Received: 14 November 2023 | Revised: 8 May 2024 | Accepted: 12 May 2024

DOI: 10.1111/all.16178

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

ORIGINAL ARTICLE

Real-world biologics response and super-response in the International Severe Asthma Registry cohort

Eve Denton[1,2] | Mark Hew[1,3] | Matthew J. Peters[4,5] | John W. Upham[6] | Lakmini Bulathsinhala[7,8] | Trung N. Tran[9] | Neil Martin[9,10] | Celine Bergeron[11,12] | Mona Al-Ahmad[13,14] | Alan Altraja[15] | Désirée Larenas-Linnemann[16] | Ruth Murray[7] | Carlos Andrés Celis-Preciado[17,18] | Riyad Al-Lehebi[19,20] | Manon Belhassen[21] | Mohit Bhutani[22] | Sinthia Z. Bosnic-Anticevich[23,24] | Arnaud Bourdin[25] | Guy G. Brusselle[26,27] | John Busby[28] | Giorgio Walter Canonica[29,30] | Enrico Heffler[29,30] | Kenneth R. Chapman[31] | Jérémy Charriot[25] | George C. Christoff[32] | Li Ping Chung[33] | Borja G. Cosio[34] | Andréanne Côté[35] | Richard W. Costello[36] | Breda Cushen[37] | James Fingleton[38] | João A. Fonseca[39] | Peter G. Gibson[40,41] | Liam G. Heaney[42] | Erick Wan-Chun Huang[43] | Takashi Iwanaga[44] | David J. Jackson[45] | Mariko Siyue Koh[46] | Lauri Lehtimäki[47,48] | Jorge Máspero[49,50] | Bassam Mahboub[51] | Andrew N. Menzies-Gow[52,53] | Patrick D. Mitchell[54] | Nikolaos G. Papadopoulos[55,56] | Andriana I. Papaioannou[57] | Luis Perez-de-Llano[58] | Diahn-Warng Perng[59,60] | Paul E. Pfeffer[61,62] | Todor A. Popov[63] | Celeste M. Porsbjerg[64] | Chin Kook Rhee[65] | Nicolas Roche[66] | Mohsen Sadatsafavi[67] | Sundeep Salvi[68] | Johannes Martin Schmid[69] | Chau-Chyun Sheu[70,71] | Concetta Sirena[72] | Carlos A. Torres-Duque[73,74] | Laila Salameh[51,75] | Pujan H. Patel[76] | Charlotte Suppli Ulrik[77] | Eileen Wang[78] | Michael E. Wechsler[79] | David B. Price[7,8,80] | on behalf of the ISAR LUMINANT Working Group

Correspondence
David B. Price, Observational and Pragmatic Research Institute, Singapore, Singapore.
Email: dprice@opri.sg

Funding information
AstraZeneca; Optimum Patient Care

Abstract

Background: Biologic asthma therapies reduce exacerbations and long-term oral corticosteroids (LTOCS) use in randomized controlled trials (RCTs); however, there are limited data on outcomes among patients ineligible for RCTs. Hence, we investigated responsiveness to biologics in a real-world population of adults with severe asthma.

Methods: Adults in the International Severe Asthma Registry (ISAR) with ≥24 weeks of follow-up were grouped into those who did, or did not, initiate biologics (anti-IgE, anti-IL5/IL5R, anti-IL4/13). Treatment responses were examined across four

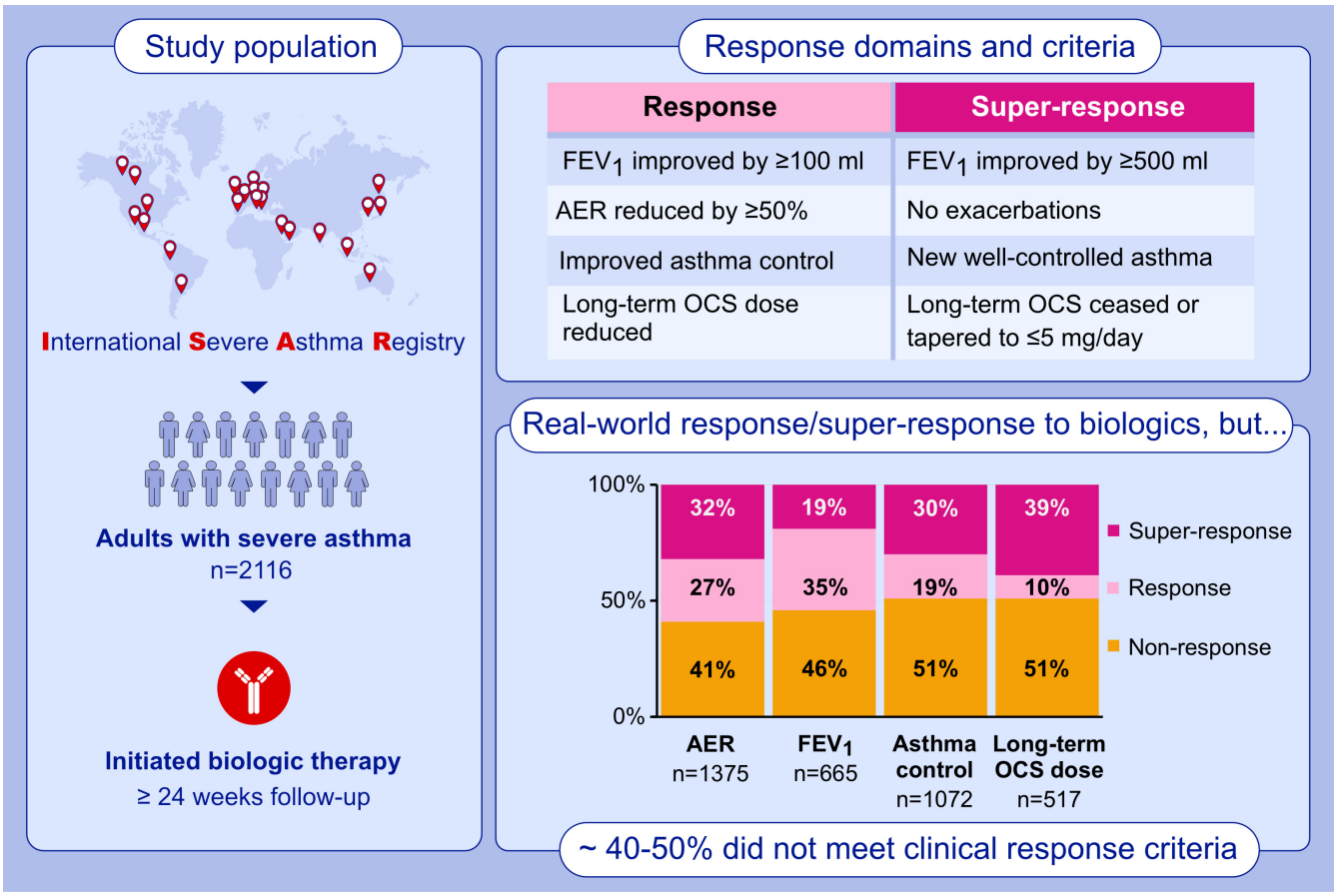
For affiliations refer to page 11.

domains: forced expiratory volume in 1 second (FEV_1) increase by ≥100 mL, improved asthma control, annualized exacerbation rate (AER) reduction ≥50%, and any LTOCS dose reduction. Super-response criteria were: FEV_1 increase by ≥500 mL, new well-controlled asthma, no exacerbations, and LTOCS cessation or tapering to ≤5 mg/day.

Results: 5.3% of ISAR patients met basic RCT inclusion criteria; 2116/8451 started biologics. Biologic initiators had worse baseline impairment than non-initiators, despite having similar biomarker levels. Half or more of initiators had treatment responses: 59% AER reduction, 54% FEV_1 increase, 49% improved control, 49% reduced LTOCS, of which 32%, 19%, 30%, and 39%, respectively, were super-responses. Responses/super-responses were more frequent in biologic initiators than in non-initiators; nevertheless, ~40–50% of initiators did not meet response criteria.

Conclusions: Most patients with severe asthma are ineligible for RCTs of biologic therapies. Biologics are initiated in patients who have worse baseline impairments than non-initiators despite similar biomarker levels. Although biologic initiators exhibited clinical responses and super-responses in all outcome domains, 40–50% did not meet the response criteria.

KEYWORDS
asthma, biologics, clinical response, International Severe Asthma Registry (ISAR), monoclonal antibodies, super-responders



GRAPHICAL ABSTRACT

Data on real-world responsiveness to biologic asthma therapies are lacking. Only ~5% of International Severe Asthma Registry (ISAR) patients met biologic randomized controlled trial eligibility criteria. Compared with ISAR non-biologic users, biologic initiators had more frequent responses/super-responses (lower exacerbation rate, improved lung function and asthma control, and diminished oral corticosteroids use); nevertheless, 40%–50% did not meet clinical response criteria.

Abbreviations: AER, annualized exacerbation rate; FEV_1, forced expiratory volume in 1 second; ISAR, International Severe Asthma Registry; OCS, oral corticosteroids.

1 | INTRODUCTION

Targeted monoclonal antibodies for patients with severe asthma and type 2-high inflammation have been shown to decrease exacerbations, reduce symptoms, improve lung function, and enhance quality of life.[1–9] Anti-interleukin (IL) 5/IL5 receptor (anti-IL5/IL5R) and anti-IL4/13, and, more recently, anti-immunoglobulin E (anti-IgE) agents have also been shown to reduce the long-term oral corticosteroids (LTOCS) burden.[1,5,10,11] However, because only a minority of patients with severe asthma meet entry criteria for the randomized controlled trials (RCTs) of biologic treatments,[12] important clinical questions remain. Pertinently, it is uncertain what proportions of patients in real-world settings achieve responses in different outcome domains and whether treatment responses differ between biologic classes, although data are emerging.[13–15]

RCT participants are generally enriched for the frequent exacerbator phenotype. Evaluating the performance of biologics in a real-world severe asthma population outside of stringently controlled trial conditions is necessary to determine the generalizability of RCT results.[16,17] This is particularly important considering the heterogeneity of severe asthma, which involves the activation of a variety of underlying inflammatory pathways and reflects the impact of differing patient factors and comorbidities.[13,18] Patients with severe asthma often have impairments across different asthma domains, and their responses to biologics may also differ. There are emerging data on real-world responsiveness to biologic medications, but these data typically focus on the response to a single biologic or class of biologics, or come from a single country with uniform biologic eligibility criteria.[15,19–25] Although there are emerging data on the demographics and characteristics of real-world patients with severe asthma who initiate biologics, little is known about those who do not initiate such treatments.[26] For patients with severe asthma who may be eligible for multiple biologic classes, there are no head-to-head studies comparing responses to different biologic agents.

Measuring responses to biologic treatment is also complex.[27] Multiple domains in which responses can be measured include asthma exacerbations, lung function, asthma control, health-related quality of life, and oral corticosteroid (OCS) burden; however, no single measure has shown to be superior or sufficient.[27] Not all patients have the potential to respond in single outcome domains, and clinical responses are likely to be heterogeneous within the severe asthma population. Consequently, single outcome measures may not necessarily allow reliable comparisons between different patients, and it is important to examine multiple outcomes. More data are needed to better understand the nuances and complexity of biologic responses.

With increasing use of biologics to treat severe asthma, it has become evident that some patients respond especially well to these modalities, achieving stabilization or normalization of lung function, freedom from exacerbations and asthma symptoms, and cessation of LTOCS. This group was recently termed "super-responders" by an expert consensus panel.[28] Because most clinical trials report average changes in asthma outcomes, the proportions of super-responders among patients with severe asthma who initiate different biologic therapies remains unknown; estimates from observational studies are between 14% and 24%, depending on the definitions used.[19,29] Little is known about why some patients respond very well to biologics, whereas limited or no clinical effect is apparent in others. As it is also unknown to what extent response and super-response are due to regression to the mean, it is important to observe treatment outcomes in different domains among patients who do not initiate biologics; the impact of comorbid conditions should also be considered.

This study analyzed data from the International Severe Asthma Registry (ISAR), which is unique in including patients from 28 countries across five continents that have diverse criteria for initiating biologic treatments. The objectives were to describe an international, real-world, heterogeneous population of patients with severe asthma, some of whom initiated biologic medications, and to explore treatment responses and super-responses across different asthma outcome domains: annualized exacerbations, lung function, asthma control, and LTOCS dose.

2 | METHODS

2.1 | Study population

LUMINANT was a longitudinal cohort study of patients from ISAR, the largest severe asthma registry in the world (details published previously),[30] which held data from >11,000 patients from 21 countries between May 2017 and 29 October 2021, when data for this study were acquired. The pragmatic design included all patients who met study eligibility criteria, with the primary aim of describing responsiveness to biologic therapies in a real-world severe asthma population; all patients had asthma confirmed by standard lung function criteria described previously,[30] and had uncontrolled asthma on Global Initiative for Asthma (GINA) Step 4 treatment or were on GINA Step 5 treatment, as per the ISAR inclusion criteria.[31] This study included adults aged ≥18 years who were first prescribed a biologic medication after their baseline visit (first ISAR visit) and had a follow-up visit ≥24 weeks after biologic initiation. As a benchmark, responses to ongoing asthma therapies were also studied in ISAR patients who had baseline impairment in predefined study outcome domains (Table 1) but were not initiated on biologics, and whose data were available for baseline and a follow-up visit ≥24 weeks later. Biologic users within the eligible ISAR population were excluded if they had stopped using the biologic before 24 weeks from initiation or had incomplete follow-up data (<24 weeks). Patients who had incomplete data (i.e., no follow-up data related to the outcome domain of interest) or no capacity to respond in a particular outcome domain, such as those who had no exacerbations at baseline, had well-controlled asthma, or were not on LTOCS (Table 1), were excluded from the analysis relating to that particular domain; however, they remained in analyses related to other domains.

TABLE 1 Single-domain definitions of response and super-response in patients with severe asthma between baseline and 12-month visit.

Outcome domain	Definition of responders	Definition of super-responders	Excluded from analysis if
Asthma exacerbations	≥50% reduction in annualized exacerbation rate	Exacerbation elimination	No exacerbations at baseline
FEV_1	≥100 mL improvement in post-bronchodilator FEV_1	≥500 mL improvement in post-bronchodilator FEV_1	Not applicable
Asthma control	Improved asthma control by category (controlled, partial, uncontrolled)	New achievement of well-controlled asthma	Well-controlled asthma at baseline
LTOCS burden	Any reduction in LTOCS dose (mg)	Cessation of LTOCS or tapering to ≤5 mg/day	Not on LTOCS at baseline

Abbreviations: FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids.

2.2 | Exposure

Patients were grouped into those who first started using biologic agents (initiators) and those who continued conventional non-biologic treatments, such as inhaled corticosteroids (ICS), leukotriene receptor antagonists, and long-acting bronchodilators (non-initiators). Initiators were subdivided by biologic class to compare response and super-response attainment between anti-IgE, anti-IL5/IL5R, and anti-IL4/13 treatments. Biologic prescribing criteria differ by country[32] and were not specifically recorded.

2.3 | Outcomes

The index date for follow-up was defined as either the date of biologics initiation or the date of the first ISAR visit for non-initiators. Each response domain was assessed at, or closest to, 12-months post-index (minimum of 24 weeks). Annualized exacerbations were calculated from the date of biologic initiation or the baseline visit, as relevant. For patients with multiple follow-up visits, the visit closest to 12 months was used.

2.3.1 | Definitions of responders and super-responders by outcome domain

The ISAR LUMINANT Working Group predefined four outcome domains and criteria for a response in each (Table 1), based on core items proposed by Pérez de Llano et al to quantify responses to biologics in patients with severe uncontrolled asthma[33]: exacerbations, lung function (FEV_1), symptoms (evaluated by Asthma Control Test), and OCS use. Asthma exacerbations were defined according to American Thoracic Society/European Respiratory Society (ATS/ERS) criteria.[34] Super-responses were defined by Working Group consensus, based on criteria modified from Upham et al.,[28] as summarized in Table 1.

2.4 | Sub-group analyses

Three subgroup analyses were prespecified. First, according to the presence or absence of bronchodilator reversibility in biologics initiators, defined as ≥12% and ≥200 mL FEV_1 improvement following short-acting bronchodilator administration. Second, by Type 2 inflammation gradient in the total cohort, defined by the criteria modified by Heaney et al.[35] Third, based on eligibility (versus ineligibility) for pharmaceutical RCTs, defined as severe asthma and all three of: bronchodilator reversibility on high-dose ICS and a second controller, FEV_1 <80% predicted, and smoking history of <10 pack years. The proportion of the total population that met these three RCT eligibility criteria was determined.

Baseline characteristics were described separately for those initiating different classes of biologic medications—specifically, anti-IgE, anti-IL5/IL5R, and anti-IL4/13—and for non-initiators. The proportions of responders and super-responders among biologic initiators in each outcome domain (assessed closest to 12 months since index date) were compared between biologic classes.

2.5 | Ethical standards and compliance

This study was designed, conducted, and reported in compliance with the European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct (EUPAS30430), and registered with the European Union PAS Register (reference: EUPAS44027), with approval from the Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (reference: ADEPT1421). All ISAR data collection sites have obtained regulatory agreements in compliance with specific data transfer laws, country-specific legislation, and relevant ethical boards. All members of the LUMINANT Working Group approved the protocol.

2.6 | Statistical methods

Baseline characteristics and sub-group analyses, as well as analyses by biologic class, were presented on cross tables with Chi-squared tests, with the pairwise Z-test with Bonferroni correction for comparison of column proportions for categorical variables and independent-sample *t*-test (for two groups), or one-way ANOVA with post-hoc Tukey test (for more than two groups) for continuous variables. $p < 0.05$ was deemed statistically significant. Statistical

analyses were performed with IBM SPSS Statistics for Windows, Version 24 (IBM Corp. Armonk, NY, USA).

3 | RESULTS

Among 8451 eligible adult ISAR patients, 2116 first initiated a biologic after their baseline visit and 6335 did not (Figure 1); 2767 patients were excluded due to biologic use at baseline, 118 due to discontinuing biologic treatment within the first 24 weeks, and 183 due to inadequate follow-up or missing data. Paired data (outcome data available at both the index visit and follow-up visit for a single patient) were available for each of the four outcome domains in subsets of eligible biologic initiators and non-initiators (Figure 1).

3.1 | Baseline characteristics

Baseline characteristics of the study cohorts are provided in Table 2. Compared to non-initiators, biologic initiators were younger (53 vs. 58 years, $p<0.001$), with earlier asthma onset (29 vs. 31 years, $p<0.001$), and a higher proportion were never smokers (62% vs. 45%, $p<0.001$). Biologic initiators had significantly worse baseline asthma status than non-initiators across all outcome domains; however, mean biomarker concentrations (blood eosinophils, exhaled nitric oxide, and total IgE) did not differ significantly between the two groups.

The mean follow-up durations between the index ISAR visit and the follow-up visit closest to 12 months afterwards were 623 ± 662 days in biologic initiators and 385 ± 229 days for non-initiators ($p<0.001$). Tables S1 and S2 show data on time to follow-up.

The baseline (pre-biologic or first ISAR visit) mean annualized exacerbation rate (AER) was significantly higher in biologic initiators compared to non-initiators (3.8 ± 4.0 vs. 1.6 ± 2.0, $p<0.001$); initiators also had significantly inferior baseline mean pre-bronchodilator FEV_1 (1.9 ± 0.8 L vs. 2.1 ± 0.8 L, $p<0.001$). Proportionally more biologic initiators were uncontrolled at baseline (75% vs. 56%, $p<0.001$). Compared with non-initiators, a higher proportion of patients who initiated biologics were on LTOCS at baseline (43% vs. 14%, $p<0.001$).

3.2 | Treatment responsiveness

Tables 3 and 4, and Figure 2, show data on the responses at the visit closest to 12 months after the index date (biologic initiation or first ISAR visit) for FEV_1, asthma exacerbations, asthma control, and LTOCS dose. Statistical comparisons between the responses in biologics initiators and non-initiators are not shown

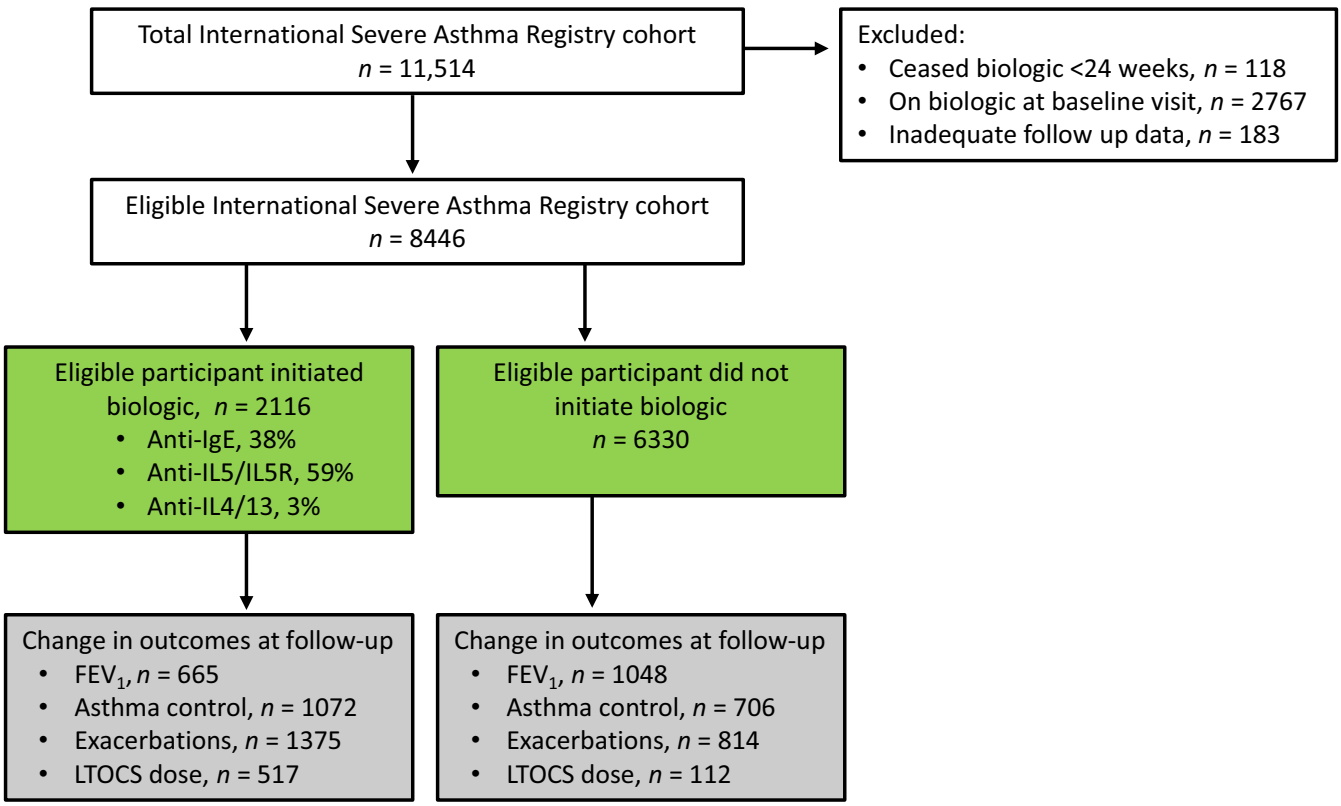


FIGURE 1 LUMINANT study population flow.
Abbreviations: FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; IL4/13, interleukin 4/13; IL5, interleukin 5; IL5R, interleukin 5 receptor; LTOCS, long-term oral corticosteroids.

TABLE 2 Baseline characteristics of LUMINANT cohorts who did or did not initiate biologics.

	Biologic initiators *N* = 2116	Non-biologic *N* = 6335	*p*-Value
Demographics			
Female, % (number)	62 (1311/2116)	62 (3893/6330)	0.71
White, % (number)	78 (1471/1876)	79 (4380/5573)	ND
Age (years), mean ± SD (number)	53 ± 15 (2115)	58 ± 17 (6335)	<0.001
BMI (mg/m^2), mean ± SD	29.1 ± 7.0 (1862)	29.6 ± 8.0 (4995)	0.03
Never smoker, % (number)	62 (1309/2116)	45 (2858/6335)	<0.001
Asthma status			
Asthma onset age (years), mean ± SD (number)	29 ± 19 (1449)	31 ± 20 (2126)	<0.001
PB-FEV$_1$ (L), mean ± SD (number)	1.9 ± 0.8 (1516)	2.1 ± 0.8 (3678)	<0.001
PB-FEV$_1$% predicted, mean ± SD (number)	70 ± 22 (912)	74 ± 25 (1059)	<0.001
FEV$_1$ reversibility, % (number)	16 (178/1116)	12 (346/2885)	<0.001
Uncontrolled asthma, % (number)	75 (973/1299)	56 (1277/2268)	<0.001
Annualized exacerbations, mean ± SD (number)	3.8 ± 4.0 (1711)	1.6 ± 2.0 (2688)	<0.001
Annualized exacerbations, (categorical)			
0	11%	30%	<0.001
1–3	48%	58%	
4–5	20%	7%	
≥6	21%	5%	
Medications			
LTOCS, % (number)	43 (901/2116)	14 (878/6335)	<0.001
Anti-IgE, % (number)	38 (809/2116)	N/A	
Anti-IL5/IL5R, % (number)	59 (1244/2116)	N/A	
Anti-IL4/13, % (number)	3 (63/2116)	N/A	
Biomarkers			
Blood eosinophil count (cells/μL), mean ± SD (number)	598 ± 893 (504)	617 ± 820 (954)	0.7
FeNO (ppb), mean ± SD (number)	49 ± 46 (800)	47 ± 46 (1532)	0.3
IgE (IU/mL), mean ± SD (number)	443 ± 1003 (1273)	417 ± 1306 (2441)	0.5
Sensitized to perennial allergens, % (number)	39 (671/1724)	44 (1844/4177)	0.001

Abbreviations: BMI, body mass index; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL4/13, interleukin 4/13; IL5, interleukin 5; IL5R, interleukin 5 receptor; IU, International Units; LTOCS, long-term oral corticosteroids; ND, comparison not done; PB-FEV$_1$, pre-bronchodilator forced expiratory volume in 1 second; ppb, parts per billion; SD, standard deviation.

TABLE 3 Proportions of the patients who met criteria for responses in single outcome domains among those who did or did not initiate biologic medications.

Response outcome domain	Biologic initiators	Non-biologic
AER reduced ≥50%, % (number)	59 (806/1375)	44 (359/814)
FEV$_1$ improved ≥100 mL, % (number)	54 (358/665)	34 (354/1048)
Asthma control improved, % (number)	49 (524/1072)	42 (299/706)
LTOCS dose reduced, % (number)	49 (255/517)	28 (32/112)

Abbreviations: AER, annualized exacerbation rate; FEV$_1$, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids.

due to significantly differing baseline severity between the groups (Table 1), which was not adjusted for by matching or multivariable adjustment methods. At follow-up, 59% of biologic initiators had a ≥50% reduction in AER (Table 3), 54% had an FEV$_1$ improvement of ≥100 mL, 49% had improved asthma control, and 49% had an LTOCS dose reduction. Examining treatment responsiveness entailed analyzing data on the post-treatment change in each outcome domain at follow-up; Figure S1 shows the changes from baseline in biologic initiators, who had a 32% decrease in AER, a mean FEV$_1$ improvement of 200 mL, a 47% decrease in the proportion with poor asthma control, and a mean OCS dose reduction of 4 mg.

As a benchmark, the same treatment response domains were also examined in non-initiators. Like biologic initiators, the highest response rate in non-initiators was in the AER domain (44%), with

TABLE 4 Proportions of the patients who met criteria for super-responses in single outcome domains among those who did or did not initiate biologic medications.

Super-response outcome domains	Biologic initiators	Non-biologic
Exacerbation elimination, % (number)	32 (442/1375)	30 (242/814)
FEV_1 improved ≥500 mL, % (number)	19 (124/665)	8 (86/1048)
New well-controlled asthma, % (number)	30 (318/1072)	25 (196/706)
LTOCS ceased or tapered to <5 mg/day, % (number)	39 (200/517)	22 (25/112)

Abbreviations: FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids.

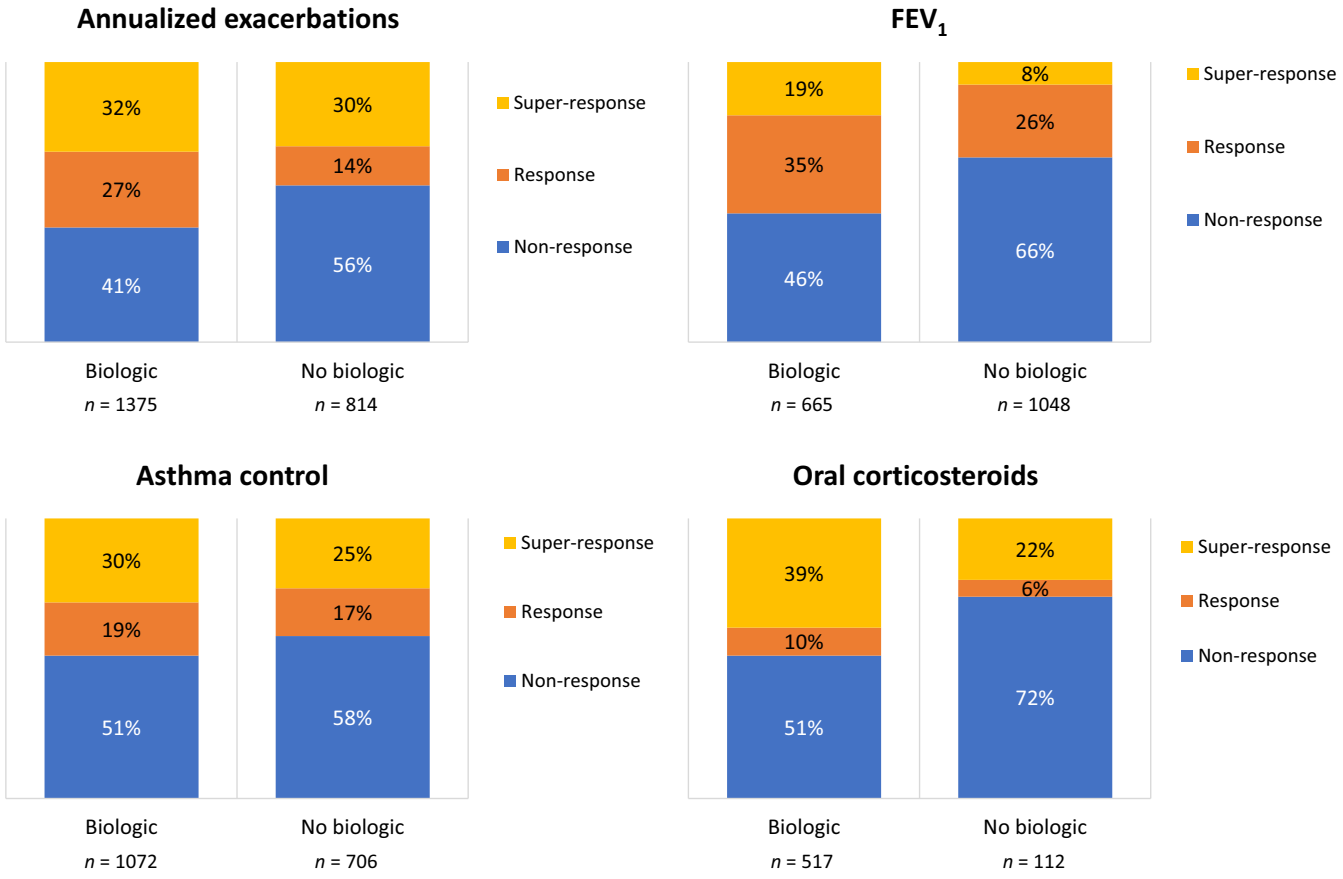


FIGURE 2 Proportions of super-responders (yellow), responders (orange), and non-responders (blue) across single domains among patients who did or did not initiate a biologic medication. Refer to Table 1 for definitions of response and super-response in each outcome. Abbreviation: FEV_1, Forced expiratory volume in 1 second.

34%, 42%, and 28%, respectively, achieving responses in the FEV_1, asthma control, and LTOCS domains (Table 3). However, dissimilar to the before and after results pattern in biologic initiators, the AER in non-initiators increased by 50% from baseline, with no improvement in mean FEV_1, and smaller reductions in mean OCS dose and in the proportion achieving asthma control (Figure S1).

3.2.1 | Super-responders

Biologics initiators had super-responses in all outcome domains (Table 4), with a higher proportion of super-responders in LTOCS reduction (39%), than in AER (32%), FEV_1 (19%), or asthma control (30%). Except for FEV_1, proportionally more biologic initiators achieved super-responses than had responses (Figure 2); nevertheless, super-responders constituted a minority of all biologic initiators, 40%–50% of whom did not reach the predefined response thresholds. Figure 2 also shows that responses and super-responses were consistently more frequent in biologic initiators than they were in non-initiators, across all outcome domains.

3.3 | Subgroup analyses

3.3.1 | Bronchodilator reversibility

Biologic initiators with baseline FEV_1 reversibility were more likely to have an FEV_1 response than were those without (72% vs. 52%, $p < 0.001$), but were not more likely to have responses in other outcome domains (Table S3).

3.3.2 | Type 2 inflammation gradient

Table S4 shows responses in single outcome domains across the T2 inflammation gradient[35] for the entire LUMINANT cohort (the sample was too small to analyze biologic initiators separately); patients with T2 gradient Grade 3 (most likely eosinophilic) had higher response rates than lower grades in AER reduction and elimination of exacerbations (both $p < 0.001$).

3.3.3 | Randomized controlled trial eligibility

Among 4001 study subjects with enough data to determine potential severe asthma RCT eligibility based on satisfying all three criteria (FEV_1 reversibility on high-dose ICS; FEV_1 <80%; smoking history of <10 pack years), only 5.3% (211) fulfilled these RCT eligibility criteria at baseline. Due to limited paired outcome data for this small sub-cohort, further analyses were not performed.

3.3.4 | Sub-analyses by biologic class

Sub-analyses of baseline characteristics by the biologic class subsequently initiated revealed differences in age, body mass index (BMI), smoking status, age at asthma onset, and baseline asthma status, but not in biomarker levels between sub-groups (Table 5). Compared with patients, who initiated an anti-IgE agent, those who started anti-IL5/IL5R therapy were older, had lower BMI and older age of asthma onset, were more likely to be male, had higher exacerbation rates, and were more frequently OCS users.

Table 6 and Figure S2 show responses in the domains of exacerbation reduction, lung function improvement, asthma control, and LTOCS cessation by biologic class. Compared to anti-IgE initiators, patients who initiated anti-IL5/IL5Rs had worse baseline impairment but a greater improvement in AER (response, 62% vs. 52%, $p < 0.001$; super-response, 31% vs. 22%, $p < 0.001$). Anti-IL4/13 initiators had the highest proportions of responders in all domains, with 75% achieving improved asthma control and 58% new well-controlled asthma, although numbers for this group were small.

TABLE 5 Baseline characteristics according to biologic class initiated.

	Anti-IgE	Anti-IL5/IL5R	Anti-IL4/13	Non-biologic	
	n = 809	*n* = 1244	*n* = 63	*n* = 6335	*p*-Value
Demographics					
Female, % (number)	66 (531/809)†	59 (736/1244)†	70 (44/63)	62 (3893/6330)	0.015
White, % (number)	76 (548/725)	80 (878/1099)	87 (45/52)	79 (4380/5573)	ND
Age (years), mean ± SD	50 ± 15 (809)†‡	55 ± 14 (1242)†§¶	49 ± 16 (63)§#	58 ± 17 (6335)‡¶#	<0.001
BMI (mg/m^2), mean ± SD	30 ± 7 (713)†	28.6 ± 7 (1098)†‡	29.3 ± 8 (51)	29.6 ± 8 (4994)‡	<0.001
Never smoker, % (number)	63 (510/809)†	61 (762/1244)‡	59 (37/63)	45 (2858/6335)†‡	<0.001
Asthma status					
Asthma onset age (years), mean ± SD	25 ± 18 (529)†‡	31 ± 19 (885)†	28 ± 21 (35)	31 ± 20 (2126)‡	<0.001
Pre-bronchodilator FEV_1 (L), mean ± SD (number)	1.9 ± 0.8 (580)†‡	1.9 ± 0.8 (892)†§	1.8 ± 0.7 (44)	2.1 ± 0.8 (3679)‡§	<0.001
Post-bronchodilator FEV_1 (L), mean ± SD (number)	2.0 ± 0.8 (611)†	2.0 ± 0.8 (949)‡	2.0 ± 0.7 (44)	2.2 ± 0.8 (3967)†‡	<0.001
FEV_1 reversibility, % (number)	17 (71)	16 (104)†	11 (3)	12 (346)†	0.008
Uncontrolled asthma, % (number)	76 (402/527)†	75 (556/741)‡§	48 (15/31)‡	56 (1277/2268)†§	<0.001
Annualized exacerbations, mean ± SD (number)	3.4 ± 3 (599)†‡§	4.1 ± 4 (1066)†¶#	2.1 ± 2 (46)‡¶	1.6 ± 2 (2688)§#	<0.001
Medications					
LTOCS, % (number)	24 (197)†‡	35 (440)†§¶	19 (12)§	14 (878)‡¶	<0.001
Biomarkers					
IgE (IU/mL), mean ± SD (number)	517 ± 1304 (515)	387 ± 736 (723)	515 ± 548 (35)	417 ± 1306 (2441)	0.27
Blood eosinophil count (cells/μL), mean ± SD (number)	596 ± 584 (187)	605 ± 962 (297)	505 ± 428 (20)	617 ± 820 (954)	0.14
FeNO (ppb), mean ± SD (number)	49 ± 46 (311)	49 ± 47 (473)	23 ± 12 (16)	47 ± 46 (1532)	0.13
Sensitized to perennial allergens, % (number)	40 (267/663)	38 (380/1010)†	47 (24/51)	44 (1844/4177)†	0.001

Note: †, ‡, §, ¶, # denote columns with significant difference on post-hoc testing ($p < 0.05$).

Abbreviations: BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; IL4/13, interleukin 4/13; IL5, interleukin 5; IL5R, interleukin 5 receptor; IU, International Units; LTOCS, long-term oral corticosteroids; ND, comparison not done; ppb, parts per billion; SD, standard deviation.

TABLE 6 Proportions of patients who met criteria for response and super-response in single outcome domains, by biologic class.

	Anti-IgE	Anti-IL5/IL5R	Anti-IL4/13[a]	
	n = 809	*n* = 1244	*n* = 63	*p*-Value
Response				
AER reduced ≥50%, % (number)	52 (253/489)†	62 (542/874)†	69 (18/26)	<0.001
FEV_1 pre improved ≥100 mL, % (number)	49 (144/292)	58 (212/369)	67 (10/15)	<0.001
Asthma control improved, % (number)	49 (215/437)	48 (293/616)	75 (18/24)	0.001
LTOCS dose reduced, % (number)	40 (37/92)	52 (125/240)	50 (2/4)	<0.001
Super-response				
Exacerbation elimination, % (number)	22 (134/618)†	31 (303/987)†	32 (10/31)	<0.001
FEV_1 pre improved ≥500 mL, % (number)	15 (44/292)	22 (80/369)	27 (4/15)	<0.001
New well-controlled asthma, % (number)	27 (116/437)†	31 (188/616)‡	58 (14/24)†‡	<0.001
LTOCS ceased or tapered to <5 mg/day, % (number)	34 (31/92)	43 (103/240)	25 (1/4)	<0.001

Note: †, ‡ denote columns with significant difference on post-hoc testing ($p < 0.05$).

Abbreviations: AER, annualized exacerbation rate; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; IL 4/13, interleukin 4/13; IL 5, interleukin 5; IL5R, interleukin 5 receptor; LTOCS, long-term oral corticosteroids.

[a]Note small numbers of patients on anti-IL4/13 therapy limit interpretation of data from this group.

4 | DISCUSSION

This multicenter, multi-country study of responses to biologic therapies for severe asthma in a non-RCT setting, augments previous single-agent/single-country studies to provide additional insights that can inform the management of severe asthma in real-world practice. Our results show that biologic therapies for severe asthma were associated with improvements in exacerbations, lung function, and symptom control, and with reduced LTOCS use in real-world patients, most of whom did not meet standard eligibility criteria for RCTs. This supports extrapolation of the published efficacy data from RCTs to the real-world setting. In each outcome domain, responses and super-responses were more frequent in biologic initiators than they were in non-initiators. Although a proportion of both biologic initiators and non-initiators achieved a super-response in each outcome domain, these constituted a minority of all patients in each group. The substantial proportion of non-responders, even among biologic initiators, highlights persisting unmet needs and challenges in treating patients with severe asthma. Our findings raise several questions that warrant further investigation; for example, whether starting a biologic treatment earlier, before asthma has caused too much lung damage, might increase the ratio of responders/super-responders.

Compared to non-initiators, patients in ISAR who initiated biologics were more impaired at baseline in all outcome domains; however, both groups had similarly elevated biomarker levels. This is probably because only the most impaired of those patients who met ATS/ERS criteria for severe asthma were selected for biologic treatment, whereas non-initiators, by definition, have done better on conventional treatments. OCS use may be a major driver for biologic initiation. Biologic initiators were also significantly younger than non-initiators, with earlier asthma onset, and were more frequently never-smokers, suggesting possible selection bias among prescribers against older patients and former or current smokers. It remains possible that diagnostic uncertainty (more obesity, more smokers) may be a factor in not initiating biologics; there may also be country-specific reasons, including lack of reimbursement and budgetary constraints. Given markedly differing baseline severity between biologic initiators and non-initiators that was not adjusted for by matching or any multivariable adjustment methods, we cannot draw firm conclusions about the significance of differences in treatment responses between the two groups. Biomarker levels did not distinguish between initiators and non-initiators despite biomarker levels generally predicting response to biologics, highlighting that a "treatable traits" approach is not always being applied in real-world severe asthma populations.

Only 5.3% of this real-world population of patients with severe asthma would have met basic inclusion criteria for RCTs, and even fewer may have met more stringent criteria including exclusion for co-morbidities and the requirement for a certain number of exacerbations in the recent past. Nevertheless, aggregate responses to biologics were similar to the magnitude of response

seen in RCT populations.[1,2,4–7,36–38] Surprisingly, approximately 10% of biologic initiators and 30% of non-initiators had no exacerbations at baseline (and therefore could not "respond" or have responses in this domain evaluated). Such patients meet the ATS/ERS criteria for severe asthma based on other criteria, but are not represented in RCTs that enroll frequent exacerbators. Patients with frequent exacerbations have been shown to have poorer asthma control, higher burdens of ICS and OCS, poorer quality of life, and faster deterioration in lung function compared to those without exacerbations.[39] Less is known about the natural history and characteristics of patients who have severe asthma without recent exacerbations. The low frequency of meeting RCT eligibility criteria among this real-world severe asthma population is important. Hence, we contend that more trials are needed, with a focus on inclusivity and the aim of wider representation of the heterogeneous severe asthma population.

Our results showed that different subgroups had differing responses in asthma outcome domains. For example, FEV_1 response was more frequently seen on univariate analysis of patients with lung function reversibility, but the presence of reversibility was not associated with improvement in other outcomes such as exacerbations.

In most outcome domains, there was a treatment response, although smaller, even among non-initiators, a finding that is often seen in the placebo group of clinical trials, as well as in observational studies of patients treated at severe asthma clinics.[40–42] This indicates that the current standard of care is sufficient for some patients and/or may represent "regression to the mean", an effect of management in specialist centers.[42] The increase in mean AER among non-initiators was largely seen in electronic medical records (EMR) data, in which the "baseline" for non-biologic users may potentially be misclassified, as their first visits in EMR may not fully capture exacerbations; this would lead to an apparent increase in the first year of follow-up.

The degree to which patients responded to treatment with biologic or non-biologic therapies in each outcome domain (non-response, response, super-response) highlights another facet of complex severe asthma heterogeneity. Response rates ranged from 49% to 59% across different outcomes in biologics initiators, and from 28% to 44% in non-initiators. The relatively large proportions of non-responders in each outcome domain suggests an ongoing need for multidimensional assessment in patients with severe asthma, particularly in those who fail to improve or worsen despite biologic therapies.[43] Biologics non-responders deserve particular attention, especially because they cannot be identified based on baseline biomarker levels. Given the complexity of severe asthma and the multiple factors influencing asthma status and outcomes, an individualized approach that addresses multiple treatable traits relevant to each patient—not only inflammatory traits—should be adopted.[44,45] The identification of biologic non-responders also raises the question of whether clinicians facing suboptimal responses should switch biologics earlier or more frequently;[46–48] more data on outcomes after switching are needed.

LTOCS use is one of the most important outcome measures in severe asthma due to the high burden of toxicity associated with OCS exposure.[49] LTOCS and associated toxicities remained a concern in the ISAR cohort, with 43% of biologic initiators and 14% of non-initiators using these medications. Just under half of biologic initiators had at least some reduction of their LTOCS dose at 12 months, and 39% were able to cease these medications (or wean to ≤5 mg/day), whereas only 22% of non-initiators were able to reduce LTOCS to ≤5 mg/day, and even fewer ceased completely. A protocolized steroid reduction program has been shown to be effective in LTOCS cessation (or weaning to adrenal insufficiency) in >80% of patients initiated on benralizumab.[10] As more than 60% of patients in this study were unable to wean from LTOCS even after biologic initiation, it appears that corticosteroid weaning following biologic initiation remains problematic.

Super-response in severe asthma is defined by meeting certain criteria for change in each asthma outcome domain; however, asthma remission is another concept gaining traction.[28,50] A consensus statement on asthma remission allowed different definitions, but the basic premise was that patients should attain normalization (or near normalization) of function—minimal symptoms, and freedom from exacerbations and OCS.[50] The inclusion of lung function in the definition of remission remains controversial due to the presence of patients with "fixed" airflow obstruction; moreover, true remission should be maintained over time. Our data from patients on biologics show super-responses in only one-fifth for FEV_1 (although we did not measure normalization of lung function), one-quarter for asthma control, one-third for exacerbations, and two-fifths for LTOCS dose. Smaller proportions of patients appeared to attain a super-response in these domains without the use of biologics; however, without matching for baseline characteristics, such comparisons should be interpreted with caution. Due to regional inconsistencies in outcome recording, this study was not able to examine overlap of response—how many patients experience normalization across all outcome measures—but it seems likely that only a small fraction of the population would be super-responders across all outcome domains. Remission is an important focus of future investigations in registry studies.

Our analyses are subject to the limitations of an uncontrolled, observational study. For instance, results are the crude proportions that met definitions of response and super-response and may be influenced by differences at baseline. As not all data points were available for all participants, outcomes were examined in subgroups with availability of paired data over the time-course of 24–52 weeks; this has the potential to introduce bias. These limitations also highlight the need for standardized collection of paired outcome measures across multiple outcome domains in severe asthma. Within countries that contribute to ISAR, the historical approach to outcome data collection has been driven largely by region-specific prescribing criteria (for example, exacerbation frequency in the United Kingdom and symptom control scores in Australia). Thus, even this well-characterized severe asthma registry population had incomplete paired data available across all outcome domains, precluding analyses of overall response and super-response across all four outcome measures. In addition, there are regional differences in

biologic prescribing for severe asthma, and it is unclear how region-specific approaches may have influenced outcomes.[32] The low proportion that met inclusion criteria for RCTs may reflect the real-world heterogeneity in severe asthma outside of strict trial inclusion criteria; however, it may also reflect the heterogeneity of biologic prescribing internationally.[32] Requiring ≥24 weeks of biologics use may have excluded patients who did not respond and either stopped or switched biologics, biasing the results towards those for whom biologics worked. Although the visit closest to 12 months after the baseline visit was chosen, the variability in follow-up time may also have influenced the results. Investigating medication side effects was outside the scope of this study but is important and should be done in future studies. Results for patients who did not initiate a biologic treatment are provided only for context and are not appropriate for direct statistical comparison. Regression to the mean may have influenced the super-responder results and could be further evaluated by investigating the baseline severity of responders and super-responders. The LUMINANT study was not designed to identify factors associated with responsiveness to biologic treatments (e.g., sex, race, comorbidities etc.), differences between anti-IL5 and anti-IL5R therapies, or how different biologics affect inflammatory markers. Further examinations of baseline differences and factors that predict response are needed and studies to address such questions are already underway in the ISAR population, the results of which will be published in due course. Also, the data acquisition period included the COVID-19 pandemic, and it is unclear how this may have influenced the outcomes.

5 | CONCLUSIONS

Adults with severe asthma who initiated biologics had greater baseline disease severity than those who did not, but similar biomarker levels. Clinical responses and super-responses to newly prescribed biologics were observed in all four domains of exacerbations, lung function, symptom control, and LTOCS use. In the context of differing baseline impairment, responses to biologics differed by biologic class, but were not complete in any class, thus highlighting persisting unmet treatment needs even among biologic initiators. These findings justify further research to determine whether initiating biologics earlier—before asthma causes irreversible lung damage—may increase the likelihood of achieving a response or super-response.

AUTHOR CONTRIBUTIONS

David B. Price agrees to be accountable for all content and aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Eve Denton, David Price, Lakmini Bulathsinhala, and Ruth Murray had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in data acquisition or analysis and interpretation, as well as the critical revision of the manuscript for important intellectual content. All authors were involved in the conception and design of the study. All authors were responsible for drafting the manuscript. All authors provided additional administrative, technical, and material support. The study was supervised by David Price and Mark Hew. All authors approved the final version of this manuscript and agree to be accountable for all aspects of the work.

AFFILIATIONS

[1]Allergy, Asthma & Clinical Immunology, Alfred Health, Melbourne, Victoria, Australia
[2]Department of Medicine, Central Clinical School, Monash University, Melbourne, Victoria, Australia
[3]Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
[4]Department of Thoracic Medicine, Concord Hospital, Sydney, New South Wales, Australia
[5]Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, New South Wales, Australia
[6]Frazer Institute & PA-Southside Clinical Unit, The University of Queensland, Brisbane, Queensland, Australia
[7]Optimum Patient Care Global, Cambridge, UK
[8]Observational and Pragmatic Research Institute, Singapore, Singapore
[9]BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, Maryland, USA
[10]Department of Respiratory Medicine, University of Leicester, Leicester, UK
[11]Centre for Lung Health, Vancouver General Hospital, Vancouver, British Columbia, Canada
[12]University of British Columbia, Vancouver, British Columbia, Canada
[13]Microbiology Department, College of Medicine, Kuwait University, Kuwait City, Kuwait
[14]Al-Rashed Allergy Center, Ministry of Health, Kuwait City, Kuwait
[15]Department of Pulmonology, University of Tartu and Lung Clinic, Tartu University Hospital, Tartu, Estonia
[16]Centro de Excelencia en Asma y Alergia, Hospital Médica Sur, Mexico City, Mexico
[17]Pulmonary Unit, Hospital Universitario San Ignacio, Bogota, Colombia
[18]Faculty of Medicine, Pontificia Universidad Javeriana, Bogota, Colombia
[19]Department of Pulmonology, King Fahad Medical City, Riyadh, Saudi Arabia
[20]Alfaisal University, Riyadh, Saudi Arabia
[21]PELyon, Lyon, France
[22]Department of Medicine, Division of Pulmonary Medicine, University of Alberta, Alberta, Canada
[23]Faculty of Medicine, Health and Human Sciences, Macquarie Medical School, Macquarie University, Sydney, New South Wales, Australia
[24]Woolcock Institute of Medical Research, Sydney, New South Wales, Australia
[25]PhyMedExp, University of Montpellier, CNRS, INSERM, CHU Montpellier, Montpellier, France
[26]Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium
[27]Department of Epidemiology and Respiratory Medicine, Erasmus Medical Center Rotterdam, Rotterdam, the Netherlands
[28]Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK
[29]Personalized Medicine, Asthma and Allergy, IRCCS Humanitas Research Hospital, Rozzano, Italy
[30]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy
[31]University of Toronto, Toronto, Ontario, Canada
[32]Faculty of Public Health, Medical University, Sofia, Bulgaria
[33]Fiona Stanley Hospital, Perth, Western Australia, Australia
[34]Son Espases University Hospital-IdISBa-Ciberes, Mallorca, Spain
[35]Department of Medicine, Laval University, Quebec City, Quebec, Canada
[36]Department of Respiratory Medicine, Clinical Research Centre, Smurfit Building Beaumont Hospital, RCSI, Dublin, Ireland
[37]Department of Respiratory Medicine, Beaumont Hospital, Dublin, Ireland
[38]Capital and Coast District Health Board, Wellington, New Zealand

[39]CINTESIS@RISE, MEDCIDS, Faculty of Medicine of the University of Porto, Porto, Portugal
[40]Australian Severe Asthma Network, Priority Research Centre for Healthy Lungs, University of Newcastle, Newcastle, New South Wales, Australia
[41]Department of Respiratory and Sleep Medicine, Hunter Medical Research Institute, John Hunter Hospital, New Lambton Heights, New South Wales, Australia
[42]Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, UK
[43]Department of Internal Medicine, Division of Pulmonary Medicine, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan
[44]Kindai University Hospital, Osakasayama, Japan
[45]Guy's Severe Asthma Centre, Guy's Hospital, King's College London, London, UK
[46]Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore, Singapore
[47]Allergy Centre, Tampere University Hospital, Tampere, Finland
[48]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
[49]Clinical Research for Allergy and Respiratory Medicine, CIDEA Foundation, Buenos Aires, Argentina
[50]University Career of Specialists in Allergy and Clinical Immunology at the Buenos Aires University School of Medicine, Buenos Aires, Argentina
[51]Rashid hospital, Dubai Health Authority (DHA), Dubai, United Arab Emirates
[52]AstraZeneca, Cambridge, UK
[53]Lung Division, Royal Brompton & Harefield Hospital, London, UK
[54]School of Medicine, Trinity College Dublin, Dublin, Ireland
[55]Division of Infection, Immunity & Respiratory Medicine, University of Manchester, Manchester, UK
[56]Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece
[57]2nd Respiratory Medicine Department, National and Kapodistrian University of Athens Medical School, Attikon University Hospital, Athens, Greece
[58]Pneumology Service, Lucus Augusti University Hospital, EOXI Lugo, Monforte, Cervo, Spain
[59]School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
[60]Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[61]Department of Respiratory Medicine, Barts Health NHS Trust, London, UK
[62]Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[63]University Hospital St. Ivan Rilski, Sofia, Bulgaria
[64]Department of Respiratory Medicine and Infectious Diseases, Research Unit, Bispebjerg Hospital, Copenhagen, Denmark
[65]Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea
[66]Department of Respiratory Medicine, APHP-Centre University Paris Cité, Cochin Hospital and Institute (UMR1016), Paris, France
[67]Respiratory Evaluation Sciences Program, Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia, Canada
[68]Pulmocare Research and Education Foundation, Pune, India
[69]University Hospital of Aarhus, Aarhus, Denmark
[70]Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan
[71]Department of Internal Medicine, School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
[72]Severe Asthma Network Italy (SANI), Milan, Italy
[73]CINEUMO, Respiratory Research Center, Fundación Neumológica Colombiana, Bogotá, Colombia
[74]Universidad de La Sabana, Chia, Colombia
[75]College of Medicine, University of Sharjah, Sharjah, United Arab Emirates
[76]Respiratory Medicine, Royal Brompton Hospital, London, UK
[77]Department of Respiratory Medicine, Copenhagen University Hospital, Hvidovre, Denmark
[78]Department of Medicine, Division of Allergy and Clinical Immunology, National Jewish Health and University of Colorado School of Medicine, Denver, Colorado, USA
[79]Department of Medicine, NJH Cohen Family Asthma Institute, National Jewish Health, Denver, Colorado, USA
[80]Division of Applied Health Sciences, Centre of Academic Primary Care, University of Aberdeen, Aberdeen, UK

ACKNOWLEDGMENTS

The authors thank Dr David Neil (PhD) of the Observational and Pragmatic Research Institute (OPRI), Ms Pui Yee Lai (MA) of OPRI, and Ms Andrea Lim (BSc, Hons) of OPRI, for editorial support, which was funded by the Observational and Pragmatic Research Institute Pte. Ltd. Finally, a big thank you to our International Severe Asthma Registry collaborators (see online Supplement in Data S1).

FUNDING INFORMATION

This study was conducted by the Observational and Pragmatic Research Institute (OPRI) Pte Ltd and was partially funded by Optimum Patient Care Global Ltd (OPCG) and AstraZeneca. No funding was received by the OPRI for its contribution. The International Severe Asthma Registry (ISAR) is operated by OPCG and co-funded by OPCG and AstraZeneca.

CONFLICT OF INTEREST STATEMENT

Eve Denton declares grants to her institution from AstraZeneca, GlaxoSmithKline, Novartis, Sanofi, Teva, and Seqirus, for unrelated projects and speaker fees from Sanofi. **Mark Hew** declares grants and other advisory board fees (made to his institutional employer) from AstraZeneca, GlaxoSmithKline, Novartis, Sanofi, Teva, and Seqirus, for unrelated projects. **Matthew J. Peters** declares personal fees and non-financial support from AstraZeneca, GlaxoSmithKline, and Sanofi. **John W. Upham** has received speaker fees and consulting fees from Novartis, AstraZeneca, GlaxoSmithKline, Sanofi, and Boehringer Ingelheim. **Lakmini Bulathsinhala** is an employee of the Observational and Pragmatic Research Institute (OPRI), which conducted this study in collaboration with Optimum Patient Care and AstraZeneca. **Trung N. Tran** is an employee of AstraZeneca and may own stock or stock options in AstraZeneca. **Neil Martin** is an employee of AstraZeneca and may own stock or stock options in AstraZeneca. **Celine Bergeron** reports advisory board participation of Sanofi-Regeneron, AstraZeneca, Takeda, and ValeoPharma, honorarium for presentations for AstraZeneca/Amgen, GlaxoSmithKline, Grifols, Sanofi-Regeneron, and ValeoPharma, and grants paid to UBC from BioHaven, Sanofi-Regeneron, AstraZeneca, and GlaxoSmithKline. **Mona Al-Ahmad** has received advisory board and speaker fees from AstraZeneca, Sanofi, Novartis, and GlaxoSmithKline, and received a grant from Kuwait Foundation for the Advancement of Sciences (KFAS). **Alan Altraja** has received lecture fees from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, CSL Behring, GlaxoSmithKline, MSD, Norameda, Novartis, Orion, Sanofi, and Zentiva; sponsorships

from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, CSL Behring, GlaxoSmithKline, MSD, Norameda, Novartis, Sanofi, and Teva; and has participated in advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, MSD, Novartis, Sanofi, and Teva. **Désirée Larenas-Linnemann** reports personal fees from ALK-Abelló, AstraZeneca national and global, Bayer, Chiesi, Grunenthal, Grin, GlaxoSmithKline national and global, Viatris, Menarini, MSD, Novartis, Pfizer, Sanofi, Siegfried, UCB, and Carnot, grants from Abbvie, Bayer, Lilly, Sanofi, AstraZeneca, Pfizer, Novartis, Circassia, UCB, and GlaxoSmithKline, outside the submitted work. **Ruth Murray** is a consultant for Observational and Pragmatic Research Institute (OPRI), which conducted this study in collaboration with Optimum Patient Care and AstraZeneca. **Carlos Andrés Celis-Preciado** declares no relevant conflict of interest. **Riyad Al-Lehebi** has given lectures at meetings supported by AstraZeneca, Boehringer Ingelheim, Novartis, GlaxoSmithKline, and Sanofi, and participated in advisory board fees from GlaxoSmithKline, AstraZeneca, Novartis, and Abbott. **Manon Belhassen** is a full-time employee of PELyon. **Mohit Bhutani** has received speaker and consultant fees for AstraZeneca, GlaxoSmithKline, Sanofi, Covis, Boerhinger Ingelheim, and Valeo. **Sinthia Z. Bosnic-Anticevich** has received honorarium for participation in expert advisory boards and given lectures for Teva Pharmaceuticals, AstraZeneca, GlaxoSmithKline, Meda, Mundipharma, Sanofi, and Mylan, and received unrestricted research grants from Mylan, AstraZeneca, Teva, Mundipharma International, GlaxoSmithKline, and Viatris. **Arnaud Bourdin** has received industry-sponsored grants from AstraZeneca/MedImmune, Boehringer Ingelheim, Cephalon/Teva, GlaxoSmithKline, Novartis, and Sanofi-Regeneron, and has consultancies with AstraZeneca/MedImmune, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Regeneron-Sanofi, Med-in-Cell, Actelion, Merck, Roche, and Chiesi. **Guy G. Brusselle** has received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Teva. He is a member of advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi/Regeneron, and Teva. **John Busby** has received research grants from AstraZeneca and personnel fees from NuvoAir, outside the submitted work. **Giorgio Walter Canonica** has received research grants, as well as lecture or advisory board fees from A. Menarini, Alk-Albello, Allergy Therapeutics, Anallergo, AstraZeneca, MedImmune, Boehringer Ingelheim, Chiesi Farmaceutici, Circassia, Danone, Faes, Genentech, Guidotti Malesci, GlaxoSmithKline, Hal Allergy, Merck, MSD, Mundipharma, Novartis, Orion, Sanofi Aventis, Sanofi, Genzyme/Regeneron, Stallergenes, UCB Pharma, Uriach Pharma, Teva, Thermo Fisher, and Valeas. **Enrico Heffler** declares personal fees for advisory boards participation and/or speaker activities from: Sanofi, Regeneron, GlaxoSmithKline, Novartis, AstraZeneca, Stallergenes-Greer, Circassia, Bosch, Celltrion-Healthcare, Chiesi, and Almirall. **Kenneth R. Chapman** has received grants from AstraZeneca, Boehringer Ingelheim, Bellus, CSL Behring, GlaxoSmithKline, Grifols, Inhibrx, Novartis, Regeneron, Sanofi, Takeda, and Vertex, consulting fees from AstraZeneca, CSL Behring, GlaxoSmithKline, Grifols, Inhibrx, Novartis, Sanofi, and Takeda. He has leadership or fiduciary role in Alpha-1 Canada, the Canadian Thoracic Society, the Alpha-1 Foundation, and AlphaNet Canada. **Jérémy Charriot** reports receiving advisory board and lecture fees from AstraZeneca, GlaxoSmithKline, and Sanofi, receiving consulting fees for Chiesi, and serving as a trial co-investigator for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Sanofi. **George C. Christoff** declares relevant support from AstraZeneca, Sanofi, and Novartis. **Chung, Li Ping** has received speaker and consultancy fees and conference expenses from AstraZeneca, Novartis, GlaxoSmithKline, Boehringer Ingelheim, and Menarini. **Borja 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, and AstraZeneca, outside the submitted work. **Andréanne Côté** declares she has received speaking fees and consultant fees from Sanofi, Regeneron, AstraZeneca, GlaxoSmithKline, and ValeoPharma. She received unrestricted grant support from GlaxoSmithKline. **Richard W. Costello** has received honoraria for lectures from Aerogen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Teva. He is a member of advisory boards for GlaxoSmithKline and Novartis, has received grant support from GlaxoSmithKline and Aerogen, and has patents in the use of acoustics in the diagnosis of lung disease, assessment of adherence and prediction of exacerbations. **Breda Cushen** has received honoraria for lectures and received sponsorship for attending meetings from AstraZeneca, Novartis, and Boehringer Ingelheim. She has participated in advisory boards for Chiesi. **James Fingleton** reports grants, personal fees and non-financial support from AstraZeneca, grants from Genentech, grants, personal fees and non-financial support from GlaxoSmithKline, personal fees and non-financial support from Boehringer Ingelheim, outside the submitted work. **João A. Fonseca** reports grants from, or research agreements with, AstraZeneca, Mundipharma, Sanofi Regeneron, and Novartis. Personal fees for lectures and attending advisory boards: AstraZeneca, GlaxoSmithKline, Mundipharma, Novartis, Sanofi Regeneron, and Teva. **Peter G. Gibson** has received speaker fees and grants to his institution from AstraZeneca, GlaxoSmithKline, and Novartis. **Liam G. Heaney** has received grant funding, participated in advisory boards and given lectures at meetings supported by Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Hoffmann la Roche, GlaxoSmithKline, Novartis, Theravance, Evelo Biosciences, Sanofi, and Teva; he has received grants from MedImmune, Novartis UK, Roche/Genentech Inc, and GlaxoSmithKline, Amgen, Genentech/Hoffman la Roche, AstraZeneca, MedImmune, GlaxoSmithKline, Aerocrine, and Vitalograph; he has received sponsorship for attending international scientific meetings from AstraZeneca, Boehringer Ingelheim, Chiesi, 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. **Erick Wan-Chun Huang** declares no relevant conflict of interest. **Takashi Iwanaga** received speaker bureau fees from Kyorin, GlaxoSmithKline, Novartis, Boehringer Ingelheim, AstraZeneca, and Sanofi. **David J. Jackson** has received speaker fees and consultancy fees from AstraZeneca, GlaxoSmithKline, Sanofi Regeneron, and Boehringer Ingelheim, and research funding from AstraZeneca. **Mariko Siyue Koh** reports grant support from AstraZeneca, and honoraria for lectures and advisory board meetings paid to her hospital (Singapore General Hospital) from GlaxoSmithKline, AstraZeneca, Novartis, Sanofi, and Boehringer Ingelheim, outside the submitted work. **Lauri Lehtimäki** has received personal fees from ALK, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, Novartis, Orion Pharma, and Sanofi. **Jorge Máspero** reports speaker fees, grants or advisory boards for AstraZeneca, Sanofi, GlaxoSmithKline, Novartis, Inmunotek, Menarini, and Noucor. **Bassam Mahboub** reports no conflict of interest. **Andrew N. Menzies-Gow** is an employee of AstraZeneca and may own stock or stock options in AstraZeneca. **Patrick D. Mitchell** has received speaker fees from GlaxoSmithKline, AstraZeneca, Teva and Novartis, and has received grants from AstraZeneca and Teva. **Nikolaos G. Papadopoulos** has been a speaker and/or advisory board member for Abbott, Abbvie, ALK, Asit Biotech, AstraZeneca, Biomay, Boehringer Ingelheim, GlaxoSmithKline, HAL, Faes Farma, Medscape, Menarini, MSD, Novartis, Nutricia, OM Pharma, Regeneron, Sanofi, Takeda, and Viatris. **Andriana I. Papaioannou** has received fees and honoraria from Menarini, GlaxoSmithKline, Novartis, Elpen, Boehringer Ingelheim, AstraZeneca, and Chiesi. **Luis Perez-de-Llano** reports grants, personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from GlaxoSmithKline, grants, personal fees and non-financial support from Teva, personal fees and non-financial support from Chiesi, grants, personal fees and non-financial support from Sanofi, personal fees from MSD, personal fees from Techdow Pharma, grants, personal fees and non-financial support from Faes Farma, personal fees from Leo-Pharma, grants and personal fees from Gebro, and personal fees from Gilead, outside the submitted work. **Diahn-Warng Perng (Steve)** received sponsorship to attend or speak at international meetings, honoraria for lecturing or attending advisory boards, and research grants from the following companies: AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Daiichi Sankyo, Shionogi, and Orient Pharma. **Paul E. Pfeffer** has attended advisory boards for AstraZeneca, GlaxoSmithKline, and Sanofi; has given lectures at meetings supported by AstraZeneca and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca, GlaxoSmithKline, Novartis, and Sanofi, for which his institution received remuneration; and has a current research grant funded by GlaxoSmithKline. **Todor A. Popov** declares relevant research support from Novartis and Chiesi Pharma. **Celeste M. Porsbjerg** has attended advisory boards for AstraZeneca, Novartis, TEVA, and Sanofi-Genzyme; has given lectures at meetings supported by AstraZeneca, Novartis, TEVA, Sanofi-Genzyme, and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca, Novartis, MSD, Sanofi-Genzyme, GlaxoSmithKline, and Novartis; and has received educational and research grants from AstraZeneca, Novartis, TEVA, GlaxoSmithKline, ALK, and Sanofi-Genzyme. **Chin Kook Rhee** received consulting/lecture fees from MSD, AstraZeneca, GlaxoSmithKline, Novartis, Takeda, Mundipharma, Boehringer-Ingelheim, Teva, Sanofi, and Bayer. **Nicolas Roche** reports research funds and fees: Boehringer Ingelheim, Novartis, Pfizer, GlaxoSmithKline. Fees (advisory boards, consultation, education, presentations): Austral, Biosency, AstraZeneca, Chiesi, Menarini, MSD, Nuvaira, Sanofi, and Zambon. **Mohsen Sadatsafavi** has received honoraria from AstraZeneca, Boehringer Ingelheim, Teva, and GlaxoSmithKline for purposes unrelated to the content of this manuscript and has received research funding from AstraZeneca and Boehringer Ingelheim directly into his research account from AstraZeneca for unrelated projects. **Sundeep Salvi** declares research support and speaker fees from Cipla, Glenmark, and GlaxoSmithKline. **Johannes Martin Schmid** declares no relevant conflicts of interest. **Chau-Chyun Sheu** has received speaker fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Pfizer, and has acted as an investigator for trials sponsored by AstraZeneca, Novartis, Roche, Sanofi-Regeneron, Galapagos, Shionogi, Aridis, Bristol Myers Squibb, Insmed, United Therapeutics, Enanta Pharmaceuticals, Areteia Therapeutics, Meiji, and Horizon Therapeutics. **Concetta Sirena** declares no relevant conflict of interest. **Carlos A. Torres-Duque** has received fees as advisory board participant and/or speaker from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis and Sanofi-Aventis; has taken part in clinical trials from AstraZeneca, Novartis, and Sanofi-Aventis; has received unrestricted grants for investigator-initiated studies at Fundacion Neumologica Colombiana from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Grifols, and Novartis. **Laila Salameh** declares no relevant conflict of interest. **Pujan H. Patel** has received advisory board and speaker fees from AstraZeneca, GlaxoSmithKline, Novartis, and Sanofi/Regeneron. **Charlotte Suppli Ulrik** reports personal fees for talks, participation in advisory boards etc. from AstraZeneca, GlaxoSmithKline, Teva, Boehringer Ingelheim, Orion Pharma, Sanofi Genzyme, TFF Pharmaceuticals, Covis Pharma, Berlin-Chemie, Takeda, Chiesi, and Pfizer, outside the submitted work. **Eileen Wang** has received honoraria from AstraZeneca, GlaxoSmithKline, and Genentech. She has been an investigator on studies sponsored by AstraZeneca, GlaxoSmithKline, Genentech, Sanofi, Novartis, and Teva, for which her institution has received funding. **Michael E. Wechsler** reports grants and/or personal fees from Novartis, Sanofi,

Regeneron, Genentech, Sentien, Restorbio, Equillium, Genzyme, Cohero Health, Teva, Boehringer Ingelheim, AstraZeneca, Amgen, GlaxoSmithKline, Cytoreason, Cerecor, Sound Biologics, Incyte, and Kinaset. **David B. Price** has advisory board membership with AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Viatris, and Teva Pharmaceuticals; consultancy agreements with AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Viatris, and Teva Pharmaceuticals; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Chiesi, Viatris, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, and the UK National Health Service; payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Commune Digital, GlaxoSmithKline, Medscape, Viatris, Novartis, Regeneron Pharmaceuticals and Sanofi Genzyme, and Teva Pharmaceuticals; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Novartis, Medscape, and Teva Pharmaceuticals; stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 92.61% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); 5% shareholding in Timestamp which develops adherence monitoring technology; is peer reviewer for grant committees of the UK Efficacy and Mechanism Evaluation Programme, and Health Technology Assessment; and was an expert witness for GlaxoSmithKline.

DATA AVAILABILITY STATEMENT

The de-identified data collected for LUMINANT may be made available to entities wishing to perform appropriate, ethics-approved analyses after approval of the protocol by the International Severe Asthma Registry Steering Committee, with an appropriate signed data access agreement. The LUMINANT study protocol will be made available upon reasonable request to the corresponding author.

ORCID

Eve Denton https://orcid.org/0000-0003-1482-7626
Mark Hew https://orcid.org/0000-0002-7498-0000
Matthew J. Peters https://orcid.org/0000-0002-9649-8741
John W. Upham https://orcid.org/0000-0002-0017-3433
Lakmini Bulathsinhala https://orcid.org/0009-0007-0466-4671
Trung N. Tran https://orcid.org/0000-0001-8003-7601
Neil Martin https://orcid.org/0000-0003-3115-3328
Celine Bergeron https://orcid.org/0000-0003-2585-5411
Mona Al-Ahmad https://orcid.org/0000-0003-2950-5363
Alan Altraja https://orcid.org/0000-0001-7798-9871
Désirée Larenas-Linnemann https://orcid.org/0000-0002-5713-5331
Ruth Murray https://orcid.org/0000-0002-2821-978X
Carlos Andrés Celis-Preciado https://orcid.org/0000-0001-8405-4513
Riyad Al-Lehebi https://orcid.org/0000-0002-3232-6668
Manon Belhassen https://orcid.org/0000-0002-9478-5464
Mohit Bhutani https://orcid.org/0000-0002-1911-4169
Sinthia Z. Bosnic-Anticevich https://orcid.org/0000-0001-5077-8329
Arnaud Bourdin https://orcid.org/0000-0002-4645-5209
Guy G. Brusselle https://orcid.org/0000-0001-7021-8505
John Busby https://orcid.org/0000-0003-4831-7464
Giorgio Walter Canonica https://orcid.org/0000-0001-8467-2557
Enrico Heffler https://orcid.org/0000-0002-0492-5663
Jérémy Charriot https://orcid.org/0000-0002-1420-5774
George C. Christoff https://orcid.org/0000-0003-4549-7711
Li Ping Chung https://orcid.org/0000-0002-7601-9678
Borja G. Cosio https://orcid.org/0000-0002-6388-8209
Andréanne Côté https://orcid.org/0000-0001-5653-4931
Richard W. Costello https://orcid.org/0000-0003-1179-6692
Breda Cushen https://orcid.org/0000-0003-4954-5354
James Fingleton https://orcid.org/0000-0001-9148-196X
João A. Fonseca https://orcid.org/0000-0002-0887-8796
Peter G. Gibson https://orcid.org/0000-0001-5865-489X
Liam G. Heaney https://orcid.org/0000-0002-9176-5564
Erick Wan-Chun Huang https://orcid.org/0000-0002-8462-5790
Takashi Iwanaga https://orcid.org/0000-0001-9155-265X
David J. Jackson https://orcid.org/0000-0002-2299-868X
Mariko Siyue Koh https://orcid.org/0000-0002-1230-0129
Lauri Lehtimäki https://orcid.org/0000-0003-1586-4998
Jorge Máspero https://orcid.org/0000-0001-9750-2346
Bassam Mahboub https://orcid.org/0000-0002-6089-438X
Andrew N. Menzies-Gow https://orcid.org/0000-0001-9707-4986
Patrick D. Mitchell https://orcid.org/0000-0001-5705-9618
Nikolaos G. Papadopoulos https://orcid.org/0000-0002-4448-3468
Andriana I. Papaioannou https://orcid.org/0000-0001-9708-3241
Luis Perez-de-Llano https://orcid.org/0000-0003-2652-6847
Diahn-Warng Perng https://orcid.org/0000-0002-8529-6626
Paul E. Pfeffer https://orcid.org/0000-0003-0369-2885
Todor A. Popov https://orcid.org/0000-0001-5052-5866
Celeste M. Porsbjerg https://orcid.org/0000-0003-4825-9436
Chin Kook Rhee https://orcid.org/0000-0003-4533-7937
Nicolas Roche https://orcid.org/0000-0002-3162-5033
Mohsen Sadatsafavi https://orcid.org/0000-0002-0419-7862
Sundeep Salvi https://orcid.org/0000-0003-4657-9663
Johannes Martin Schmid https://orcid.org/0000-0002-4558-2943
Chau-Chyun Sheu https://orcid.org/0000-0002-7979-3749
Concetta Sirena https://orcid.org/0000-0003-2896-7208
Carlos A. Torres-Duque https://orcid.org/0000-0003-0004-8955
Charlotte Suppli Ulrik https://orcid.org/0000-0001-8689-3695
Eileen Wang https://orcid.org/0000-0002-3149-3229
Michael E. Wechsler https://orcid.org/0000-0003-3505-2946
David B. Price https://orcid.org/0000-0002-9728-9992

REFERENCES

1. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev*. 2014;2014(1):CD003559.
2. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2115-2127.
3. FitzGerald JM, Bleecker ER, Menzies-Gow A, 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(1):51-64.
4. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128-2141.
5. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371(13):1189-1197.
6. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371(13):1198-1207.
7. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9842):651-659.
8. Castro M, Zangrilli J, Wechsler ME, 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(5):355-366.
9. Farne HA, Wilson A, Milan S, Banchoff E, Yang F, Powell CVE. Anti-IL-5 therapies for asthma. *Cochrane Database Syst Rev*. 2022;7(7):CD010834.
10. Menzies-Gow A, Gurnell M, Heaney LG, et al. Oral corticosteroid elimination via a personalised reduction algorithm in adults with severe, eosinophilic asthma treated with benralizumab (PONENTE): a multicentre, open-label, single-arm study. *Lancet Respir Med*. 2022;10(1):47-58.
11. Bousquet J, Humbert M, Gibson PG, et al. Real-world effectiveness of omalizumab in severe allergic asthma: a meta-analysis of observational studies. *J Allergy Clin Immunol Pract*. 2021;9(7):2702-2714.
12. Chen W, Tran TN, Sadatsafavi M, et al. Impact of initiating biologics in patients with severe asthma on long-term oral corticosteroids or frequent rescue steroids (GLITTER): data from the international severe asthma registry. *J Allergy Clin Immunol Pract*. 2023;11(9):2732-2747.
13. Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. 2020;55(1):1900588.
14. McGregor MC, Krings JG, Nair P, Castro M. Role of biologics in asthma. *Am J Respir Crit Care Med*. 2018;199(4):433-445.
15. Milger K, Suhling H, Skowasch D, et al. Response to biologics and clinical remission in the adult German asthma net severe asthma registry cohort. *J Allergy Clin Immunol Pract*. 2023;11(9):2701-2712.e2.
16. Paoletti G, Pepys J, Casini M, et al. Biologics in severe asthma: the role of real-world evidence from registries. *Eur Respir Rev*. 2022;31(164):210278.
17. Lemiere C, Taillé C, Lee JK, et al. Impact of baseline clinical asthma characteristics on the response to mepolizumab: a post hoc meta-analysis of two phase III trials. *Respir Res*. 2021;22(1):184.
18. McDowell PJ, Heaney LG. Different endotypes and phenotypes drive the heterogeneity in severe asthma. *Allergy*. 2020;75(2):302-310.
19. Harvey ES, Langton D, Katelaris C, et al. Mepolizumab effectiveness and identification of super-responders in severe asthma. *Eur Respir J*. 2020;55(5):1902420.
20. Jackson DJ, Burhan H, Menzies-Gow A, et al. Benralizumab effectiveness in severe asthma is independent of previous biologic use. *J Allergy Clin Immunol Pract*. 2022;10(6):1534-1544.e4.
21. Charles D, Shanley J, Temple S-N, Rattu A, Khaleva E, Roberts G. Real-world efficacy of treatment with benralizumab, dupilumab, mepolizumab and reslizumab for severe asthma: a systematic review and meta-analysis. *Clin Exp Allergy*. 2022;52(5):616-627.
22. Rojo-Tolosa S, González-Gutiérrez MV, Sánchez-Martínez JA, et al. Impact of Omalizumab in patients with severe uncontrolled asthma and possible predictive biomarkers of response: a real-life study. *Pharmaceutics*. 2023;15(2):523.
23. Soendergaard MB, Hansen S, Bjerrum A-S, 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(4):238-2022.
24. Kallieri M, Zervas E, Fouka 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. *Eur Respir J*. 2022;60(66):468.
25. Di Bona D, Crimi C, D'Uggento AM, et al. Effectiveness of benralizumab in severe eosinophilic asthma: distinct sub-phenotypes of response identified by cluster analysis. *Clin Exp Allergy*. 2022;52(2):312-323.
26. Mansur AH, Gonem S, Brown T, et al. Biologic therapy practices in severe asthma; outcomes from the UK severe asthma registry and survey of specialist opinion. *Clin Exp Allergy*. 2023;53(2):173-185.
27. Khaleva E, Rattu A, Brightling C, et al. Definitions of non-response and response to biological therapy for severe asthma: a systematic review. *ERJ Open Res*. 2023;9(3):444-2022.
28. Upham JW, Le Lievre C, Jackson DJ, et al. Defining a severe asthma super-responder: findings from a Delphi process. *J Allergy Clin Immunol Pract*. 2021;9(11):3997-4004.
29. Eger K, Kroes JA, Ten Brinke A, Bel EH. Long-term therapy response to anti–IL-5 biologics in severe asthma—a real-life evaluation. *J Allergy Clin Immunol Pract*. 2021;9(3):1194-1200.
30. FitzGerald JM, Tran TN, Alacqua M, et al. International severe asthma registry (ISAR): protocol for a global registry. *BMC Med Res Methodol*. 2020;20(1):212.
31. Wang E, Wechsler ME, Tran TN, et al. Characterization of severe asthma worldwide: data from the international severe asthma registry. *Chest*. 2020;157(4):790-804.
32. Porsbjerg CM, Menzies-Gow AN, Tran TN, et al. Global variability in administrative approval prescription criteria for biologic therapy in severe asthma. *J Allergy Clin Immunol Pract*. 2022;10(5):1202-1216.e23.
33. Pérez de Llano L, Dávila I, Martínez-Moragón E, et al. Development of a tool to measure the clinical response to biologic therapy in uncontrolled severe asthma: the FEV(1), exacerbations, oral corticosteroids, symptoms score. *J Allergy Clin Immunol Pract*. 2021;9(7):2725-2731.
34. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343-373.
35. Heaney LG, Perez de Llano L, Al-Ahmad M, et al. Eosinophilic and noneosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort. *Chest*. 2021;160(3):814-830.
36. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid–sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376(25):2448-2458.
37. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486-2496.

38. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378(26):2475-2485.
39. Kupczyk M, Ten Brinke A, Sterk PJ, et al. Frequent exacerbators–a distinct phenotype of severe asthma. *Clin Exp Allergy*. 2014;44(2):212-221.
40. Gibeon D, Heaney LG, Brightling CE, et al. Dedicated severe asthma services improve health-care use and quality of life. *Chest*. 2015;148(4):870-876.
41. Denton E, Lee J, Tay T, et al. Systematic assessment for difficult and severe asthma improves outcomes and halves oral corticosteroid burden independent of monoclonal biologic use. *J Allergy Clin Immunol Pract*. 2020;8(5):1616-1624.
42. Redmond C, Heaney LG, Chaudhuri R, et al. Benefits of specialist severe asthma management: demographic and geographic disparities. *Eur Respir J*. 2022;60(6):2200660.
43. Hew M, Menzies-Gow A, Hull JH, et al. Systematic assessment of difficult-to-treat asthma: principles and perspectives. *J Allergy Clin Immunol Pract*. 2020;8(7):2222-2233.
44. Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. *Lancet*. 2018;391(10118):350-400.
45. Pérez de Llano L, Cisneros C, Domínguez-Ortega J, et al. Response to monoclonal antibodies in asthma: definitions, potential reasons for failure, and therapeutic options for suboptimal response. *J Investig Allergol Clin Immunol*. 2023;33(1):1-13.
46. Numata T, Araya J, Miyagawa H, et al. Effectiveness of switching biologics for severe asthma patients in Japan: a single-center retrospective study. *J Asthma Allergy*. 2021;14:609-618.
47. Papaioannou AI, Fouka E, Papakosta D, Papiris S, Loukides S. Switching between biologics in severe asthma patients. When the first choice is not proven to be the best. *Clin Exp Allergy*. 2021;51(2):221-227.
48. Bakakos A, Rovina N, Bakakos P. Treatment challenges in severe eosinophilic asthma: differential response to anti-IL-5 and anti-IL-5R therapy. *Int J Mol Sci*. 2021;22(8):3969.
49. Timm V, Timo E, Christoph T, Roland B. Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature. *Eur Respir J*. 2018;52(4):1800703.
50. Menzies-Gow A, Bafadhel M, Busse WW, et al. An expert consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol*. 2020;145(3):757-765.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Denton E, Hew M, Peters MJ, et al. Real-world biologics response and super-response in the International Severe Asthma Registry cohort. *Allergy*. 2024;00:1-17. doi:10.1111/all.16178