (55.56)	5 (50.00)	10 (40.00)	20 (45.45)
Partly controlled, n (%)	3 (33.33)	4 (40.00)	6 (24.00)	13 (29.55)
Uncontrolled, n (%)	1 (11.11)	1 (10.00)	9 (36.00)	11 (25.00)

Abbreviation: GINA, Global Initiative for Asthma.
[a]Control assessed using GINA control criteria,[3] Asthma Control Test,[21] or Asthma Control Questionnaire.[22]

eTable 2C
Distribution of Post-Biologic LTOCS Daily Dose Categories by Pre-Biologic LTOCS Daily Dose Categories, Overall and by Biologic Classes

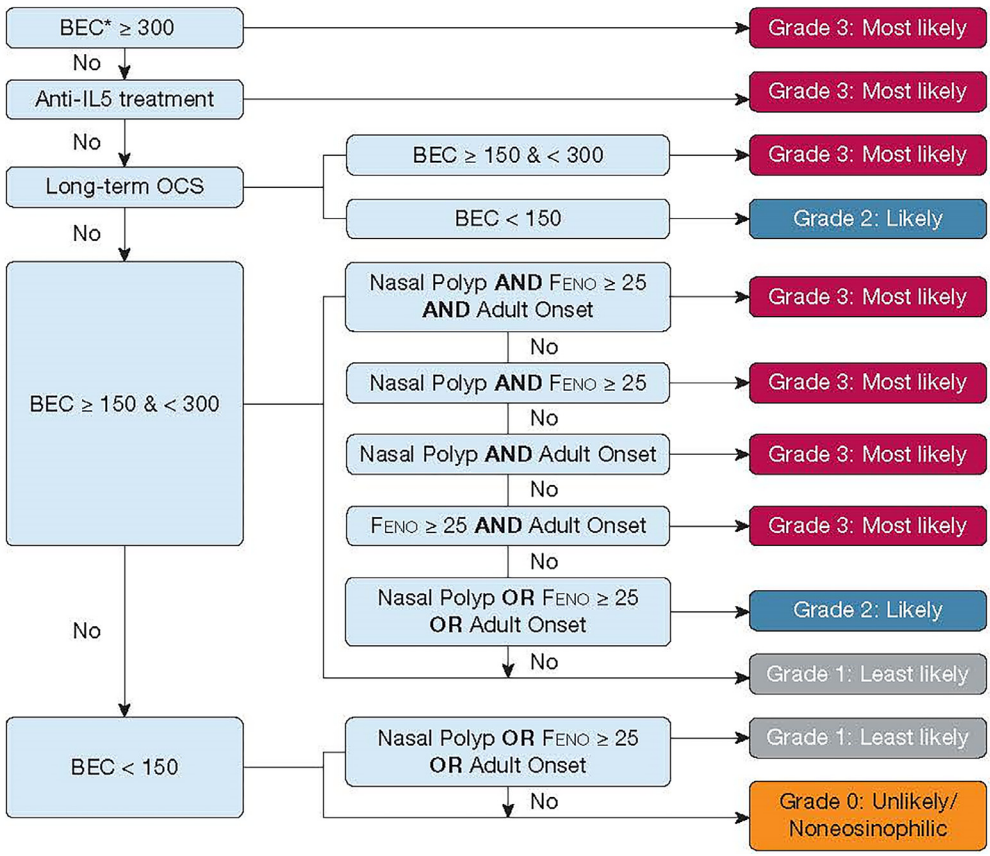
Post-biologic LTOCS daily dose (mg/d)	Zero	Low (>0-5)	Moderate (>5-10)	High (>10-30)	Very high (>30)	Total
All biologics						
N	1836	328	360	300	53	2877
Zero, n (%)	1783 (97.11)	102 (31.10)	94 (26.11)	106 (35.33)	18 (33.96)	2103 (73.10)
Low (>0-5), n (%)	20 (1.09)	206 (62.80)	72 (20.00)	25 (8.33)	3 (5.66)	326 (11.33)
Moderate (>5-10), n (%)	19 (1.03)	12 (3.66)	175 (48.61)	37 (12.33)	3 (5.66)	246 (8.55)
High (>10-30), n (%)	9 (0.49)	7 (2.13)	18 (5.00)	127 (42.33)	7 (13.21)	168 (5.84)
Very high (>30), n (%)	5 (0.27)	1 (0.30)	1 (0.28)	5 (1.67)	22 (41.51)	34 (1.18)
Anti-IgE						
N	724	96	99	81	21	1021
Zero, n (%)	705 (97.38)	33 (34.38)	32 (32.32)	32 (39.51)	6 (28.57)	808 (79.14)
Low (>0-5), n (%)	6 (0.83)	57 (59.38)	12 (12.12)	4 (4.94)	1 (4.76)	80 (7.84)
Moderate (>5-10), n (%)	6 (0.83)	3 (3.12)	51 (51.52)	11 (13.58)	3 (14.29)	74 (7.25)
High (>10-30), n (%)	2 (0.28)	3 (3.12)	4 (4.04)	32 (39.51)	3 (14.29)	44 (4.31)
Very high (>30), n (%)	5 (0.69)	0 (0.00)	0 (0.00)	2 (2.47)	8 (38.10)	15 (1.47)
Anti–IL-5/5R						
N	964	217	248	204	32	1665
Zero, n (%)	932 (96.68)	64 (29.49)	56 (22.58)	65 (31.86)	12 (37.50)	1129 (67.81)
Low (>0-5), n (%)	13 (1.35)	141 (64.98)	59 (23.79)	19 (9.31)	2 (6.25)	234 (14.05)
Moderate (>5-10), n (%)	12 (1.24)	8 (3.69)	118 (47.58)	26 (12.75)	0 (0.00)	164 (9.85)
High (>10-30), n (%)	7 (0.73)	3 (1.38)	14 (5.65)	91 (44.61)	4 (12.50)	119 (7.15)
Very high (>30), n (%)	0 (0.00)	1 (0.46)	1 (0.40)	3 (1.47)	14 (43.75)	19 (1.14)
Anti–IL-4Rα						
N	148	15	13	15	0	191
Zero, n (%)	146 (98.65)	5 (33.33)	6 (46.15)	9 (60.00)	0	166 (86.91)
Low (>0-5), n (%)	1 (0.68)	8 (53.33)	1 (7.69)	2 (13.33)	0	12 (6.28)
Moderate (>5-10), n (%)	1 (0.68)	1 (6.67)	6 (46.15)	0 (0.00)	0	8 (4.19)
High (>10-30), n (%)	0 (0.00)	1 (6.67)	0 (0.00)	4 (26.67)	0	5 (2.62)
Very high (>30), n (%)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0	0 (0.00)

Abbreviation: LTOCS, long-term oral corticosteroid.

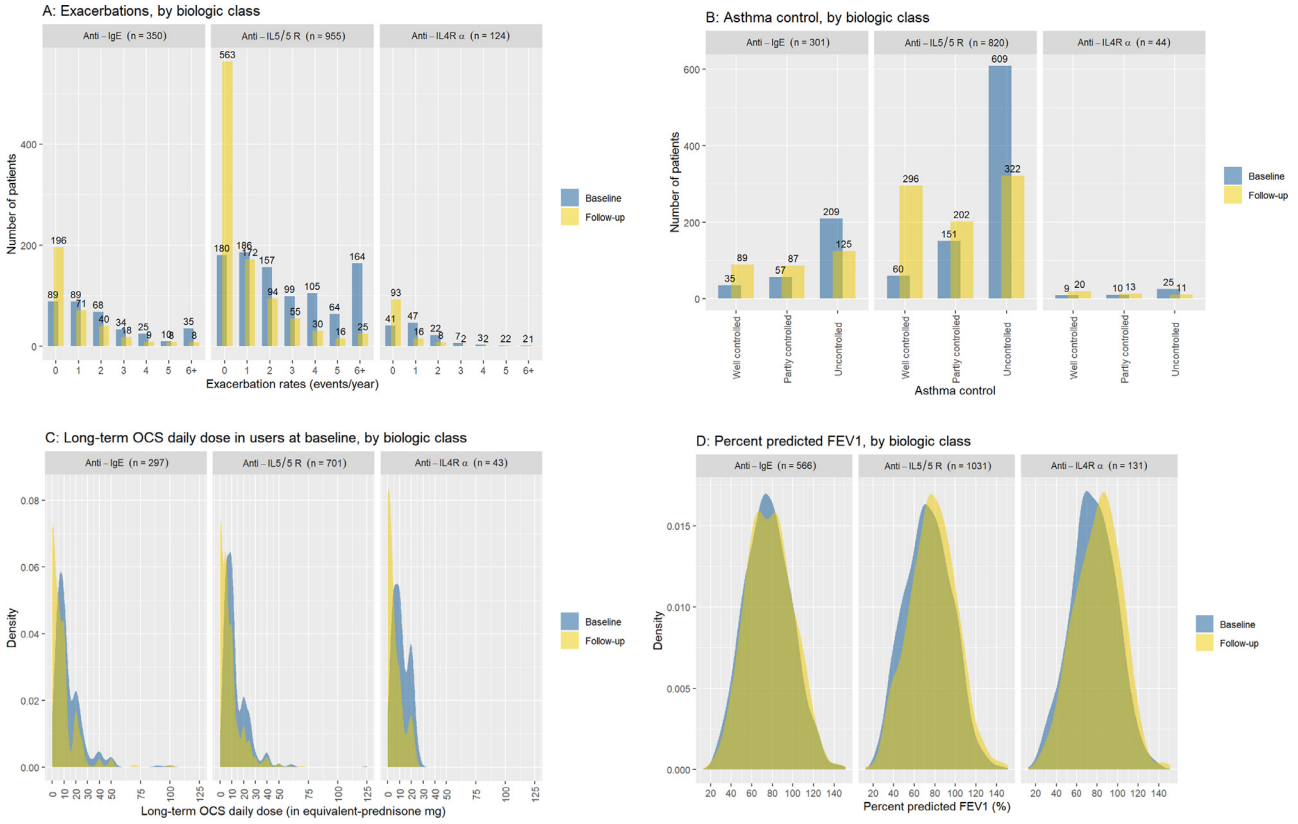
eTable 2D
Distribution of Post-Biologic ppFEV$_1$ Categories by Pre-Biologic ppFEV$_1$ Categories, Overall and by Biologic Classes

Post-biologic ppFEV$_1$	≥80%	65%-79%	50%-64%	<50%	Total
All biologics					
N	698	438	332	260	1728
≥80, n (%)	581 (83.24)	157 (35.84)	57 (17.17)	14 (5.38)	809 (46.82)
65-79, n (%)	88 (12.61)	193 (44.06)	111 (33.43)	28 (10.77)	420 (24.31)
50-64, n (%)	21 (3.01)	78 (17.81)	126 (37.95)	78 (30.00)	303 (17.53)
<50, n (%)	8 (1.15)	10 (2.28)	38 (11.45)	140 (53.85)	196 (11.34)
Anti-IgE					
N	237	147	109	73	566
≥80, n (%)	192 (81.01)	48 (32.65)	13 (11.93)	4 (5.48)	257 (45.41)
65-79, n (%)	31 (13.08)	66 (44.90)	34 (31.19)	7 (9.59)	138 (24.38)
50-64, n (%)	11 (4.64)	31 (21.09)	47 (43.12)	20 (27.40)	109 (19.26)
<50, n (%)	3 (1.27)	2 (1.36)	15 (13.76)	42 (57.53)	62 (10.95)
Anti–IL-5/5R					
N	403	256	200	172	1031
≥80, n (%)	337 (83.62)	97 (37.89)	38 (19.00)	9 (5.23)	481 (46.65)
65-79, n (%)	51 (12.66)	112 (43.75)	71 (35.50)	21 (12.21)	255 (24.73)
50-64, n (%)	10 (2.48)	39 (15.23)	71 (35.50)	51 (29.65)	171 (16.59)
<50, n (%)	5 (1.24)	8 (3.12)	20 (10.00)	91 (52.91)	124 (12.03)
Anti–IL-4Rα					
N	58	35	23	15	131
≥80, n (%)	52 (89.66)	12 (34.29)	6 (26.09)	1 (6.67)	71 (54.20)
65-79, n (%)	6 (10.34)	15 (42.86)	6 (26.09)	0 (0.00)	27 (20.61)
50-64, n (%)	0 (0.00)	8 (22.86)	8 (34.78)	7 (46.67)	23 (17.56)
<50, n (%)	0 (0.00)	0 (0.00)	3 (13.04)	7 (46.67)	10 (7.63)

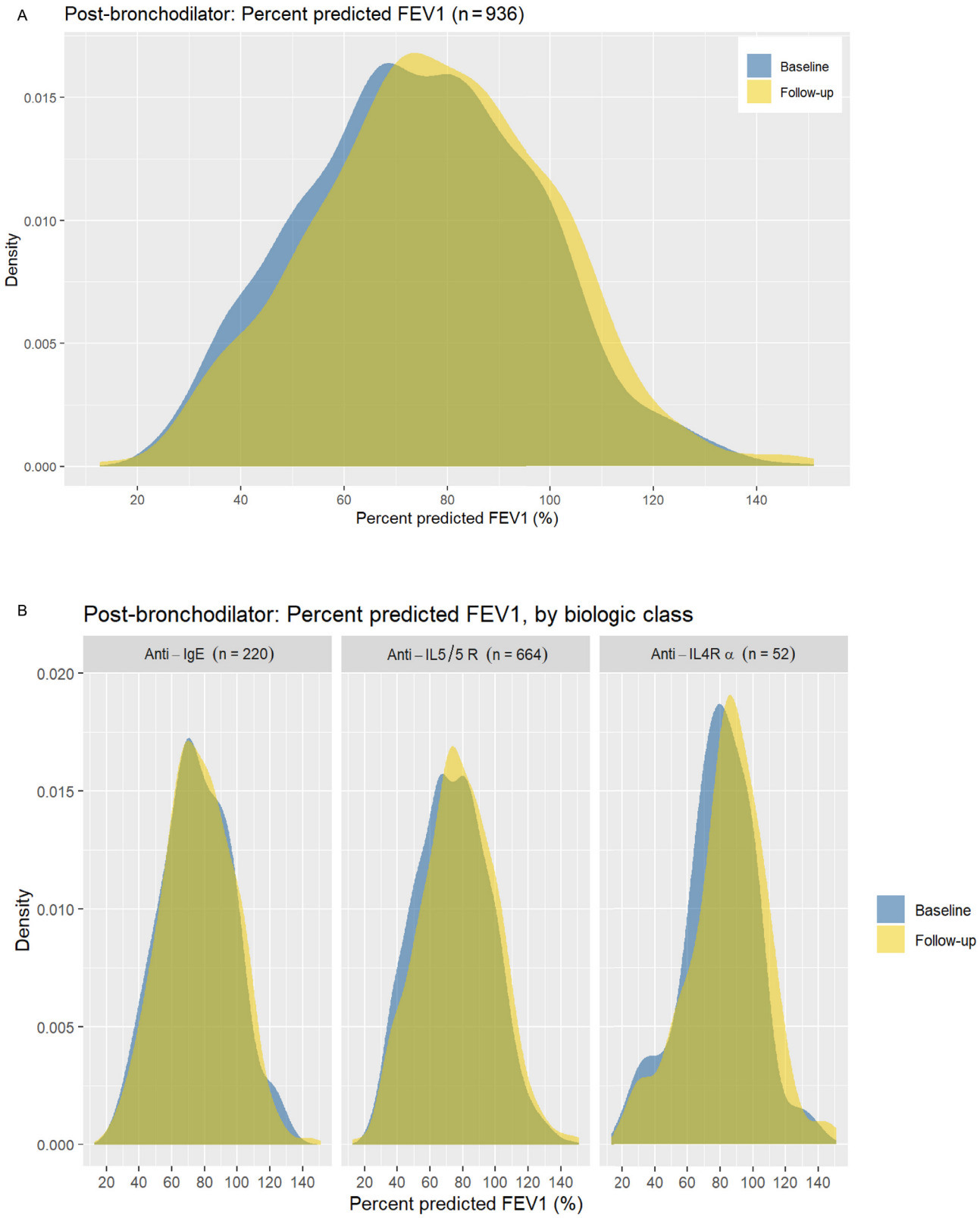
Abbreviation: ppFEV$_1$, percent-predicted forced expiratory volume in 1 second.



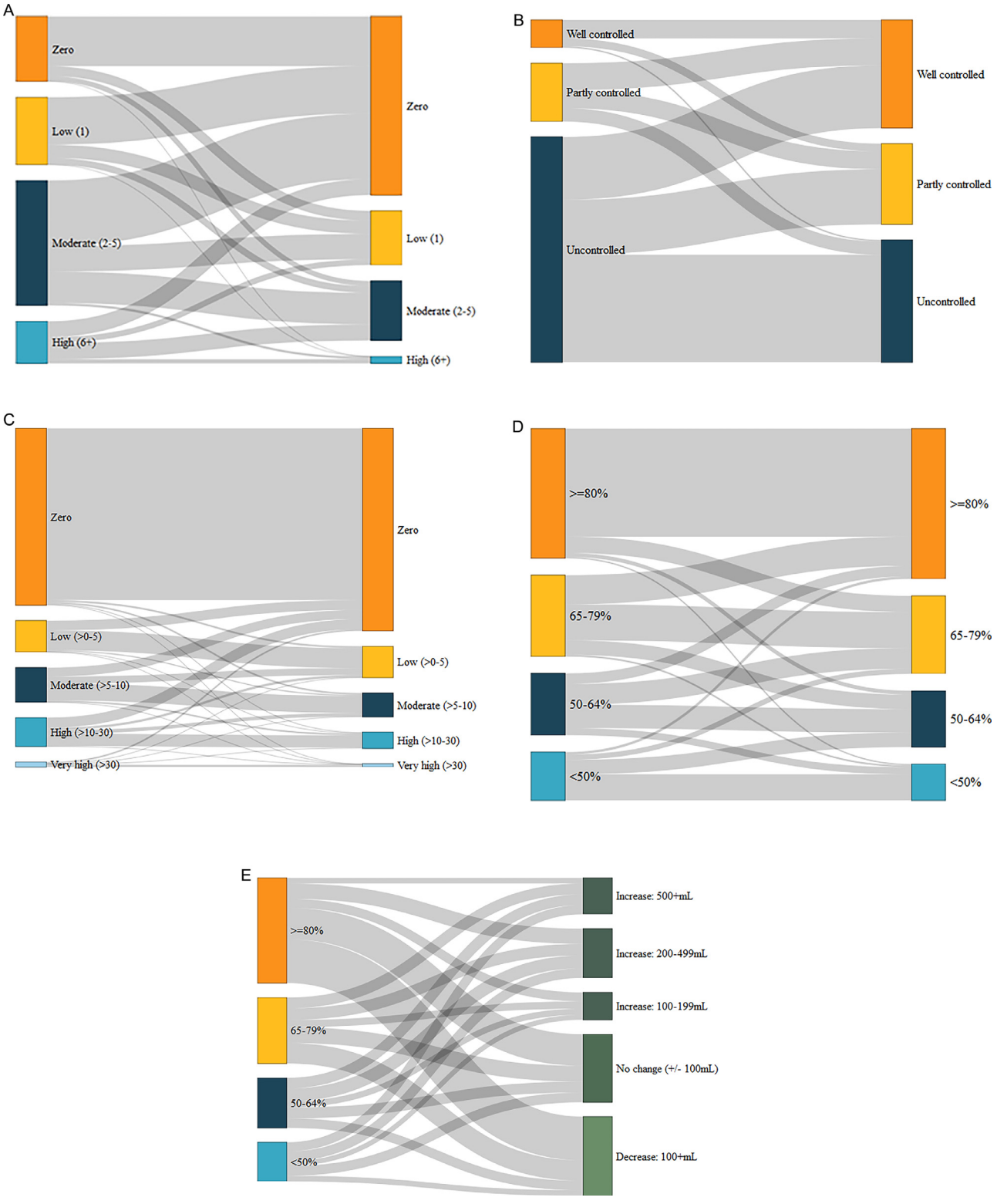
eFigure 1. Flowchart illustrating original eosinophilic and noneosinophilic severe asthma phenotype algorithm. Reprinted with permission from Heaney et al.[25] BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; OCS, oral corticosteroid.



eFigure 2. (A) Distribution of number of exacerbations per year before and approximately 1 year after biologic therapy by biologic class. *P* values (McNemar nominal symmetry test): anti-IgE: <.001; anti–IL-5/5R: <.001; anti–IL-4Rα: Not calculated. (B) Distribution of asthma control status before and approximately 1 year after biologic therapy by biologic class. *P* values (McNemar nominal symmetry test): anti-IgE: <.001; anti–IL-5/5R: <.001; anti–IL-4Rα: .010. (C) Distribution of long-term OCS daily dose (mg) before and approximately 1 year after biologic therapy by biologic class. *P* values (Wilcoxon sign rank test): anti-IgE: <.001; anti–IL-5/5R: <.001; anti–IL-4Rα: <.001. (D) Distribution of percent-predicted FEV_1 before and approximately 1 year after biologic therapy by biologic class. *P* values (paired *t* test): anti-IgE: .005; anti–IL-5/5R: <.001; anti–IL-4Rα: <.001. FEV_1: forced expiratory volume in one second; OCS, oral corticosteroid.



eFigure 3. (A) Distribution of post-bronchodilator percent predicted FEV_1 pre- and approximately 1-year post-biologic therapy in adults with severe asthma. *P* values for pre- and post-biologic distribution comparisons: <.001 (paired *t* test). *P* value (paired *t* test): <.001. (B) Distribution of post-bronchodilator percent-predicted FEV_1 before and approximately 1 year after biologic therapy by biologic class. *P* values (paired *t* test): anti-IgE: .350 (+0.9 $ppFEV_1$); anti–IL-5/5R: <.001 (+3.4 $ppFEV_1$); and anti–IL-4Rα: .028 (+5.0 $ppFEV_1$). FEV_1, forced expiratory volume in 1 second.



eFigure 4. (A) Proportion of patients transitioning from pre- (left) to approximately 1 year post-biologic (right) along a categorical gradient for exacerbation rate (n = 1429). (B) Proportion of patients transitioning from pre- (left) to approximately 1-year post-biologic (right) along a categorical gradient for asthma control (Assessed using GINA criteria, Asthma Control Test or Asthma Control Questionnaire [n = 1165]). (C) Proportion of patients transitioning from pre- (left) to approximately 1-year post-biologic (right) along a categorical gradient for LTOCS daily dose (n = 2877). (D) Proportion of patients transitioning from pre- (left) to approximately 1-year post-biologic (right) along a categorical gradient for $ppFEV_1$ (n = 1728). (E) $ppFEV_1$ to absolute FEV_1 category transitions pre-biologic (left) to post-biologic (right) (n = 1728). **eTable 2** provides % values and N-numbers for each transition. Improved: moved to lower (better) category post-biologic; Unchanged: remained at the same category post-biologic; worsened: moved to higher (poorer) category post-biologic (See Table 1). FEV_1, forced expiratory volume in one second; $ppFEV_1$, percent predicted; forced expiratory volume in one second; LTOCS, long-term oral corticosteroid; NA, not applicable.

eFigure 5. Post-biologic status (worsened, unchanged, improved) according to pre-biologic impairment and biologic class for each asthma outcome domain—(A) exacerbation rate; (B) asthma control; (C) LTOCS daily dose; and (D) lung function. Worsened: moved to a higher (poorer) category post-biologic; Unchanged; remained at the same category post-biologic; improved: moved to a lower (better) category post-biologic (Table 1). FEV_1: forced expiratory volume in one second; LTOCS: long-term oral corticosteroid.