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► **To cite this version:**

Eve Denton, Mark Hew, Matthew Peters, John Upham, Lakmini Bulathsinhala, et al.. Real-world biologics response and super-response in the International Severe Asthma Registry cohort. *Allergy*, 2024, 79 (10), pp.2700-2716. 10.1111/all.16178 . hal-04621544

**HAL Id: hal-04621544**

**<https://hal.science/hal-04621544v1>**

Submitted on 17 Oct 2024

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

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# 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

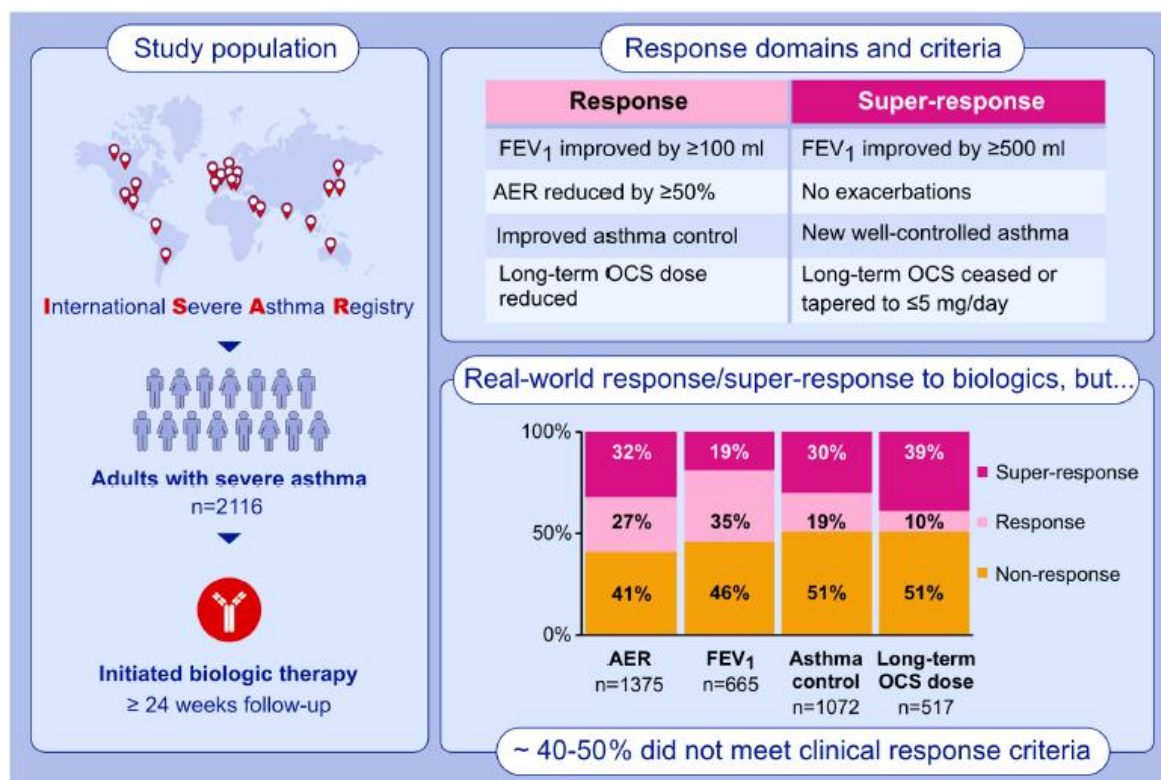
Adults in the International Severe Asthma Registry (ISAR) with  $\geq 24$  weeks of follow-up were grouped into those who did, or did not, initiate biologics (anti-IgE, anti-IL5/IL5R, anti-IL4/13). Treatment responses were examined across four domains: forced expiratory volume in 1 second (FEV<sub>1</sub>) increase by  $\geq 100$  mL, improved asthma control, annualized exacerbation rate (AER) reduction  $\geq 50\%$ , and any LTOCS dose reduction. Super-response criteria were: FEV<sub>1</sub> increase by  $\geq 500$  mL, new well-controlled asthma, no exacerbations, and LTOCS cessation or tapering to  $\leq 5$  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<sub>1</sub> 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.



#### 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<sub>1</sub>, 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.<sup>1-9</sup> 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.<sup>1, 5, 10, 11</sup> However, because only a minority of patients with severe asthma meet entry criteria for the randomized controlled trials (RCTs) of biologic treatments,<sup>12</sup> 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.<sup>13-15</sup>

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.<sup>16, 17</sup> 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.<sup>13, 18</sup> 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.<sup>15, 19-25</sup> 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.<sup>26</sup> 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.<sup>27</sup> 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.<sup>27</sup> 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.<sup>28</sup> 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.<sup>19, 29</sup> 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),<sup>30</sup> 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,<sup>30</sup> 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.<sup>31</sup> This

study included adults aged  $\geq 18$  years who were first prescribed a biologic medication after their baseline visit (first ISAR visit) and had a follow-up visit  $\geq 24$  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  $\geq 24$  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	$\geq 50\%$ reduction in annualized exacerbation rate	Exacerbation elimination	No exacerbations at baseline
FEV <sub>1</sub>	$\geq 100$ mL improvement in post-bronchodilator FEV <sub>1</sub>	$\geq 500$ mL improvement in post-bronchodilator FEV <sub>1</sub>	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 $\leq 5$ mg/day	Not on LTOCS at baseline

Abbreviations: FEV<sub>1</sub>, 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<sup>32</sup> 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<sup>33</sup>: exacerbations, lung function (FEV<sub>1</sub>), symptoms (evaluated by Asthma Control Test), and OCS use. Asthma exacerbations were defined according to American Thoracic Society/European Respiratory Society (ATS/ERS) criteria.<sup>34</sup> Super-responses were defined by Working Group consensus, based on criteria modified from Upham et al.,<sup>28</sup> 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  $\geq 12\%$  and  $\geq 200$  mL FEV<sub>1</sub> 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.<sup>35</sup> 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<sub>1</sub>  $< 80\%$  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.

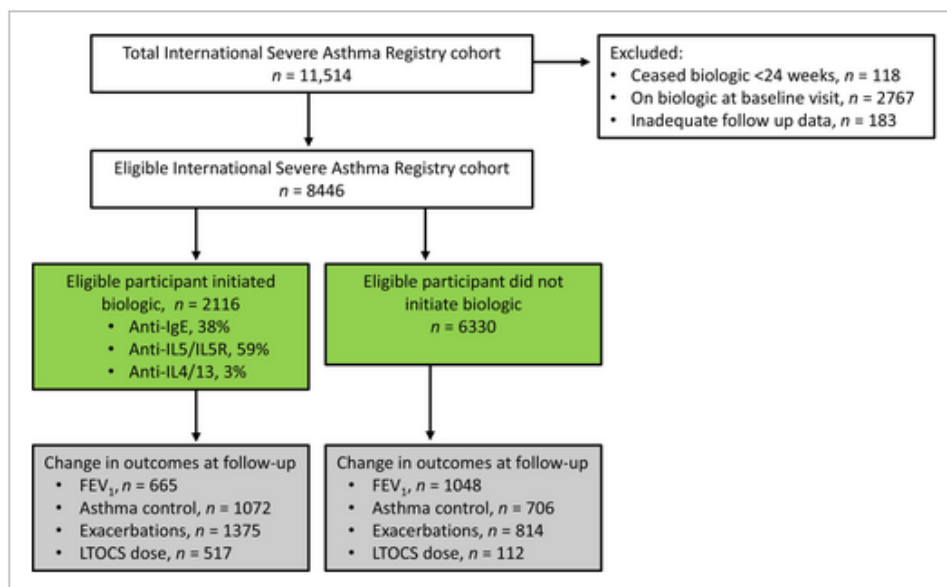
## 2.6 Statistical methods

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).



**FIGURE 1**

LUMINANT study population flow. Abbreviations: FEV<sub>1</sub>, 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.

#### 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.

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

	Biologic initiators	Non-biologic	<i>p</i> -Value
	<i>N</i> = 2116	<i>N</i> = 6335	
<b>Demographics</b>			
Female, % (number)	62 (1311/2116)	62 (3893/6330)	0.71
White, % (number)	78 (1471/1876)	79 (4380/5573)	ND
Age (years), mean $\pm$ SD (number)	53 $\pm$ 15 (2115)	58 $\pm$ 17 (6335)	<0.001
BMI (mg/m <sup>2</sup> ), mean $\pm$ SD	29.1 $\pm$ 7.0 (1862)	29.6 $\pm$ 8.0 (4995)	0.03
Never smoker, % (number)	62 (1309/2116)	45 (2858/6335)	<0.001
<b>Asthma status</b>			
Asthma onset age (years), mean $\pm$ SD (number)	29 $\pm$ 19 (1449)	31 $\pm$ 20 (2126)	<0.001
<b>PB-FEV<sub>1</sub> (L), mean <math>\pm</math> SD (number)</b>			
PB-FEV <sub>1</sub> (L), mean $\pm$ SD (number)	1.9 $\pm$ 0.8 (1516)	2.1 $\pm$ 0.8 (3678)	<0.001
<b>PB-FEV<sub>1</sub>% predicted, mean <math>\pm</math> SD (number)</b>			
PB-FEV <sub>1</sub> % predicted, mean $\pm$ SD (number)	70 $\pm$ 22 (912)	74 $\pm$ 25 (1059)	<0.001
<b>FEV<sub>1</sub> reversibility, % (number)</b>			
FEV <sub>1</sub> reversibility, % (number)	16 (178/1116)	12 (346/2885)	<0.001
<b>Uncontrolled asthma, % (number)</b>			
Uncontrolled asthma, % (number)	75 (973/1299)	56 (1277/2268)	<0.001
<b>Annualized exacerbations, mean <math>\pm</math> SD (number)</b>			
Annualized exacerbations, mean $\pm$ SD (number)	3.8 $\pm$ 4.0 (1711)	1.6 $\pm$ 2.0 (2688)	<0.001
<b>Annualized exacerbations, (categorical)</b>			
0	11%	30%	<0.001
1–3	48%	58%	
4–5	20%	7%	
$\geq 6$	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/ $\mu$ L), mean $\pm$ SD (number)	598 $\pm$ 893 (504)	617 $\pm$ 820 (954)	0.7
FeNO (ppb), mean $\pm$ SD (number)	49 $\pm$ 46 (800)	47 $\pm$ 46 (1532)	0.3
IgE (IU/mL), mean $\pm$ SD (number)	443 $\pm$ 1003 (1273)	417 $\pm$ 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<sub>1</sub>, pre-bronchodilator forced expiratory volume in 1 second; ppb, parts per billion; SD, standard deviation.

The mean follow-up durations between the index ISAR visit and the follow-up visit closest to 12 months afterwards were 623  $\pm$  662 days in biologic initiators and 385  $\pm$  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  $\pm$  4.0 vs. 1.6  $\pm$  2.0,  $p < 0.001$ ); initiators also had significantly inferior baseline mean pre-bronchodilator FEV<sub>1</sub> (1.9  $\pm$  0.8 L vs. 2.1  $\pm$  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<sub>1</sub>, asthma exacerbations, asthma control, and LTOCS dose. Statistical comparisons between the responses in biologics initiators and non-initiators are not shown 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  $\geq 50\%$  reduction in AER

(Table 3), 54% had an FEV<sub>1</sub> improvement of  $\geq 100$  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<sub>1</sub> improvement of 200 mL, a 47% decrease in the proportion with poor asthma control, and a mean OCS dose reduction of 4 mg.

**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.

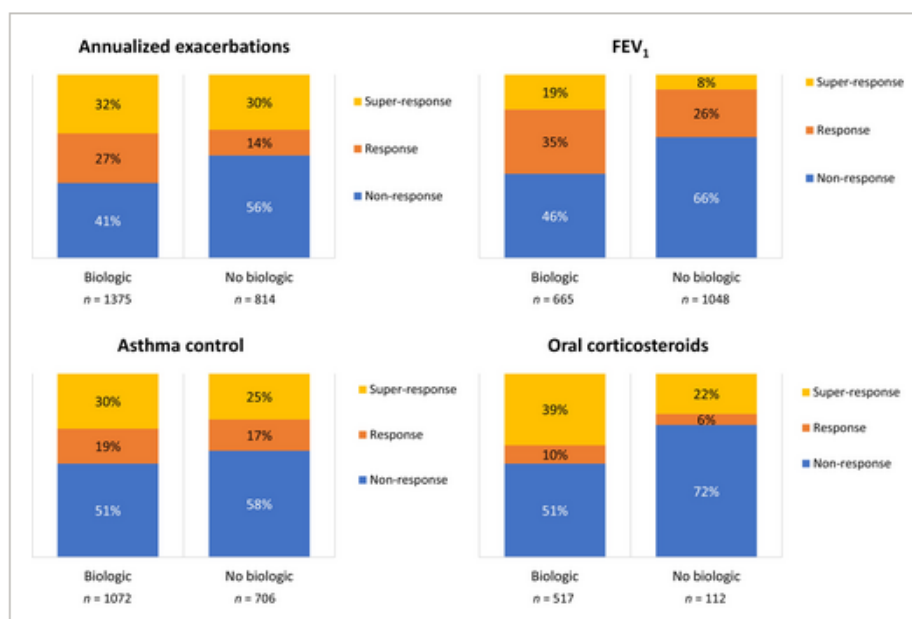
Response outcome domain	Biologic initiators	Non-biologic
AER reduced $\geq 50\%$ , % (number)	59 (806/1375)	44 (359/814)
FEV <sub>1</sub> improved $\geq 100$ mL, % (number)	54 (358/665)	34 (354/1048)
Asthma control improved, % (number)	49 (524/1072)	42 (299/706)
LTOCS dose reduced, % (number)	49 (255/517)	28 (32/112)

Abbreviations: AER, annualized exacerbation rate; FEV<sub>1</sub>, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids.

**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 <sub>1</sub> improved $\geq 500$ 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<sub>1</sub>, 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<sub>1</sub>, Forced expiratory volume in 1 second.

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 34%, 42%, and 28%, respectively, achieving responses in the FEV<sub>1</sub>, 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<sub>1</sub>, 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<sub>1</sub> (19%), or asthma control (30%). Except for FEV<sub>1</sub>, 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<sub>1</sub> reversibility were more likely to have an FEV<sub>1</sub> 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<sup>35</sup> 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<sub>1</sub> reversibility on high-dose ICS; FEV<sub>1</sub> <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 5.** Baseline characteristics according to biologic class initiated.

	Anti-IgE	Anti-IL5/IL5R	Anti-IL4/13	Non-biologic	p-Value
	n = 809	n = 1244	n = 63	n = 6335	
<b>Demographics</b>					
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 <sup>2</sup> ), 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
<b>Asthma status</b>					
Asthma onset age (years), mean ± SD	25 ± 18 (529)†‡	31 ± 19 (885)†	28 ± 21 (35)	31 ± 20 (2126)‡	<0.001
Pre-bronchodilator FEV <sub>1</sub> (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 <sub>1</sub> (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 <sub>1</sub> 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

<b>Medications</b>					
LTOCS, % (number)	24 (197)†‡	35 (440)†§¶	19 (12)§	14 (878)‡¶	<0.001
<b>Biomarkers</b>					
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<sub>1</sub>, 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 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 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 <sup>a</sup>	p-Value
	n = 809	n = 1244	n = 63	
<b>Response</b>				
AER reduced ≥50%, % (number)	52 (253/489)†	62 (542/874)†	69 (18/26)	<0.001
FEV <sub>1</sub> 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
<b>Super-response</b>				
Exacerbation elimination, % (number)	22 (134/618)†	31 (303/987)†	32 (10/31)	<0.001
FEV <sub>1</sub> 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<sub>1</sub>, 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.

<sup>a</sup> 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.<sup>1, 2, 4-7, 36-38</sup> 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.<sup>39</sup> 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<sub>1</sub> 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.<sup>40-42</sup> 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.<sup>42</sup> 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.<sup>43</sup> 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.<sup>44, 45</sup> The identification of biologic non-responders also raises the question of whether clinicians facing suboptimal responses should switch biologics earlier or more frequently;<sup>46-48</sup> 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.<sup>49</sup> 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  $\leq 5$  mg/day), whereas only 22% of non-initiators were able to reduce LTOCS to  $\leq 5$  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.<sup>10</sup> 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.<sup>28, 50</sup> 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.<sup>50</sup> 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<sub>1</sub> (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.<sup>32</sup> 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.<sup>32</sup> Requiring  $\geq 24$  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.

## 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, Viatrix, 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, Boehringer 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 Viatrix. **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, Immunotek, 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.**

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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, Viatriis, and Teva Pharmaceuticals; consultancy agreements with AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Viatriis, and Teva Pharmaceuticals; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Chiesi, Viatriis, 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, Viatriis, 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.

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