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REVIEW

Efficacy of Biologics in Reducing Exacerbations Requiring Hospitalization or an Emergency Department Visit in Patients with Moderate or Severe, Uncontrolled Asthma

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ABSTRACT

Introduction: Patients with moderate or severe, uncontrolled asthma are often prescribed biologic therapies to improve disease control and reduce asthma exacerbations. The efficacy of different biologics in reducing asthma exacerbations associated with hospitalization or an emergency department (ED) visit has varied across randomized controlled trials (RCTs). This study summarizes published US Food and Drug Administration-approved biologic efficacy data for exacerbations that required hospitalization or an ED visit in patients with moderate or severe, uncontrolled asthma.

Prior Presentation: Findings from this literature review were previously presented in a poster at the American Thoracic Society (ATS) International Conference, May 17–22, 2024, San Diego, CA, USA; however, the literature search dates for this manuscript differ from the published abstract (Panettieri RA et al. *Am J Respir Crit Care Med* 2024;209:A5379) and poster presentation.

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***Methods*:** A PubMed literature search (24 May 2024) identified phase 2b/3 RCTs of omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, or tezepelumab. Annualized asthma exacerbation rate (AAER) ratios for exacerbations that required hospitalization or an ED visit, or hospitalization regardless of an ED visit, were extracted. A pooled efficacy estimate of the AAER ratio for exacerbations that required hospitalization or an ED visit across the RCTs was assessed using a meta-analysis based on a random effects model. The percentage of total variation across all included RCTs that was due to heterogeneity was calculated (I^2).

***Results*:** Among 308 articles identified, nine publications describing 10 RCTs reported relevant AAER ratio data. No suitable omalizumab data were identified. In all trials, biologic treatment showed a reduction versus placebo in the AAER for exacerbations that required hospitalization or an ED visit, except in one of two benralizumab studies and both reslizumab studies. The pooled efficacy estimate showed a 56% reduction (95% CI 37–69) in the AAER for exacerbations requiring hospitalization or an ED visit (I^2, 59.93%; $p = 0.0075$). One of three mepolizumab trials and both tezepelumab trials showed a reduction versus placebo in the AAER for exacerbations that required hospitalization regardless of an ED visit.

***Conclusion*:** These findings suggest that there may be differential effects of biologics in reducing exacerbations that require hospitalization or an ED visit in patients with moderate or severe, uncontrolled asthma.

Keywords: Biologic; Efficacy; Emergency department; Exacerbations; Hospitalization; Literature review; Moderate asthma; Randomized placebo-controlled trial; Severe asthma

Key Summary Points

Why carry out this study?

Severe asthma is associated with increased mortality, morbidity, and healthcare resource utilization, particularly hospitalization and emergency department (ED) visits.

Patients with moderate or severe, uncontrolled asthma are often prescribed biologic therapies to improve disease control and reduce asthma exacerbations. The efficacy of different biologics in reducing asthma exacerbations associated with hospitalization or an ED visit has varied across randomized controlled trials.

This analysis summarized published data from phase 2b and phase 3 randomized controlled trials of US Food and Drug Administration-approved biologics that reported the annualized asthma exacerbation rate for exacerbations that required hospitalization or an ED visit in patients with moderate or severe, uncontrolled asthma.

What was learned from the study?

Mepolizumab, benralizumab, dupilumab, and tezepelumab demonstrated efficacy in reducing exacerbations that required hospitalization or an ED visit compared with placebo. The mepolizumab and tezepelumab studies also showed a reduction in exacerbations that required hospitalization regardless of an ED visit.

There may be differential effects of biologics in reducing exacerbations that require hospitalization or an ED visit; further investigation of large, real-world data sources is warranted.

INTRODUCTION

Severe asthma is associated with increased mortality, morbidity, and healthcare resource utilization [1–3]. Furthermore, direct medical costs for treatment and hospitalization associated with severe, uncontrolled asthma are three times greater than those for patients with severe, controlled disease [4, 5]. Several biologics are approved by the US Food and Drug Administration (FDA) for the treatment of moderate or severe, uncontrolled asthma, with varying indications depending on the underlying inflammation they treat [6]. Four biologics have indications for patients with an eosinophilic phenotype (mepolizumab, reslizumab, benralizumab, and dupilumab [dupilumab is also indicated for oral corticosteroid-dependent asthma]) [7–10], one biologic (omalizumab) is indicated for allergic asthma [11], and one biologic (tezepelumab) is approved for severe asthma without restriction by phenotype [12].

Across randomized controlled trials (RCTs), FDA-approved biologics for moderate or severe, uncontrolled asthma have demonstrated variable efficacy in reducing asthma exacerbations that require hospitalization or an emergency department (ED) visit [13–22]. This analysis summarizes published data from phase 2b and phase 3 RCTs of FDA-approved biologics that reported the annualized asthma exacerbation rate (AAER) for exacerbations that required hospitalization or an ED visit in patients with moderate or severe, uncontrolled asthma.

METHODS

Literature Search

A PubMed literature search was performed on 24 May 2024, to identify publications from phase 2b and phase 3 RCTs of FDA-approved biologics (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, and tezepelumab) in patients with moderate or severe, uncontrolled asthma [7–12]. The definition of moderate or severe, uncontrolled asthma must have been consistent with the Global Initiative for Asthma (GINA) 2023 report (i.e., receiving medium-to-high-dose inhaled corticosteroids with up to two additional controllers) [23]. The full search terms can be found in Table S1 (see Supplementary Material).

Inclusion and Exclusion Criteria

Included publications assessed AAER reductions for exacerbations associated with hospitalization or an ED visit. The terms 'hospital admission' or 'admission' were accepted as hospitalization. The terms 'emergency room' and 'emergency department' were considered synonymous. Data inclusion focused on FDA-approved doses and the indicated population for each biologic. Pooled approved doses from a single trial were included if they enabled a comparison. Pooled data reported from multiple trials were excluded to simplify comparisons of data across biologics. Long-term extension studies and studies that did not meet the GINA 2023 definition of moderate or severe, uncontrolled asthma (e.g., studies of patients with mild-to-moderate asthma or oral corticosteroid dose reduction studies) were also excluded. There were no restrictions on the date of publication or other aspects of the RCT design.

Data Extraction

Data were extracted for exacerbations that required hospitalization or an ED visit and/or those that required hospitalization regardless of an ED visit. AAERs were captured as rate ratios (biologic treatment:placebo). A 95% confidence interval (CI) that excluded 1 (null effect) for the AAER ratio was considered evidence of efficacy in reducing exacerbations.

Statistical Analysis

The meta-analysis was conducted using 'metafor', a meta-analysis package for R. A pooled efficacy estimate across RCTs was assessed using a meta-analysis based on a random effects model (DerSimonian–Laird method) [24] for

studies reporting AAER ratio data for exacerbations that required hospitalization or an ED visit. The model estimated the percentage of total variation across all RCTs included that was due to heterogeneity rather than chance (I^2) [25]. An I^2 of 0% to less than 50% indicated low heterogeneity, 50–75% indicated moderate heterogeneity, and greater than 75–100% indicated high heterogeneity. For the heterogeneity test, a p value that rejected the null hypothesis of no heterogeneity at a significance level of 5% indicated that heterogeneity exists. Owing to the limited data available, a meta-analysis of the studies reporting exacerbations that required hospitalization regardless of an ED visit was not conducted.

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Among 308 articles identified, nine publications reported AAER ratio data for exacerbations that required hospitalization or an ED visit from 10 RCTs and were included in this analysis [13–17, 19–22]. These publications accounted for five out of six licensed biologic therapies for moderate or severe, uncontrolled asthma. No omalizumab publications were identified that used the 2023 GINA definition of moderate or severe, uncontrolled asthma and reported AAER ratio data for exacerbations requiring hospitalization or an ED visit [26]. Data from the phase 2b PATHWAY study reporting exacerbations that required hospitalization or an ED visit for tezepelumab were previously not published. However, because the data were available to the authors, they were included to enable comparison with published data from other studies. Five of the identified publications reported AAER ratios for exacerbations requiring hospitalization regardless of an ED visit for two biologics only: mepolizumab and tezepelumab [16–18, 21, 22]. Study designs varied between the different biologics, including treatment duration, number of prior asthma exacerbations, baseline inhaled corticosteroid dose, and baseline blood eosinophil counts (Table 1).

A total of 7 out of 10 biologic studies (3/3 for mepolizumab, 1/2 for benralizumab, 1/1 for dupilumab, and 2/2 for tezepelumab) demonstrated efficacy compared with placebo in reducing the AAER of exacerbations that required hospitalization or an ED visit (Fig. 1) [13, 14, 16, 20–22]. Both reslizumab studies (Study 1 and Study 2) had upper 95% CIs greater than or equal to 1 and therefore did not show efficacy in reducing the AAER compared with placebo [AAER ratios (95% CI): 0.66 (0.32–1.36) and 0.69 (0.29–1.65), respectively] [15]. The benralizumab study (CALIMA) also did not demonstrate efficacy in reducing exacerbations that required hospitalization or an ED visit compared with placebo [AAER ratio (95% CI): 1.23 (0.64–2.35)] [19]. The calculated pooled efficacy estimate across all included RCTs showed a reduction of 56% (95% CI 37–69) in the AAER for exacerbations that required hospitalization or an ED visit with biologic treatment compared with placebo (Fig. 1). Moderate heterogeneity of 59.93% (p = 0.0075) was calculated for the effect estimates between trials.

Of the five out of ten biologic studies identified with data available for exacerbations that required hospitalization regardless of an ED visit, three studies showed an improvement compared with placebo in the AAER for exacerbations that required hospitalization regardless of an ED visit [1/3 for mepolizumab (MENSA) and 2/2 for tezepelumab (NAVIGATOR and PATHWAY)] (Fig. 2) [17, 20, 21]. Mepolizumab demonstrated a numerical trend of reducing the AAER; however, two out of the three mepolizumab studies (MUSCA and DREAM) had upper 95% CIs of greater than or equal to 1 and therefore did not demonstrate a reduction in the AAER compared with placebo [AAER ratios (95% CI): 0.31 (0.08–1.24) and 0.61 (0.28–1.33), respectively] [16, 22]. Tezepelumab demonstrated an improvement in the AAER for exacerbations that required hospitalization regardless of an ED visit

Table 1 Characteristics of included RCTs

Biologic and approved dose regimen	Trial (NCT number)	Dose regimen and route of administration	Treatment duration, weeks	Study population, *N*[a]	Number of prior asthma exacerbations[b]	ICS dose at baseline	BEC at baseline, cells/μL	Percentage of exacerbations that required hospitalization or ED visit	Percentage of exacerbations that required hospitalization
Mepolizumab 100 mg SC Q4W [7]	MUSCA phase 3b (NCT02281318) [16]	100 mg SC Q4W	24	551	≥ 2	High	≥ 300 cells/μL in previous year or ≥ 150 cells/μL at screening	Tx: 6% Pbo: 8%	Tx: 4% Pbo: 6%
	MENSA phase 3 (NCT01691521) [21]	100 mg SC Q4W	32	385	≥ 2			Tx: 10% Pbo: 11%	Tx: 4% Pbo: 6%
	DREAM phase 2b (NCT01000506) [22]	75 mg IV Q4W	52	308	≥ 2	High	History of eosinophilic inflammation[c] (e.g., ≥ 300 cells/μL)	Tx: 14% Pbo: 18%	Tx: 9% Pbo: 8%
Reslizumab 3 mg/kg IV Q4W[d] [10]	Study 1, phase 3 (NCT01287039) [15]	3 mg/kg IV Q4W	52	489	≥ 1	Medium to high	≥ 400 cells/μL	Tx: 16% Pbo:12%	Tx: NR Pbo: NR
	Study 2, phase 3 (NCT01285323) [15]	3 mg/kg IV Q4W	52	464	≥ 1			Tx: 3% Pbo: 2%	Tx: NR Pbo: NR
Benralizumab 30 mg SC Q8W [9]	SIROCCO phase 3 (NCT01928771) [13]	30 mg SC Q8W	48	534[e]	≥ 2	Medium to high	Study population grouped by < or ≥ 300 cells/μL[f]	Tx: 9% Pbo: 14%	Tx: NR Pbo: NR
	CALIMA phase 3 (NCT01914757) [19]	30 mg SC Q8W	56	487[e]	≥ 2			Tx: 8% Pbo: 4%	Tx: NR Pbo: NR

Table 1 continued

Biologic and approved dose regimen	Trial (NCT number)	Dose regimen and route of administration	Treatment duration, weeks	Study population, *N*[a]	Number of prior asthma exacerbations[b]	ICS dose at baseline	BEC at baseline, cells/μL	Percentage of exacerbations that required hospitalization or ED visit	Percentage of exacerbations that required hospitalization
Dupilumab 200 mg SC Q2W 300 mg SC Q2W [8]	LIBERTY ASTHMA QUEST phase 3 (NCT02414854) [14]	Pooled doses 200 mg/300 mg SC Q2W	52	1902	≥ 1	Medium to high	No minimum criteria	Tx: 7% Pbo: 7%	Tx: NR Pbo: NR
Tezepelumab 210 mg SC Q4W [12]	NAVIGATOR phase 3 (NCT03347279) [20]	210 mg SC Q4W	52	1059	≥ 2	Medium to high	No minimum criteria	Tx: 6% Pbo: 13%	Tx: 3% Pbo: 9%
	PATHWAY phase 2b (NCT02054130) [17, 18]	210 mg SC Q4W	52	275	≥ 2			Tx: 15% Pbo: 25%	Tx: 10% Pbo: 19%

Data for the DREAM (mepolizumab) study were reported only for the 75 mg IV Q4W dosage and not the approved 100-mg SC Q4W dosage. For dupilumab, only pooled data from one study (QUEST) were available and were included to enable comparisons. Data for the PATHWAY (tezepelumab) study for exacerbations associated with hospitalization or an ED visit are unpublished; however, because the data were available to the authors, they were included to enable comparisons with published data from other studies

BEC blood eosinophil count, *ED* emergency department, *FeNO* fractional exhaled nitric oxide, *ICS* inhaled corticosteroid, *IgE* immunoglobulin E, *IV* intravenously, *NR* not reported, *Pbo*, placebo, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q8W* every 8 weeks, *RCT* randomized controlled trial, *SC* subcutaneously, *Tx* treatment

[a]Based on the number of patients receiving the biologic dosage stated or matched placebo

[b]In the 12 months before enrolment into each study

[c]Defined as at least one of the following at study entry or in the previous year: a sputum eosinophil count of ≥ 3%, a FeNO level of ≥ 50 ppb, an asthma-related peripheral BEC of ≥ 300 cells/μL, or prompt deterioration of asthma control after a ≤ 25% reduction in regular maintenance ICS or oral corticosteroids

[d]Administration dose and frequency dependent on serum IgE and body weight

[e]Number of patients from SIROCCO and CALIMA with baseline BECs of ≥ 300 cells/μL (primary analysis population)

[f]Exacerbation data were extracted for patients with baseline BECs of ≥ 300 cells/μL (primary analysis population)

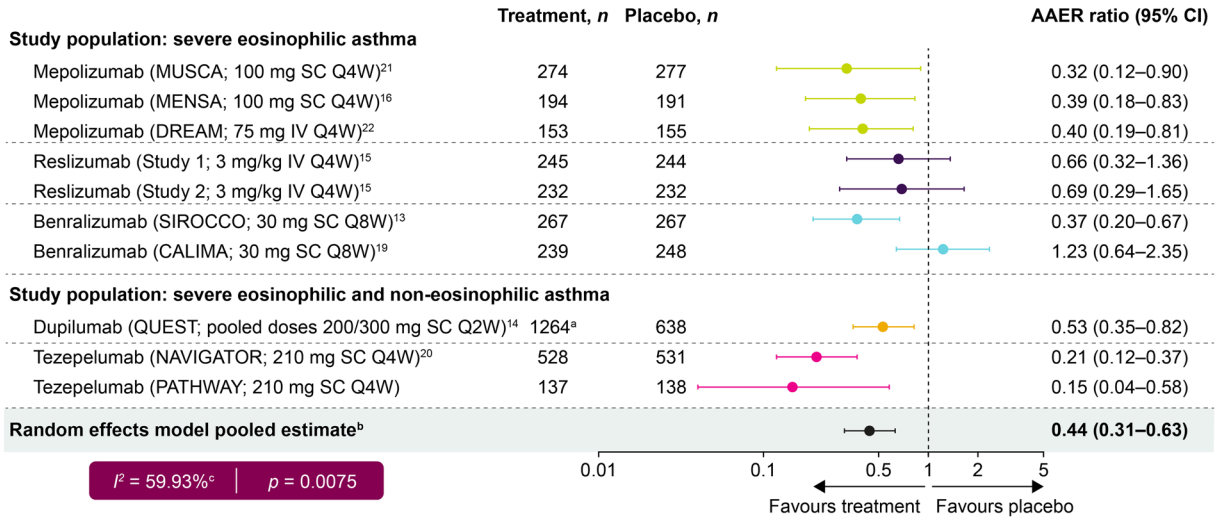

Fig. 1 AAER ratios for exacerbations requiring hospitalization or an ED visit. [a]*n* denotes the number of pooled patients receiving the 200 mg and 300 mg doses in the QUEST (dupilumab) study. [b]The model estimated the percentage of total variation across all RCTs included that was due to heterogeneity rather than chance (I^2). [c]The I^2 was 59.93% [i.e., moderate heterogeneity (range 50–75%)]. *AAER* annualized asthma exacerbation rate, *CI* confidence interval, *ED* emergency department, *IV* intravenously, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *Q8W* every 8 weeks, *SC* subcutaneously

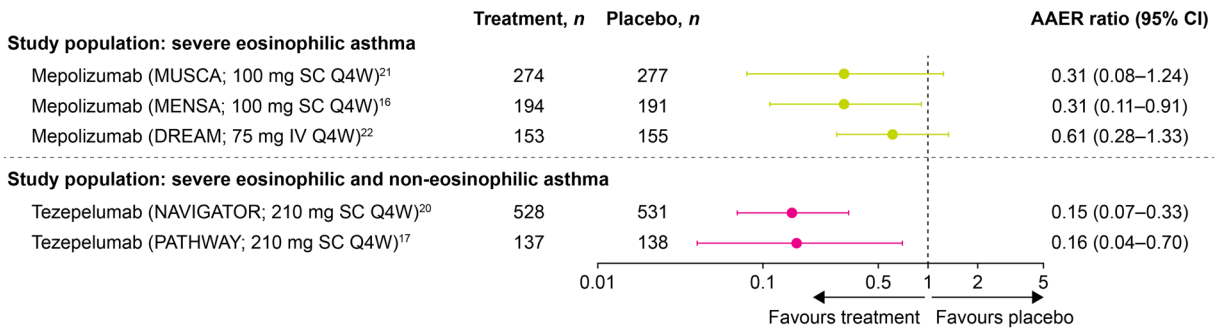

Fig. 2 AAER ratios for exacerbations requiring hospitalization regardless of an ED visit. *AAER* annualized asthma exacerbation rate, *CI* confidence interval, *IV* intravenously, *Q4W* every 4 weeks, *SC* subcutaneously

in both studies (NAVIGATOR and PATHWAY) [17, 20].

DISCUSSION

Of the FDA-approved biologics for moderate or severe, uncontrolled asthma, mepolizumab, benralizumab, dupilumab, and tezepelumab had evidence of reducing exacerbations that required hospitalization or an ED visit. A pooled efficacy estimate demonstrated that, across included phase 2b and phase 3 RCTs, exacerbations that required hospitalization or an ED visit were reduced by 56% with biologic treatment compared with placebo. Of the observed variation in the effect estimates among trials, approximately 60% was due to true heterogeneity. For exacerbations requiring hospitalization regardless of an ED visit, published data were only available for

mepolizumab and tezepelumab. One of the three mepolizumab studies and both of the tezepelumab studies demonstrated evidence of meaningful reductions in exacerbations that required hospitalization regardless of an ED visit. Among all RCTs included in this review, tezepelumab studies demonstrated the greatest reductions in exacerbations that required hospitalization or an ED visit compared with placebo.

In a recently published systematic literature review, Kyriakopoulos et al. performed a meta-analysis to assess the efficacy of FDA-approved biologics in patients with moderate or severe, or severe, uncontrolled asthma [27]. The meta-analysis found that RCTs showed a 60% reduction in exacerbations that required hospitalization [AAER ratio (95% CI): 0.40 (0.27–0.60)] with biologic treatment compared with the respective comparator groups (e.g., placebo or standard of care). Their study also noted that the greatest numerical reductions in asthma exacerbations that required hospitalization were observed with tezepelumab compared with placebo. Compared with the systematic literature review of Kyriakopoulos et al., the present review excluded RCTs that did not study moderate or severe, uncontrolled asthma as defined by the 2023 GINA guidance, long-term extension studies, and oral corticosteroid dose reduction studies [27]. Therefore, the present review reports data that are more representative of a patient population meeting the contemporary definition of moderate or severe, uncontrolled asthma, albeit restricted to RCTs.

Regarding real-world outcomes, the CHRONICLE study found that patients in the USA with specialist-treated severe asthma had a substantial burden of exacerbations requiring hospitalization and/or an ED visit, with 15% and 19% of patients experiencing exacerbation-related ED visits and hospitalizations, respectively, in the 12 months before enrolment [3]. The incidence rate of asthma-related hospitalizations was 14 per 100 person-years. The International Severe Asthma Registry reported a greater global burden in terms of healthcare resource use, with 27% and 28% of patients with severe asthma experiencing asthma-related hospitalizations and ED visits, respectively, in the 12 months before entry into their national registry [28]. The CHRONICLE study found that, during the 6 months after starting biologic therapy, patients with severe asthma had 59% and 53% reductions in the rates of asthma-related hospitalizations and ED visits, respectively, compared with the 6 months before starting therapy [3, 27].

A limitation of this analysis is that comparisons between biologics should be interpreted with caution given variances in RCT study designs and populations. As we evaluated double-blind, randomized, placebo-controlled trials, factors associated with study design and population would be present equally in both trial arms. As a result, the most relevant differences between trials would be expected to be the treatment intervention, which is consistent with the observation that 60% of the variability across estimates was due to true heterogeneity. Nevertheless, effects of other factors cannot be completely ruled out. Additionally, due to the small number of studies, it was not feasible to explore potential explanations for the observed heterogeneity (e.g., via meta-regression). In addition, the biologics have different mechanisms of action, which may partly explain the observed variance in efficacy. Furthermore, the data reported are restricted to patients within an RCT setting who meet strict eligibility and adherence criteria. However, it is reassuring that real-world outcomes from CHRONICLE are consistent with the pooled RCT efficacy estimate. Comparing the differential effects of licensed biologics on healthcare resource utilization from large, real-world data sources might provide further granularity regarding effectiveness in a real-world setting that is more representative of patients with moderate or severe, uncontrolled asthma.

CONCLUSIONS

Of the FDA-approved biologics for moderate or severe, uncontrolled asthma, mepolizumab, benralizumab, dupilumab, and tezepelumab demonstrated efficacy in reducing exacerbations that required hospitalization or an ED visit compared with placebo; however, efficacy estimates varied

across biologics and studies. These findings suggest that there may be differential effects of biologics in reducing exacerbations that require hospitalization or an ED visit in patients with moderate or severe, uncontrolled asthma. Further investigations of large, real-world data sources would be valuable to build on these randomized trial results.

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Data Availability. All data and materials used in this research are freely available. References have been provided.

Declarations

Conflict of Interest. Reynold A. Panettieri Jr. has received research support from ACTIV-1, Agomab Therapeutics, AstraZeneca, Janssen Pharmaceuticals, the Research Institute for Fragrance Materials, Teva Pharmaceuticals, and Vault Health; has served as a consultant/advisory board member for AstraZeneca, Genentech, Praesidia Biotherapeutics, and the Research Institute for Fragrance Materials; and has received speaker fees from AstraZeneca, Merck Group, and Sanofi. Monica Kraft has received research support from the American Lung Association, AstraZeneca, Janssen, the National Institutes of Health, Sanofi, and Synairgen with funds paid to the Icahn School of Medicine and University of Arizona and has received personal fees from AstraZeneca, Chiesi, Genentech, Kinaset Therapeutics, and Sanofi. Mario Castro has received grants/research support from the American Lung Association, AstraZeneca, Gala Therapeutics, Genentech, GSK, the National Institutes of Health, Novartis, the Patient-Centered Outcomes Research Institute, PULMATRiX, Sanofi-Aventis, Shionogi, and Theravance Biopharma; consultancy fees from Allakos, Amgen, Arrowhead, AstraZeneca, Genentech, Merck, Novartis, OM Pharma, Pioneering Medicines, Regeneron Pharmaceuticals, Sanofi, and Teva Pharmaceuticals; and royalties from Aer Therapeutics. Magdalena Bober, Max Shelkrot and Christopher S. Ambrose are employees of AstraZeneca and may own stock or stock options in AstraZeneca. Andrew W. Lindsley is an employee of Amgen and owns stock in Amgen.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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