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# Exploring definitions and predictors of response to biologics for severe asthma

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anti-IL4R $\alpha$ ; anti-IL5/5R; anti-IgE; control; exacerbation; lung function; oral corticosteroid.

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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:  $\geq 50\%$  reduction in exacerbation rate,  $\geq 50\%$  reduction in long-term oral corticosteroid [LTOCS] daily dose,  $\geq 1$  category improvement in asthma control, and  $\geq 100\text{mL}$  improvement in FEV1. 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.

# INTRODUCTION

Our understanding of asthma has changed over the past decades from a syndrome characterized by episodic respiratory symptoms and variable airflow obstruction to a heterogeneous disease with complex pathophysiology.<sup>1-3</sup> Asthma treatment development has mirrored this greater understanding, initially targeting symptoms (eg, with bronchodilators) and then the underlying inflammation associated with symptoms (eg, with corticosteroids), until today, when we target the mediators and process(es) that drive inflammatory mechanisms (eg, with biologic therapy).<sup>2</sup> However, response to asthma treatment is heterogeneous. There is a need for novel ways to refine the assessment of the treatment effect to fine-tune treatment strategies.<sup>4</sup> Asthma outcomes therefore underwent a complementary evolution from humble pre-post changes in outcomes (eg, exacerbation reduction) to more ambitious multi-dimension outcomes (eg, asthma control),<sup>2,5,6</sup> and eventually to response, which attempts to capture the complexity and heterogeneity of this disease.<sup>2,7</sup> However, there are important gaps in the concept of biologic response in severe asthma. How should we define response? What is the burden of residual symptoms after 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 (eg, exacerbations and oral corticosteroid [OCS] use) to the development of multicomponent tools. These tools have measured response qualitatively according to the level reached (eg, nonresponse, response, super-response, and remission) using various asthma outcomes, cutoffs, and timings of assessment (eg, 16-52 weeks after treatment), or quantitatively, measuring the extent to which a patient has improved compared with before biologic status,<sup>7-16</sup> and considering the degree of prebiologic impairment.<sup>17</sup> Much effort has been made to standardize a response definition. A recent review suggested a four-domain definition including 50% or greater reduction in exacerbation rate and long-term OCS (LTOCS) dose, improved asthma control, and an increase in FEV1 of 100 mL or greater.<sup>7</sup> Perhaps unsurprisingly, owing to the variable response definitions applied, the potential instability of the response status, the heterogeneous and variable nature of asthma itself, and the impact of prebiologic symptom burden and comorbidities on response, reported response to biologics (defined using single domains) are also variable (58% to 86% in real-life studies).<sup>12-14,16,18-21</sup> Identifying prebiologic variables that predict response and nonresponse 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 the biologic used and outcome assessed, and further hampered by homogeneous populations included in randomized controlled trials (RCTs).<sup>12,22-24</sup>

The European Academy of Allergy and Clinical Immunology has highlighted the need to define biologic response better and identify factors related to treatment failure as key areas for research.<sup>25</sup> The International Severe Asthma Registry (ISAR),<sup>26</sup> containing data on over 16,000 patients from 26 countries (August 2023), offers a unique opportunity to fill some gaps in our understanding of biologic response.<sup>27</sup> Our aims were to explore biologic responder definitions in adult patients with severe asthma in real life, quantify what residual symptoms or limitations remain in responders, and investigate associated patient characteristics, which may be used to identify predictors of response to biologic therapy.

**TABLE 1.** Asthma outcome domain definitions and timing of pre- and postbiologic assessment

Outcome	Definition	Before biologic	After biologic	Single-domain responder definitions
Exacerbation Atrate	Asthma-related hospital attendance or admission AND/OR asthma-related emergency room attendance AND/OR acute oral corticosteroid course for $\geq 3$ d	1 y before biologic (or 48 wk minimum)	Annualized after biologic (number of events assessed for minimum of 48 wk and maximum of 80 wk after biologic)	$\geq 50\%$ exacerbation reduction vs before biologic
Asthma control*	GINA control test <sup>2</sup> OR ACT <sup>5</sup> OR ACQ <sup>6</sup>	At biologic initiation (or assessment closest to biologic initiation up to a maximum of 1 y before biologic)	Closest to 1 y after biologic (24 wk minimum and 80 wk maximum)	$\geq 1$ category improvement in control status vs before biologic
Daily LTOCS dose <sup>†</sup>	Continuous oral corticosteroid treatment for $\geq 3$ mo at point of biologic initiation (and usually $>1$ y) expressed as prednisolone equivalent dose (mg)	At biologic initiation	Closest to 1 y after biologic (24 wk minimum and 80 wk maximum)	$\geq 50\%$ long-term oral corticosteroid daily dose reduction vs before biologic
Lung function <sup>‡</sup>	FEV <sub>1</sub> % predicted FEV <sub>1</sub>	At biologic initiation (or assessment closest to biologic initiation up to a maximum of 1 y before biologic)	Closest to 1-year post biologic (24 weeks minimum and 80 weeks maximum)	$\geq 100$ mL FEV <sub>1</sub> increase vs before biologic

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; GINA, Global Initiative for Asthma.

\*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: mean ACQ = well controlled ( $\leq 0.75$ ); partly controlled ( $>0.75$  to  $< 1.5$ ); or uncontrolled ( $\geq 1.5$ ). Total ACT = well controlled ( $> 19$ ); partly controlled ( $> 15$  to  $\leq 19$ ); or uncontrolled ( $\leq 15$ ). For cases in which results from more than one test were recorded, the prioritization was (1) GINA test, (2) ACT, and (3) ACQ.

<sup>†</sup>For cases in which there were different periods with different doses before the biologic, the most recent dose (ie, closest to biologic initiation) was used. For the postbiologic dose, and if changed from before the biologic, the new dose closest to 1-y postbiologic initiation (minimum 24 wk, maximum 80 wk) was used and the date of change was used to calculate the follow-up.

<sup>‡</sup>Postbronchodilator lung function parameters were used when available; prebronchodilator values were used otherwise, while ensuring that pre- and postbiologic measures were both either pre- or postbronchodilator.

## METHODS

### Study design and data source

This was a longitudinal, pre-post biologic cohort study including data from 21 countries (see [Tables E1](#) and [E2A-D](#) in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)) sharing data with ISAR27-29 from May 1, 2017 to January 25, 2023. Biologic class categorization was based on the first biologic used. We measured the change in four asthma outcomes from prebiologic initiation (ie, baseline) as close as possible to 1-year after biologic initiation ([Table 1](#) and [Figure 1](#)). We obtained ethics approval from Anonymized Data Ethics Protocols and Transparency Committee (ADEPT0922).

### Patients

Patients were aged 18 years or older at biologic initiation and had severe asthma (ie, receiving treatment at Global Initiative for Asthma [GINA] 2018 step 5 or with uncontrolled asthma (ie, severe symptoms or  $>2$  exacerbations/y requiring OCS) at GINA step 4).<sup>29,30</sup> Patients were also required to have at least one of the following: two or more exacerbations, percent predicted FEV<sub>1</sub> (ppFEV<sub>1</sub>) less than 80% in the year preceding biologic initiation, LTOCS use, or partly or uncontrolled asthma at biologic-initiation (ie, impairment in each outcome included in responder definition). Other prerequisites included treatment with anti-IgE, anti-IL-5/5R, or anti-IL-4Ra, available registry data before or on the biologic initiation date for one or more study domains, and 24 weeks or longer follow-up data). Those with a history of bronchial thermoplasty were excluded.



## Variables

Patient demographic and prebiologic asthma clinical characteristics collected included (among others) biomarker levels, age at asthma onset, asthma duration, and the presence of comorbidities (Tables II and III and E1).

## Asthma outcome domains, timing of assessments, and responder definitions

Asthma outcome domains used to define responders were the exacerbation rate, LTOCS daily dose, asthma control, and FEV<sub>1</sub>.<sup>17</sup> Table I lists definitions and timing of pre-post biologic assessments. Responder domains and cutoffs (ie, pre-post biologic change for each asthma outcome) were informed by previous severe asthma trials and ISAR study research,<sup>17</sup> which examined pre-post biologic changes in the exacerbation rate, LTOCS use, asthma control, and lung function in patients, categorized according to the degree of prebiologic impairment, and assessed the magnitude of improvement according to the starting point and outcome assessed. Domains and cutoffs were categorized a priori as 50% or greater reduction in exacerbation rate, 50% or greater reduction in LTOCS daily dose, improvement by one or more category of asthma control (assessed using either GINA control criteria, Asthma Control Test [ACT] or Asthma Control Questionnaire [ACQ] (see Table E3 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)), and 100 mL or greater improvement in FEV<sub>1</sub> (further categorized as 100- 199, 200-400, and  $\geq$ 500 mL improvement). We fitted ACQ and/ or ACT control categories to GINA 2020 control categories as: mean ACQ = well controlled ( $\leq$ 0.75), partly controlled ( $>$ 0.75 to  $<$  1.5), or uncontrolled ( $\geq$ 1.5); and total ACT = well controlled ( $>$ 19), partly controlled ( $>$ 15 to  $<$ 19), or uncontrolled ( $\leq$ 15). Similar control cutoffs and correlations<sup>32,33</sup> have been described and used by others.<sup>16,34,35</sup> Responder definitions included single and multiple domains (Figure 1). The latter included two domains (ie, exacerbations and LTOCS), three domains (ie, exacerbations and LTOCS plus asthma control or lung function), and all four domains.

## Statistical analyses

We used R software (version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria) to conduct all statistical analyses.<sup>36</sup> The proportions 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 variations in follow-up duration. For other domains, no action was taken. Table E4 (in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)) lists the distribution of follow-up time for each domain by biologic class. Pre and post biologic status were also described as cross-tabulations for individual domain responders, stratified as responders and nonresponders, and presented as stacked bar charts. Associations between prebiologic 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: nonresponder, 100-199, 200-499, or 500 or greater mL FEV<sub>1</sub> improvement) techniques. These analyses were adjusted for age, sex, and prebiologic asthma-related outcome considered for response definition. Linear or log-linear assumption was applied to continuous variables. We tested significance through log-likelihood ratios. These analyses were restricted to single-domain responder definitions because of the limited numbers of patients eligible for

multiple domain responder analysis. Prebiologic 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.<sup>12,22-24,37</sup> Models were fitted overall and for each class of biologics separately (but not anti-IL-4Ra because of the small sample size). To examine the potential effect modification of biologic class (anti-IgE vs anti-IL-5/5R), a single model was fitted in these patients, adding biologic class as an interaction term with the prebiologic variable of interest.

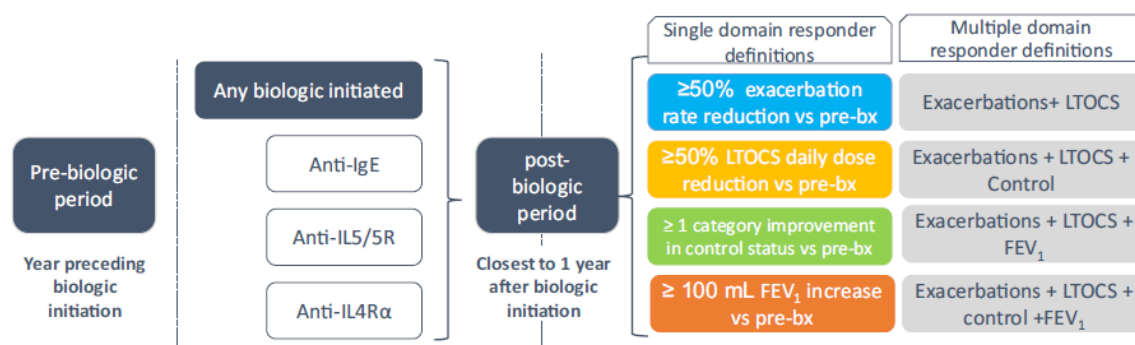


FIGURE 1. Single and multiple domain responder definitions compared with prebiologic values. *bx*, biologic; *LTOCS*, long-term oral corticosteroid.

## RESULTS

### Patients

As of January 25, 2023, 14,284 patients were enrolled in ISAR, 6,816 had initiated biologics, and of those, 3,717 had pre and post biologic initiation data for one or more asthma outcome domains. In total, 2,210 patients met inclusion criteria and were included in one or more analyses (Figure 2 and Table E2A-D). Moreover, 665, 1,405, and 140 patients received anti-IgE, anti-IL-5/R, and anti-IL-4Ra, respectively. The United States ( $n = 645$ ; 29.2%), United Kingdom ( $n = 427$ ; 19.3%), and Italy ( $n = 368$ ; 16.7%) contributed the largest proportions of patients (see Table E5 in this article's Online Repository at [www.jaciinpractice.org](http://www.jaciinpractice.org)).

### Patient demographics and prebiologic clinical characteristics

Patients were predominantly White (80.6%;  $n = 1,540$  of 1,911); had never smoked (66.0%;  $n = 1,142$  of 1,731); and had a median asthma duration of 20 years, with a tendency toward more females (59.7%;  $n = 1,319$  of 2,210 (Table II). Median age and body mass index were 55 years and 27.9 kg/m<sup>2</sup>, respectively. Biomarkers indicative of type 2 (T2)-high disease (ie, blood eosinophil count [BEC], FeNO, and IgE) were elevated; 94.7% ( $n = 1,750$  of 1,847) had an eosinophilic phenotype. Most patients (84.0%;  $n = 895$  of 1,065) had a positive allergy aeroallergen test. The prevalences of potentially T2-related comorbidities were greater than 50% for allergic rhinitis (AR) and chronic rhinosinusitis (CRS) and 30% for nasal polyposis (NP) (Table II). Table E5 lists other comorbidities. Patients experienced a median of 2 exacerbations/y prebiologic initiation. In addition, 57.1% ( $n = 1,129$  of 1,978) were treated with LTOCS, 74.2% ( $n = 1,005$  of 1,355) had uncontrolled asthma, and 68.7% ( $n = 1,239$  of 1,804) had a ppFEV1 of less than 80% (Table III). Patients who subsequently initiated anti-IL-5/5R tended to have more severe disease, and those who subsequently initiated anti-IL-4Ra had less severe disease (Table III).

**TABLE II.** Patient demographic and clinical characteristics before the biologic, overall and by biologic class

Characteristics	Total (n = 2,210)	Anti-IgE (n = 665)	Anti-IL-5/5R (n = 1405)	Anti-IL-4Rα (n = 140)
Age at biologic initiation (attained y)				
Median (Q1-Q3)	55 (45-63)	52 (41-61)	56 (47-64)	55 (45-64)
Sex, n				
Female, n (%)	1,319 (59.7)	404 (60.8)	829 (59.0)	86 (61.4)
Race or ethnicity, n				
Black, 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)
Northeast 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)
Southeast Asian, n (%)	64 (3.3)	30 (5.1)	34 (2.8)	0
White, n (%)	1,540 (80.6)	463 (78.7)	989 (81.8)	88 (77.2)
Body mass index, kg/m <sup>2</sup> , n				
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				
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)
Never smoker, n (%)	1,142 (66.0)	337 (67.3)	736 (65.9)	69 (60.5)
Age at asthma onset, continuous, n				
Median (Q1-Q3)	30 (13-45)	21 (7-40)	32 (17-46)	25 (9-45)
Age at asthma onset, categorical, n				
0-11 y, n (%)	337 (23.1)	130 (34.9)	192 (18.5)	15 (30.0)
12-40 y, n (%)	674 (46.1)	158 (42.4)	497 (47.9)	19 (38.0)
>40 y, n (%)	450 (30.8)	85 (22.8)	349 (33.6)	16 (32.0)
Asthma duration, continuous, n				
Median (Q1-Q3)	20 (9-35)	23 (13-37)	19 (9-34)	27 (7-42)
Asthma duration, categorical, n				
<10 y, n (%)	367 (25.3)	70 (18.8)	283 (27.4)	14 (28.0)
≥10 y, n (%)	1,086 (74.7)	302 (81.2)	748 (72.6)	36 (72.0)
Positive allergen test, n				
Yes, n (%)	895 (76.8)	386 (94.8)	476 (66.9)	33 (68.8)
Use of medication in year preceding biologic initiation, n				
Long-acting muscarinic antagonist, n (%)	72 (3.9)	25 (4.4)	40 (3.5)	7 (5.2)
Theophylline, n (%)	203 (11.1)	65 (11.4)	134 (11.9)	4 (3.0)
Leukotriene receptor antagonist, 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)
Prebiologic highest blood eosinophil concentration (10 <sup>9</sup> cells/L), n				
Median (Q1-Q3)	500 (230-800)	300 (150-600)	546 (300-900)	300 (200-600)
Prebiologic latest FeNO result (parts per billion), n				
Median (Q1-Q3)	36 (20-70)	28 (14-58)	40 (22-73)	31 (17-57)
Prebiologic latest blood IgE count, IU/mL, n				
Median (Q1-Q3)	167 (64-450)	262 (121-567)	133 (47-381)	91 (27-289)
History of allergic rhinitis, n				
Yes, n (%)	785 (53.1)	300 (59.5)	429 (50.8)	56 (43.1)
History of chronic rhinosinusitis, n				
Yes, n (%)	975 (52.6)	250 (45.2)	663 (56.5)	62 (48.8)
History of nasal polyposis, n				
Yes, n (%)	591 (30.0)	109 (18.6)	446 (35.5)	36 (27.7)
History of osteoporosis, n				
Yes, n (%)	335 (18.6)	115 (19.7)	196 (18.0)	24 (18.5)
Eosinophilic gradient <sup>*,37</sup> , n				
Grade 0, n (%)	2 (0.1)	2 (0.6)	0	0
Grade 1, n (%)	25 (1.4)	22 (6.2)	0	3 (3.5)
Grade 2, n (%)	70 (3.8)	63 (17.6)	0	7 (8.2)
Grade 3, n (%)	1,750 (94.7)	270 (75.6)	1,405 (100.0)	75 (88.2)

The category "Other" was not further specified and means other than listed categories.

\*Assessed using a multicomponent eosinophil phenotype classification algorithm that uses blood eosinophil concentration and other clinical parameters (ie, adult onset, long-term oral corticosteroid use, FeNO levels, the presence of nasal polyps, and class of prescribed biologic) to categorize phenotype along an eosinophilic gradient<sup>31</sup>: grade 0 (unlikely/noneosinophilic), grade 1 (least likely), grade 2 (likely), and grade 3 (most likely). Patients receiving anti-IL-5/5R were all categorized as most likely by the algorithm.

**TABLE III.** Prebiologic asthma-related characteristics used in responder definitions

Characteristics	Total (n = 2,210)	Anti-IgE (n = 665)	Anti-IL-5/5R (n = 1,405)	Anti-IL-4R $\alpha$ (n = 140)
Prebiologic exacerbations, n*	1,517	377	1,054	86
Median (Q1-Q3)	2 (1-4)	2 (1-4)	3 (1-5)	1 (0-2)
Prebiologic exacerbations, n*	1,632	425	1,095	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)
$\geq 1$ hospitalized or $\geq 3$ in total, n (%)	794 (48.7)	159 (37.4)	615 (56.2)	20 (17.9)
Missing	458	186	263	9
Prebiologic long-term oral corticosteroid daily dose, mg, n*	1,050	299	708	43
Median (Q1-Q3)	10 (5-20)	10 (5-20)	10 (5-20)	10 (5-17.5)
Prebiologic long-term oral corticosteroid, n*	1,978	539	1,333	106
Nonuser, n (%)	849 (42.9)	232 (43.0)	554 (41.6)	63 (59.4)
$\leq 5$ mg/d, n (%)	328 (16.6)	96 (17.8)	217 (16.3)	15 (14.2)
$>5$ -10 mg/d, n (%)	365 (18.5)	100 (18.6)	252 (18.9)	13 (12.3)
$>10$ mg/d, 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
Prebiologic asthma control, n $\dagger$	1,355	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)
Uncontrolled, n (%)	1,005 (74.2)	268 (72.8)	705 (75.2)	32 (65.3)
Prebiologic % predicted FEV $_1$ , n $\dagger$	1,804	525	1,155	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)
Prebiologic % predicted FEV $_1$ , n $\dagger$	1,804	525	1,155	124
$\geq 80\%$ , n (%)	565 (31.3)	132 (25.1)	401 (34.7)	32 (25.8)
$<80\%$ , n (%)	1,239 (68.7)	393 (74.9)	754 (65.3)	92 (74.2)

\*In year preceding biologic initiation.

 $\dagger$ In year preceding and closest to biologic initiation.

## Frequency of responders

The percentage of patients who met responder definitions ranged from 80.7% (n = 566 of 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 of 1,030), 21.9% (n = 226 of 1,030), and 19.8% (n = 204 of 1,030) had a 100 or greater to less than 200mL, 200 or greater to less than 500mL, and 500 mL or greater post biologic initiation FEV $_1$  improvement, respectively. The proportion of responders diminished with an increase in the number of domains included in the definition, from 33.1% (n = 80 of 242; 95% CI, 27.4- 39.2) for two domains to approximately 15% for three domains and 10.6% (n = nine of 85; 95% CI, 5.5-19.1) for four domains (Figure 3). The proportion of responders by biologic class showed a similar pattern (Table E4; see Figure E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). The prevalence of multidomain responses defined using all possible combinations of our four predefined domains is listed in Table E6 (in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

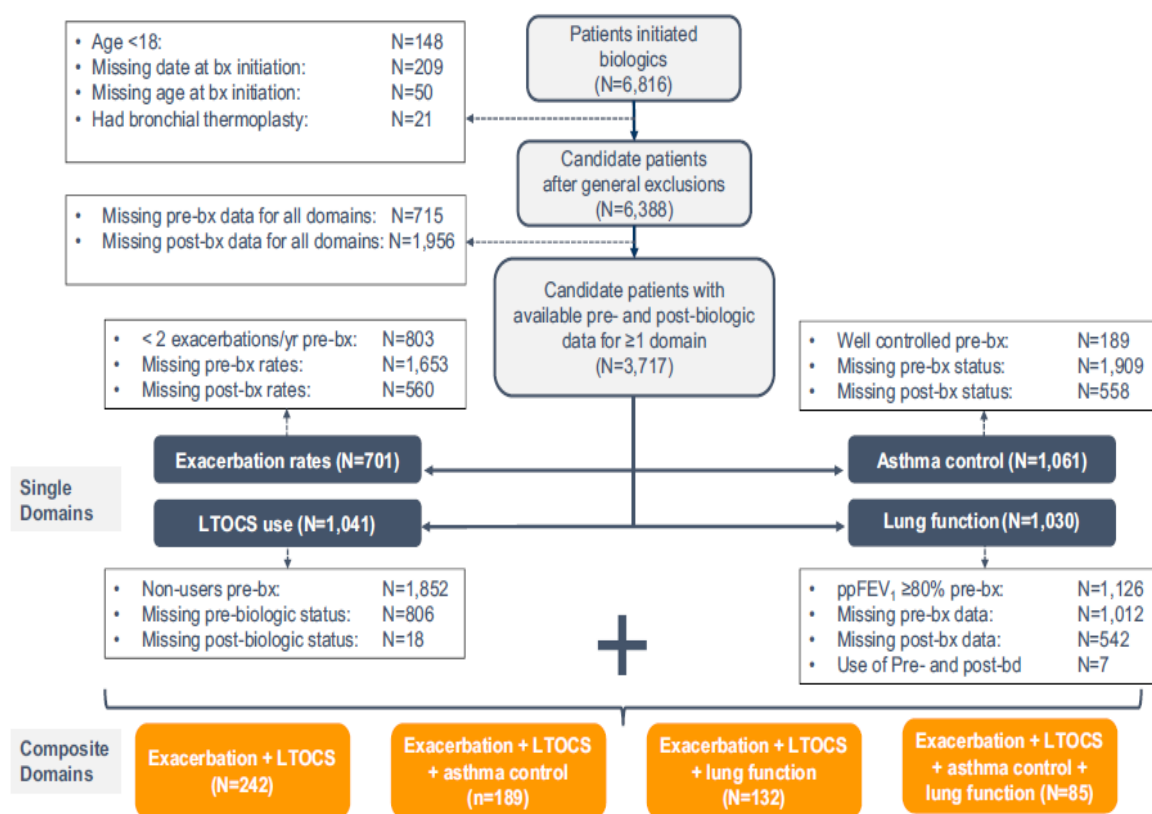


FIGURE 2. Subjects' disposition. *bx*, biologic; *LTOCS*, long-term oral corticosteroid; *ppFEV<sub>1</sub>*, percent predicted FEV<sub>1</sub>.

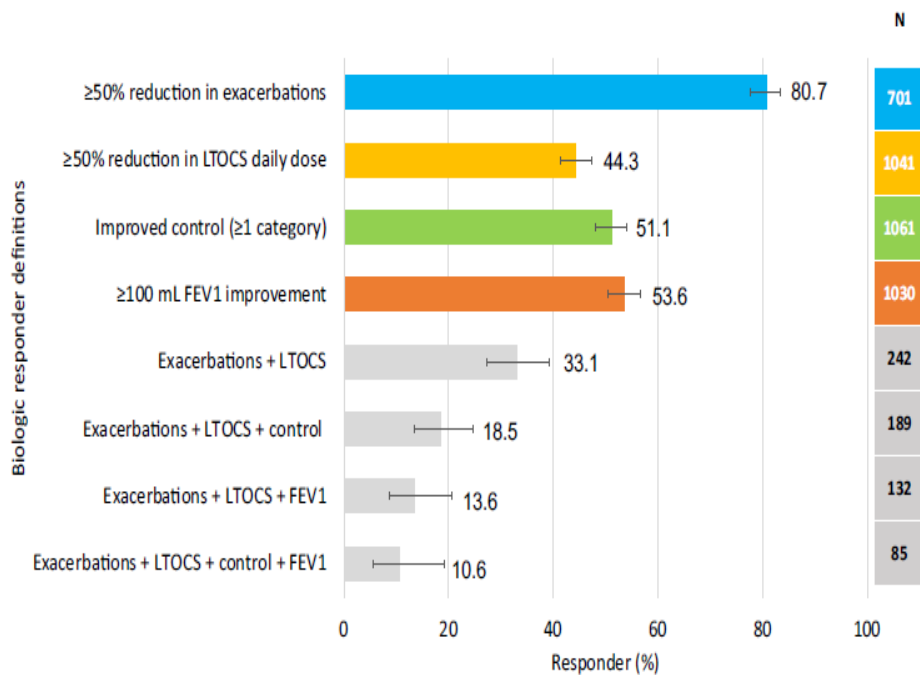
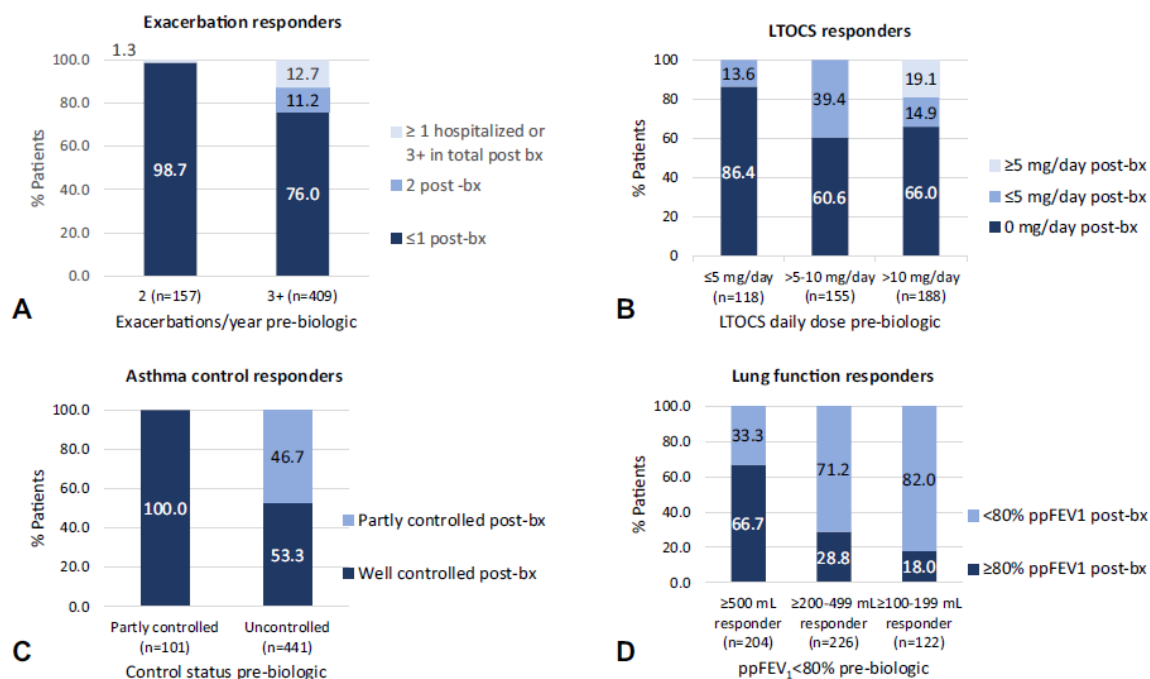


FIGURE 3. Proportion of single- and multiple-domain responders to biologic therapy. Control assessed using Global Initiative for Asthma criteria,<sup>2</sup> Asthma Control Test,<sup>5</sup> or Asthma Control Questionnaire.<sup>6</sup> *LTOCS*, long-term oral corticosteroid.



**FIGURE 4.** Postbiologic status for responders for each responder definition: (A) exacerbation responders had a 50% or greater reduction versus before the biologic; (B) LTOCS daily dose responders had a 50% or greater reduction versus before the biologic; (C) asthma control responders had one or more category improvements in control status versus before the biologic; and (D) lung function responders had a 100-mL FEV<sub>1</sub> or greater increase versus before the biologic. In (A) 1.3% refers to the percentage with one hospitalized exacerbation after the biologic was received. *Bx*, biologic; *LTOCS*, long-term oral corticosteroid *ppFEV<sub>1</sub>*, percent predicted FEV<sub>1</sub>.

## Post-biologic outcome in responders

Among exacerbation responders who had experienced three or more exacerbations before the biologic initiation or one or more that required hospitalization, 12.7% (n = 52 of 409) still experienced one or more exacerbations that required hospitalization or had  $\geq 3$  exacerbations/y after the biologic initiation (Figure 4, A; see Table E7 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Overall, 53.2% (n = 188 of 353) of patients treated with more than 10 mg/d LTOCS prebiologic initiation were classified as responders, but 19.1% (n = 36 of 188) still received more than 5 mg/d after biologic initiation (Figure 4, B) and 46.7% (n = 206 of 441) of control responders who had uncontrolled asthma before the biologic still had partly controlled disease after biologic initiation (Figure 4, C). Between 33.3% and 82.0% of lung function responders still had a ppFEV<sub>1</sub> of less than 80% after biologic initiation, depending on the magnitude of lung function improvement achieved with biologic treatment (Figure 4, D). Similar patterns were noted for anti-IgE, anti-IL-5/5R, and anti-IL-4Ra (Table E7).

## Correlates of response to biologic

In general, the odds of being a responder for each domain increased with greater prebiologic impairment in that domain (ie, intradomain). Other prebiologic characteristics that increased the odds of meeting responder criteria varied by domain (ie, interdomain) (Figure 5, A-D; see Table E8 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Exacerbations responder. Prebiologic characteristics tending to associate with greater odds of achieving

exacerbation responder status included a lower LTOCS daily dose (odds ratio [OR]<sup>1/4</sup> 0.85; 95%CI, 0.77-0.95 for every 5-mg/d increase in prebiologic LTOCS daily dose); no prebiologic prescription for theophylline (OR = 0.77; 95% CI, 0.52-1.14 for theophylline users); the absence of osteoporosis (OR = 0.60; 95% CI, 0.34-1.08 for the presence of osteoporosis); and a history of atopic dermatitis (OR = 1.54; 95% CI, 0.73-3.25) (Figure 5, A). By contrast, higher prebiologic BEC, IgE, or FeNO levels were not associated with greater odds of meeting the exacerbation responder criterion (Figures 5, A).

### **Long-term oral corticosteroid responder.**

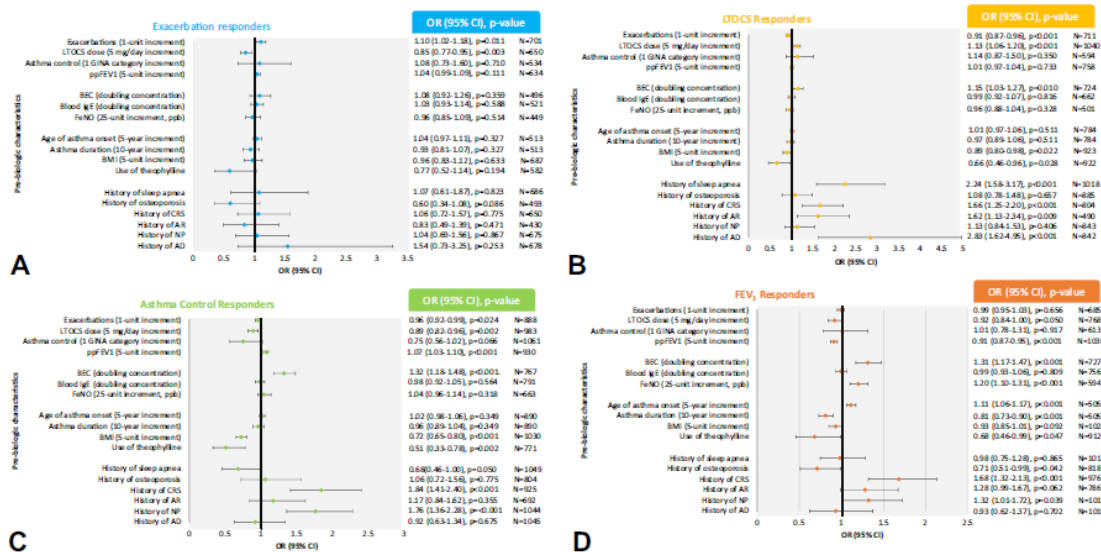
Patients with lower prebiologic initiation exacerbation rates tended toward a greater likelihood of achieving a 50% or greater reduction in LTOCS daily dose (Figure 5, B). The LTOCS responders were also more likely to have a higher prebiologic initiation BEC (OR = 1.15; 95% CI, 1.03-1.27 for every prebiologic concentration doubling), but not IgE or FeNO; a lower BMI (OR = 0.89; 95% CI, 0.80-0.98 for every five-unit increase); no prebiologic 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 5, B).

### **Asthma control responder.**

Patients more likely to be asthma control responders were those with better lung function, less exacerbations per year, and lower LTOCS daily dose before the biologic initiation (Figure 5, C). A higher prebiologic 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 five-unit increase before the biologic), no prescription for theophylline (OR = 0.51; 95% CI, 0.33-0.78 for theophylline users), an 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 toward a greater likelihood of achieving improvements in one or more categories in control status after biologic initiation (Figure 5, C).

### **FEV<sub>1</sub> responders.**

Lung function responders were also more likely to have a lower prebiologic LTOCS daily dose (OR= 0.92; 95% CI, 0.84-1.00 for every 5-mg/d increase before biologic) and higher prebiologic 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-parts per billion increase) (Figure 5, D). Asthma onset and duration predicted only lung function responders; those older at asthma onset and with shorter asthma duration more likely achieved FEV<sub>1</sub> responder status post-biologic initiation (Figure 5, D). The odds of achieving lung function responder status increased by 1.11 (95% CI, 1.06-1.17) for every 5 years of age past 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 OR for a 10-year increase 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 increase). Patients with lower prebiologic BMI, no prescription of theophylline, an absence of osteoporosis and the presence of CRS, AR, or NP also had a greater tendency to be FEV<sub>1</sub> responders (Figure 5, D).



**FIGURE 5.** Association between selected prebiologic characteristics and response to biologic for each single-domain responder definition. Odds ratios are adjusted for age and sex as well as (A) prebiologic exacerbations, (B) long-term oral corticosteroid (LTOCS) dose, (C) asthma control, or (D) percent predicted FEV<sub>1</sub> (ppFEV<sub>1</sub>). Exacerbation responders had 50% or greater reduction versus before the biologic; LTOCS daily dose responders had 50% or greater reduction versus before the biologic; asthma control responders had improvements in one or more categories in control status versus before the biologic; and lung function responders had a 100-mL FEV<sub>1</sub> or greater increase versus before the biologic. *AD*, atopic dermatitis; *AR*, allergic rhinitis; *BEC*, blood eosinophil count; *BMI*, body mass index; *CRS*, chronic rhinosinusitis; *GINA*, Global Initiative for Asthma; *NP*, nasal polyps; *OR*, odds ratio.

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*		

**FIGURE 6.** Associations between selected prebiologic characteristics and response to biologic for each single-domain responder definition. Exacerbation responders had 50% or greater reduction versus before the biologic; long-term oral corticosteroid (LTOCS) daily dose responders had 50% or greater reduction versus before the biologic; lung function responders had a 100-mL FEV<sub>1</sub> or greater increase versus before the biologic. \*Statistically significant ( $P < .05$ ) association. *AD*, atopic dermatitis; *AR*, allergic rhinitis; *BEC*, blood eosinophil count; *BMI*, body mass index; *CRS*, chronic rhinosinusitis; *NP*, nasal polyps.



### **Biologic class comparison (anti-IgE and anti-IL-5/5R).**

Overall, these trends were similar for anti-IgE and anti-IL-5/5R (Table E8) with the exception of BEC, for which some ORs were significantly different (P for heterogeneity <.05) between anti-IgE and anti-IL-5/5R. For example, a higher BEC was positively associated with the exacerbation response for anti-IL-5/5R (OR = 1.23; 95% CI, 1.01-1.49; P = .035), but negatively associated with the exacerbation response for anti-IgE (OR = 0.65; 95% CI, 0.45-0.94; P = .022) (Table E8). Similarly, a higher BEC was associated with achieving responder criteria for control in patients treated with anti-IL-5/5R (OR = 1.55; 95% CI, 1.34-1.80; P < .001) but not in patients treated with anti-IgE (Table E8). Insufficient patient numbers precluded analyses for anti-IL-4Ra.

## **DISCUSSION**

Our study shows that the concept of response is complex and dependent on patients and the outcomes assessed. Responder rates varied widely depending on the type and number of domains included in the definition, which emphasizes 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 prebiologic initiation impairment, continued to experience clinically relevant symptoms after biologic initiation, even those categorized as responders. This highlights the need to provide realistic expectations to patients at the start of their journey along the response pathway. Multiple prebiologic characteristics were associated with a better biologic response. Lung function response was more likely in those with a higher prebiologic initiation FeNO, lower LTOCS, shorter duration of asthma, and older age at asthma onset. Other prebiologic characteristics were common across all four responder domains (eg, greater prebiologic impairment in the domain of interest), in common with previous research, 38-40 or for all responder domains except exacerbations (eg, higher prebiologic 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 that govern it.

We found that biologic responder rates ranged from 44% to 81% for single domain definitions (highest for exacerbations, the primary target of biologic therapy) and 11% to 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 prebiologic impairment, ranging 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<sub>1</sub> (albeit categorizing responder in absolute terms before and after the 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 before the biologic showed post-biologic improvement; 28.5% of patients with a ppFEV<sub>1</sub> of 80% or greater before treatment achieved a post-biologic initiation improvement of 100 mL or greater. 17 These wide responder ranges show that a substantial proportion of patients do not respond to biologic therapy (by our definitions) and imply some degree of underlying disease activity, perhaps the presence of non-T2 asthma, already irreversibly damaged lungs (eg, 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 emphasize the urgency of

deciding on a common approach to assess response for use in RCTs and real-life clinical studies and to inform asthma management guidelines. Two different multimodal responder definitions have recently been published. The first defined good response using three domains ( $\geq 50\%$  exacerbation and LTOCS reduction and control),<sup>8</sup> and the second defined responder using four domains ( $\geq 50\%$  exacerbations and LTOCS reduction, improved control, and  $>100$  mL increase in FEV<sub>1</sub>).<sup>7</sup> Both of these responder definitions were 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 on the level of prebiologic impairment in each domain assessed and what is achievable for each patient based on the level of that impairment. For example, 33.3% of lung function responders still had a ppFEV<sub>1</sub> of less than 80% after the biologic although the FEV<sub>1</sub> had already improved by 500 mL or greater with biologic treatment. This residual impairment may be due to drug, treatment, and social determinants (eg, adherence and access) and/or the heterogeneity of severe asthma, including the presence of an underlying pathophysiology not targeted by existing biologics, T2-low asthma, and/or non-pulmonary comorbidities such as obesity.

Long-term nonreversible damage may also limit response in some patients, which suggests the need for earlier intervention for possibly optimum benefit. It is 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 to the final destination (ie, remission). In the current study we consider ppFEV<sub>1</sub> of less than 80% to be residual impairment, but a definition using a 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 (eg, higher FeNO, later asthma onset, and shorter duration), respectively associated with a 20%, 11%, and 19% increase in odds of achieving lung function responder status. This is in agreement with other authors, who found a greater increase in post-biologic FEV<sub>1</sub> (relative to placebo) in patients with high versus low prebiologic FeNO levels,<sup>24</sup> in those with late ( $\geq$ age 40 years) versus early (age  $<40$  years) onset asthma,<sup>41</sup> and in patients who received a diagnosis after versus before age 18 years.<sup>40</sup> A better FEV<sub>1</sub> response in patients with a high FeNO may suggest that those with poor lung function and an 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 receiving higher average daily dosages of inhaled corticosteroid.<sup>42</sup>

Other predictors of better response to biologics were apparent for all responder definitions except exacerbations (eg, higher prebiologic BEC), although a higher BEC was associated with greater odds of exacerbation response for those treated with anti-IL-5/5R group. The GINA 2023 lists high BEC as a predictor of asthma response to anti-IgE as well as to anti-IL-5/5R, anti-IL-4R, and anti-thymic stromal lymphopoietin for those with severe asthma and exacerbations in the past year,<sup>2</sup> and RCTs have found an association of higher BEC and greater exacerbation rate reduction for omalizumab.<sup>38,43</sup> Our results do not contradict that position, but rather represent a consequence of assessing the relationship between prebiologic

biomarker concentration and exacerbations in a different way (ie, relative to prebiologic status, not compared with control). Indeed, others have shown the same relatively flat association of BEC concentration with pre-post biologic-associated exacerbation rate reduction, and not just for omalizumab.<sup>44-46</sup> 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 prebiologic characteristics was complicated because whereas certain prebiologic factors were associated with meeting responder criteria in one domain, the opposite could be true for other domains. This effect was noted for all domains assessed. For example, those with a greater prebiologic exacerbation burden had increased odds of meeting the exacerbation responder criteria but were less likely to meet responder criteria for LTOCS and asthma control. Predicting response is therefore not simple, but a response in one domain was more likely in patients who were experiencing a major impairment in that same domain but were not suffering from multi-domain impairment. Further research in this area is warranted to untangle the interrelationships between prebiologic characteristics and biologic response and to develop multivariable treatment benefit prediction tools.<sup>47</sup>

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 in all observational studies). Because this was a single-arm pre-post biologic design, we could not account for a potential placebo effect. Small sample sizes for each domain limited modeling even though 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 might have led to false-positive associations. Other limitations include the small anti-IL-4Ra group, the fact that the association analysis was done only for single domain responder definitions, and the use of absolute values for FEV<sub>1</sub> alone to assess lung function response. The use of a lower limit of normal for FEV<sub>1</sub> or FEV<sub>1</sub>/FVC could be considered for future study. Employing three tools to assess asthma control (ie, GINA, ACT, and ACQ) could be considered a limitation, although these are all validated tools with good inter-test correlation<sup>32,33</sup> and reflect intercountry variability in how asthma control is assessed in real-life, including variability in control tools required for biologic eligibility and reimbursement. Although the inclusion of only patients with a certain degree of prebiologic impairment was considered necessary to observe response (ie, those with no impairment cannot improve further), it may have limited the generalizability of findings. Future research could consider alternative definitions of lung function response in those with fixed airflow obstruction and those with ppFEV<sub>1</sub> of 80% or greater, assess LTOCS response for those with and without adrenal insufficiency (a condition that is currently not systematically recorded in ISAR),<sup>29</sup> and consider prebiologic characteristics associated with nonresponse to biologics.

Study strengths were the inclusion of a large, real-life, and heterogeneous population with severe asthma receiving biologic therapy, with sufficient breadth to define responders using both single and multiple domains (including lung function) across a range of prebiologic impairment, both overall and by class.<sup>27-29,48</sup>

We assessed the likelihood of achieving responder status using a large number of prebiologic variables routinely captured in everyday clinical practice. Research is ongoing within ISAR to identify biomarker combinations predictive of response, explore remission definitions and prevalence in patients with severe asthma treated with biologics in real life, and identify

prebiologic characteristics associated with achieving it.<sup>49,50</sup> As this area of research continues to develop, it will be interesting to see whether we experience a paradigm shift from the journey (ie, response) to the destination (ie, remission).

Our findings have underscored the multimodal nature of response. Although many patients respond to biologic therapy, some respond better than others, and many responders still experience significant symptoms or impairment after using the 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 toward a more flexible approach, could also be considered. Such an approach should (1) align with patients' goals (ie, include domains of interest), (2) consider the level of prebiologic impairment, and (3) identify the presence or absence of characteristics that can affect response, to formulate a personalized likelihood of response.

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## **REFERENCES**

1. Gauthier M, Ray A, Wenzel SE. Evolving concepts of asthma. *Am J Respir Crit Care Med* 2015;192:660-8.
2. Global Initiative for Asthma. Global strategy for asthma management and prevention. Accessed June 3, 2024. <https://ginasthma.org/wp-content/uploads/2023/05/GINA-2023-Full-Report-2023-WMS.pdf>
3. Denton E, Price DB, Tran TN, Canonica GW, Menzies-Gow A, FitzGerald JM, et al. Cluster analysis of inflammatory biomarker expression in the International Severe Asthma Registry. *J Allergy Clin Immunol Pract* 2021;9:2680-2688.e7.
4. Sakagami T. Evolution of asthma treatment goals. *Respir Investig* 2023;61: 333-4.
5. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59-65.

6. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14: 902-7.
7. Papaioannou AI, Fouka E, Bartziokas K, Kallieri M, Vontetsianos A, Porpodis K, et al. Defining response to therapy with biologics in severe asthma: from global evaluation to super response and remission. *Expert Rev Respir Med* 2023;17:481-93.
8. Tiotiu A, Bikov A, Gonzalez-Barcala FJ, Novakova S, Novakova P, Chong- Neto H, et al. Criteria to evaluate efficacy of biologics in asthma: a Global Asthma Association survey. *Expert Rev Respir Med* 2023;17:507-16.
9. Khaleva E, Rattu A, Brightling C, Bush A, Bourdin A, Bossios A, et al. Definitions of non-response and response to biological therapy for severe asthma: a systematic review. *ERJ Open Res* 2023;9:00444-2022.
10. Upham JW, Le Lievre C, Jackson DJ, Masoli M, Wechsler ME, Price DB. Defining a severe asthma super-responder: findings from a Delphi process. *J Allergy Clin Immunol Pract* 2021;9:3997-4004.
11. Kallieri M, Zervas E, Fouka E, Porpodis K, Mitrova MH, Tzortzaki E, et al. RELight: a two-year REal-Life study of mepolizumab in patients with severe eosinophilic asthma in Greece: evaluating the multiple components of response. *Allergy* 2022;77:2848-52.
12. Kavanagh JE, d'Ancona G, Elstad M, Green L, Fernandes M, Thomson L, et al. Real-world effectiveness and the characteristics of a "super-responder" to mepolizumab in severe eosinophilic asthma. *Chest* 2020;158:491-500.
13. Kavanagh JE, Hearn AP, Dhariwal J, d'Ancona G, Douiri A, Roxas C, et al. Real-world effectiveness of benralizumab in severe eosinophilic asthma. *Chest* 2021;159:496-506.
14. Wechsler ME, Peters SP, Hill TD, Ariely R, DePietro MR, Driessen MT, et al. Clinical outcomes and health-care resource use associated with reslizumab treatment in adults with severe eosinophilic asthma in real-world practice *Chest*, 159; 2021:1734-46.
15. Pérez de Llano L, Dávila I, Martínez-Moragón E, Domínguez-Ortega J, Almonacid C, Colás C, et al. Development of a tool to measure the clinical response to biologic therapy in uncontrolled severe asthma: the FEV1, exacerbations, oral corticosteroids, symptoms score. *J Allergy Clin Immunol Pract* 2021;9:2725-31.
16. Hansen S, Søndergaard M, von Bülow A, Bjerrum AS, Schmid J, Rasmussen LM, et al. Clinical response and remission in severe asthma patients treated with biologic therapies. *Chest* 2024;165:253-66.
17. Perez de Llano L, Scelo G, Canonica GW, Chen W, Henley W, Larenas Linnemann D, et al. Impact of pre-biologic impairment on meeting domain-specific responder definitions in patients with severe asthma. *Ann Allergy Asthma Immunol* 2024;132:610-622.e7.

18. Niven RM, Saralaya D, Chaudhuri R, Masoli M, Clifton I, Mansur AH, et al. Impact of omalizumab on treatment of severe allergic asthma in UK clinical practice: a UK multicentre observational study (the APEX II study). *BMJ Open* 2016;6:e011857.
19. Gibson PG, Reddel H, McDonald VM, Marks G, Jenkins C, Gillman A, et al. Effectiveness and response predictors of omalizumab in a severe allergic asthma population with a high prevalence of comorbidities: the Australian Xolair Registry. *Intern Med J* 2016;46:1054-62.
20. Di Bona D, Crimi C, D'Uggento AM, Benfante A, Caiaffa MF, Calabrese C, et al. Effectiveness of benralizumab in severe eosinophilic asthma: Distinct subphenotypes of response identified by cluster analysis. *Clin Exp Allergy* 2022;52: 312-23.
21. Soendergaard MB, Hansen S, Bjerrum AS, Hilberg O, Lock-Johansson S, Håkansson KEJ, et al. Complete response to anti-interleukin-5 biologics in a real-life setting: results from the nationwide Danish Severe Asthma Register. *ERJ Open Res* 2022;8:00238-2022.
22. Kallieri M, Papaioannou AI, Papathanasiou E, Ntontsi P, Papiris S, Loukides S. Predictors of response to therapy with omalizumab in patients with severe allergic asthma – a real life study. *Postgrad Med* 2017;129:598-604.
23. Bateman ED, Djukanovi\_c R, Castro M, Canvin J, Germinaro M, Noble R, et al. Predicting responders to reslizumab after 16 weeks of treatment using an algorithm derived from clinical studies of patients with severe eosinophilic asthma. *Am J Respir Crit Care Med* 2019;199:489-95.
24. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018;378:2486-96.
25. Agache I, Akdis C, Akdis M, Canonica GW, Casale T, Chivato T, et al. EAACI biologicals guidelines: recommendations for severe asthma. *Allergy* 2021;76: 14-44.
26. ISAR: Collaborative Global Asthma Registry. International Severe Asthma Registry. Accessed June 3, 2024. <https://www.isaregistries.opcglobal.org/>
27. ISAR Study Group. International Severe Asthma Registry (ISAR): mission statement. *Chest* 2020;157:805-14.
28. Bulathsinhala L, Eleangovan N, Heaney LG, Menzies-Gow A, Gibson PG, Peters M, et al. Development of the International Severe Asthma Registry (ISAR): A Modified Delphi Study. *J Allergy Clin Immunol Pract* 2019;7: 578-588.e2.
29. FitzGerald JM, Tran TN, Alacqua M, Altraja A, Backer V, Bjermer L, et al. International severe asthma registry (ISAR): protocol for a global registry. *BMC Med Res Methodol* 2020;20:212.
30. Global Initiative for asthma (2018). Accessed June 3, 2024. <https://ginasthma.org/wp-content/uploads/2019/01/2018-GINA.pdf>

31. Heaney LG, Perez de Llano L, Al-Ahmad M, Backer V, Busby J, Canonica GW, et al. Eosinophilic and non-eosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort. *Chest* 2021;160:814-30.
32. Korn S, Both J, Jung M, Hübner M, Taube C, Buhl R. Prospective evaluation of current asthma control using ACQ and ACT compared with GINA criteria. *Ann Allergy Asthma Immunol* 2011;107:474-9.
33. Koolen BB, Pijnenburg MWH, Brackel HJL, Landstra AM, van den Berg NJ, Merkus PJFM, et al. Comparing Global Initiative for Asthma (GINA) criteria with the Childhood Asthma Control Test (C-ACT) and Asthma Control Test (ACT). *Eur Respir J* 2011;38:561-6.
34. Canonica GW, Blasi F, Carpagnano GE, Guida G, Heffler E, Paggiaro P, et al. Severe Asthma Network Italy definition of clinical remission in severe asthma: a Delphi consensus. *J Allergy Clin Immunol Pract* 2023;11:3629-37.
35. McDowell PJ, McDowell R, Busby J, Eastwood MC, Patel PH, Jackson DJ, et al. Clinical remission in severe asthma with biologic therapy: an analysis from the UK Severe Asthma Registry. *Eur Respir J* 2023;62:2300819.
36. R Core Team. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Accessed June 3, 2024. <https://www.R-project.org/>
37. Chen W, Reddel HK, FitzGerald JM, Beasley R, Janson C, Sadatsafavi M. Can we predict who will benefit most from biologics in severe asthma? A post-hoc analysis of two phase 3 trials. *Respir Res* 2023;24:120.
38. Casale TB, Chipps BE, Rosén K, Trzaskoma B, Haselkorn T, Omachi TA, et al. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. *Allergy* 2018;73:490-7.
39. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015;3:355-66.
40. Bleecker ER, Wechsler ME, FitzGerald JM, Menzies-Gow A, Wu Y, Hirsch I, et al. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. *Eur Respir J* 2018;52:1800936.
41. Brusselle G, Germinaro M, Weiss S, Zangrilli J. Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. *Pulm Pharmacol Ther* 2017;43:39-45.
42. Soremekun S, Heaney LG, Skinner D, Bulathsinhala L, Carter V, Chaudhry I, et al. Asthma exacerbations are associated with a decline in lung function: a longitudinal population-based study. *Thorax* 2023;78:643-52.

43. Hanania NA, Wenzel S, Rosén K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med* 2013;187:804-11.
44. Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med* 2016;4:549-56.
45. FitzGerald JM, Bleecker ER, Menzies-Gow A, Zangrilli JG, Hirsch I, Metcalfe P, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. *Lancet Respir Med* 2018;6:51-64.
46. Casale TB, Luskin AT, Busse W, Zeiger RS, Trzaskoma B, Yang M, et al. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from PROSPERO, a prospective real-world study. *J Allergy Clin Immunol Pract* 2019;7:156-164.e1.
47. Kent DM, Steyerberg E, van Klaveren D. Personalized evidence based medicine: predictive approaches to heterogeneous treatment effects. *BMJ* 2018;363:k4245.
48. Cushen B, Koh MS, Tran TN, Martin N, Murray RB, Uthaman T. Adult severe asthma registries: a global and growing inventory. *Pragmat Obs Res* 2023;14: 127-47.
49. Scelo G, Tran TN, Faregas M, Martin N, Menzies-Gow A, Wang E, et al. Clinical remission following biologic initiation in severe asthma: results of the International Severe Asthma Registry (ISAR). *Eur Respir J* 2023;62:PA1891.
50. Perez de Llano L, Scelo G, Tran TN, Le TT, Martin N, Fageras M, et al. Characteristics associated with clinical remission in patients with severe asthma who initiate biologics. *Eur Respir J* 2023;62:PA1892.



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### **Conflicts of interest:**

G. Scelo is a consultant for Observational and Pragmatic Research Institute, which conducted this study in collaboration with Optimum Patient Care and AstraZeneca. T.N. Tran, T.T. Le, M. Fagerås, N. Martin, and A.M. Gow are employees of AstraZeneca and may own stock or stock options in AstraZeneca. M. Al-Ahmad has received advisory board and speaker fees from AstraZeneca, Sanofi, Novartis, and GlaxoSmithKline and received a grant from Kuwait Foundation for the Advancement of Sciences. R. Al-Lehebi has given lectures at meetings supported by AstraZeneca, Boehringer Ingelheim, Novartis, GlaxoSmithKline, and Sanofi, and participated in advisory board fees from GlaxoSmithKline, AstraZeneca, Novartis, and Abbott. A. Altraja has received lecture fees from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, CSL Behring, GlaxoSmithKline, MSD, Norameda, Novartis, Orion, Sanofi, and Zentiva; and sponsorships from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, CS: Bejromg, GlaxoSmithKline, MSD, Norameda, Novartis, and Sanofi; and has participated in advisory boards for AstraZeneca, Boehringer Ingelheim, CSK Behring, GlaxoSmithKline, MSD, Novartis, Sanofi, and Teva. A. Beastall is an employee of Optimum Patient Care Global (OPCG), a co-funder of the International Severe Asthma Registry. C. Bergeron has received advisory board and speaker fees from ValeoPharma, Sanofi-Aventis, GlaxoSmithKline, Astra-Zeneca, and Grifols Aerteia Therapeutics; and has participated in clinical trials (paid to the university) sponsored by Sanofi-Aventis, GlaxoSmithKline, Astra-Zaneca, BioHaven, Regeneron, and Areteia Therapeutics. L. Bjermer received during the past 3 years consulting/lecture fees from Acucort, AstraZeneca, Birc, Chiesi, GlaxoSmithKline, Phargentis, and Sanofi. A. Bjerrum has received lecture fees from AstraZeneca, GlaxoSmithKline, and Novartis. J. Busby has received research grants from AstraZeneca and personal fees from NuvoAir, outside the submitted work. D.J. Cano-Rosales has received speaker fees from AstraZeneca, Boehringer Ingelheim, and Sanofi and has acted as an investigator for trials sponsored by AstraZeneca, Sanofi, and GlaxoSmithKline. G.W. Canonica has received research grants as well as lecture or advisory board fees from A. Menarini, Alk-Albello, Allergy Therapeutics, Anallergo, AstraZeneca, MedImmune, Boehringer Ingelheim, Chiesi Farmaceutici, Circassia, Danone, Foundation for Advanced Education in the Sciences, Genentech, Guidotti Malesci, GlaxoSmithKline, Hal Allergy, Merck, MSD, Mundipharma, Novartis, Orion, Sanofi Aventis, Sanofi, Genzyme/Regeneron, Stallergenes, UCB Pharma, Uriach Pharma, Teva, Thermo Fisher, and Valeas. V. Carter is an employee of OPCG, a co-funder of the International Severe Asthma Registry. J. Charriot reports receiving advisory board and lecture fees from AstraZeneca, GlaxoSmithKline, and Sanofi; receiving consulting fees from Chiesi; and serving as a trial coinvestigator for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Sanofi. B.G. Cosio declares grants from Chiesi and GlaxoSmithKline; personal fees for advisory board activities from Chiesi, GlaxoSmithKline, Novartis, Sanofi, Teva, and AstraZeneca; and payment for lectures/speaking engagements from Chiesi, Novartis, GlaxoSmithKline, Menarini, Sanofi, and AstraZeneca, outside the submitted work. E. Denton declares grants to her institution from AstraZeneca, GlaxoSmithKline, Novartis, Sanofi, Teva, and Seqirus, for unrelated projects; and speaker fees from Sanofi. D. Dorscheid is on the faculty at the University of British Columbia and is supported by grants from the Canadian Institutes of Health Research, British Columbia Lung Association, and Michael Smith Foundation for Health Research. In addition, he has received speaking fees, travel grants, unrestricted project grants, and writing

fees and is a paid consultant for pharma including Sanofi Regeneron, Novartis Canada, AstraZeneca, GlaxoSmithKline, and ValeoPharma. He is an active member of the Canadian Thoracic Society, American Thoracic Society, European Respiratory Society, and Allergen Research Network. He does not believe that any of the disclosed potential conflicts represent true conflicts with respect to the information and recommendations included in the manuscript. M.J Fernandez-Sanchez is a part-time employee of GlaxoSmithKline and does not hold shares in the company. She declares educational grants to her institution from AstraZeneca, GlaxoSmithKline, and Sanofi for unrelated projects; and speaker fees from AstraZeneca. J.A. Fonseca reports grants from or research agreements with AstraZeneca, Mundipharma, Sanofi Regeneron, and Novartis; and personal fees for lectures and attending advisory boards from AstraZeneca, GlaxoSmithKline, Mundipharma, Novartis, Sanofi Regeneron, and Teva. P.G. Gibson has received speaker fees and grants to his institution from AstraZeneca, GlaxoSmithKline, and Novartis. C. Goh is an employee of OPCG, a co-funder of the International Severe Asthma Registry. L.G. Heaney has received grant funding, participated in advisory boards for, and given lectures at meetings supported by Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Hoffmann la Roche, GlaxoSmithKline, Novartis, Theravance, Evelo Biosciences, Sanofi, and Teva; he has received grants from MedImmune, Novartis UK, Roche/ Genentech, GlaxoSmithKline, Amgen, Genentech/Hoffman la Roche, AstraZeneca, Aerocrine and Vitalograph; he has received sponsorship for attending international scientific meetings from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Napp Pharmaceuticals; he has also taken part in asthma clinical trials sponsored by AstraZeneca, Boehringer Ingelheim, Hoffmann la Roche, and GlaxoSmithKline for which his institution received remuneration; he is the academic lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma, which involves industrial partnerships with a number of pharmaceutical companies including Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffmann la Roche, and Janssen. E. Heffler declares personal fees from Sanofi, Regeneron, GlaxoSmithKline, Novartis, AstraZeneca, Stallergenes, Chiesi, Bosch, and Celltrion Healthcare. M. Hew declares grants and other advisory board fees (made to his institutional employer) from AstraZeneca, GlaxoSmithKline, Novartis, Sanofi, Teva, and Seqirus, for unrelated projects. T. Iwanaga received lecture fees from Kyorin, GlaxoSmithKline, Novartis, Boehringer Ingelheim, and AstraZeneca. M.S. Koh reports grant support from AstraZeneca; and honoraria for lectures and advisory board meetings paid to her hospital (Singapore General Hospital) from GlaxoSmithKline, AstraZeneca, Novartis, Sanofi, and Boehringer Ingelheim, outside the submitted work. P. Kuna reports personal fees from Adamed, AstraZeneca, Berlin Chemie Menarini, Foundation for Advanced Education in the Sciences, Glenmark, Novartis, Polpharma, Boehringer Ingelheim, Teva, and Zentiva, outside the submitted work. D.L. Linnemann reports personal fees from ALK-Abelló, AstraZeneca national and global, Bayer, Chiesi, Grunenthal, Grin, GlaxoSmithKline national and global, Viartis, Menarini, MSD, Novartis, Pfizer, Sanofi, Siegfried, UCB, and Carnot; and grants from AbbVie, Bayer, Lilly, Sanofi, AstraZeneca, Pfizer, Novartis, Circassia, UCB, and GlaxoSmithKline, outside the submitted work. L. Lehtimäki has received personal fees from ALK, AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, Novartis, Orion Pharma, and Sanofi. H. Matsumoto declares lecturer fees from Kyorin Pharma, AstraZeneca, Sanofi Co, Novartis Pharma, and GlaxoSmithKline. N.G. Papadopoulos has been a speaker and/or advisory board member for Abbott, AbbVie, ALK, Asit Biotech, AstraZeneca, Biomay, Boehringer Ingelheim, GlaxoSmithKline, HAL, Foundation for Advanced Education in the Sciences, Farma, Medscape, Menarini, MSD, Novartis, Nutricia, OM Pharma, Regeneron, Sanofi, Takeda, and Viartis. P. Patel has received advisory board and speaker fees from AstraZeneca, GlaxoSmithKline, Novartis, and Sanofi/Regeneron. L. Perez-de Llano reports

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