Original Article

Real-World Effectiveness Study of Benralizumab for Severe Eosinophilic Asthma: ZEPHYR 2

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What is already known about this topic? Benralizumab demonstrated clinical and economic benefits in real-world analyses of patients with severe eosinophilic asthma, but its effectiveness in patients with different baseline eosinophil values or previous treatment with biologics and its long-term impact are unknown.

What does this article add to our knowledge? Benralizumab reduced asthma exacerbation rates in patients with blood eosinophil counts less than 150, more than or equal to 150, 150 to less than 300, less than 300, and more than or equal to 300 cells/μL, who switched from another biologic, or with up to 24 months of follow-up after benralizumab initiation.

How does this study impact current management guidelines? The results show that add-on benralizumab is effective for long-term control of severe eosinophilic asthma in patients with varying eosinophil counts or who switched from other biologics, which can potentially reduce patients' dependence on corticosteroids.

BACKGROUND: Benralizumab is an mAb therapy for severe eosinophilic asthma. Real-world data on its clinical impact in various patient populations such as patients with varying eosinophil levels, previous biologic use, and extended follow-up in the United States are limited.

OBJECTIVE: To determine the effectiveness of benralizumab in different asthmatic patient cohorts and its long-term clinical impact.

METHODS: Patients with asthma treated with benralizumab from November 2017 to June 2019 with 2 or more exacerbations in the 12 months before benralizumab initiation (index) were included in this pre-post cohort study that used medical, laboratory, and pharmacy US insurance claims. Asthma exacerbation rates in the 12 months pre and post index were compared. Nonmutually exclusive patient cohorts were defined by blood eosinophil counts (<150, ≥150, 150-<300, <300, and ≥300 cells/μL), a switch from another biologic, or follow-up for 18 or 24 months post index.

RESULTS: There were 429 patients in the eosinophil cohort, 349 in the biologic-experienced cohort, and 419 in the extended follow-up cohort. In all eosinophil cohort subgroups, the asthma exacerbation rate decreased from 3.10-3.55 per patient-year (PPY) pre index to 1.11-1.72 PPY post index (52%-64% decrease; $P < .001$). Similar decreases were observed in patients switching from omalizumab (3.25 to 1.25 PPY [62%]) or mepolizumab (3.81 to 1.78 PPY [53%]) to benralizumab and those followed up for 18 months (3.38 to 1.18 PPY [65%]) or 24 months (3.38 to 1.08 PPY [68%]) (all $P < .001$). In the extended follow-up cohort, 39% and 49% had no exacerbations in the 0 to 12 months and the 12 to 24 months post index, respectively.

CONCLUSIONS: Benralizumab achieved significantly improved asthma control in real-world patients with different blood eosinophil counts, including eosinophil counts ranging from less than 150 to greater than or equal to 300 cells/μL, switching from

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Abbreviations used
COPD- chronic obstructive pulmonary disease
CS- corticosteroid
ICD- International Classification of Diseases
ICS- inhaled corticosteroid
LABA- long-acting β-agonist
OCS- oral corticosteroid
PPY- per patient-year

other biologics, or treated for up to 24 months. **© 2023 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).** **(J Allergy Clin Immunol Pract 2023;11:2150-61)**

Key words: *Severe eosinophilic asthma; Exacerbation; Real-world study; Benralizumab*

INTRODUCTION

The eosinophilic phenotype is observed in most cases (up to 84%)[1] of severe asthma and is distinguished by elevated eosinophil counts in the blood or sputum along with subepithelial fibrosis, thickening, and inflammation that result in airway obstruction.[2,3] The presence of subepithelial fibrosis is also associated with disease severity.[4] High blood eosinophil counts are associated with increased frequency of exacerbations and life-threatening respiratory failure,[5,6] and counts greater than 150 cells/μL can identify patients with severe eosinophilic asthma,[7] who also have a higher comorbidity burden and are more difficult to treat than those with a noneosinophilic phenotype.[8]

Immunotherapy has altered the treatment landscape for severe asthma, and the European Respiratory Society /American Thoracic Society joint task force now recommends the use of mAbs that block specific inflammatory pathways as an add-on treatment for adults with severe, uncontrolled eosinophilic asthma (>150 cells/μL) or corticosteroid (CS)-dependent asthma.[9] Benralizumab, which targets the IL-5 receptor alpha chain, was approved by the US Food and Drug Administration in November 2017 as an add-on treatment for patients 12 years and older with severe asthma and the eosinophilic phenotype.[10,11] Several randomized phase 3 trials and open-label extension studies have demonstrated the efficacy and safety of benralizumab for the treatment of severe asthma,[12-18] and real-world evidence supports its effectiveness in improving clinical outcomes such as the rate of exacerbations and oral CS (OCS) dependence.[19-21] The clinical and economic impacts of benralizumab treatment in patients with severe eosinophilic asthma in the United States were also recently reported in the ZEPHYR 1 study, where patients experienced significant reductions in the rate of exacerbations after initiating benralizumab.[22]

Nonetheless, there are limited data on the clinical impact of benralizumab in specific subsets of patients with severe asthma that are frequently seen in real-world practice settings and may be excluded from clinical trials, such as patients with different (high or low) blood eosinophil counts, who have previous experience with other biologics, or who have received benralizumab treatment over an extended period of time. Such data are needed to guide clinical management decisions (eg, regarding the use of OCSs).

To assess the real-world benefits of benralizumab for patients with severe eosinophilic asthma with various clinical profiles, the present study analyzed a larger patient population than in previous work that was stratified into the following nonmutually exclusive cohorts: patients with blood eosinophil counts ranging from less than 150 to greater than or equal to 300 cells/μL, patients who had received treatment with other biologics before benralizumab, or patients with up to 24 months of benralizumab use. We hypothesized that benralizumab treatment would lead to significant improvements in clinical parameters in these different cohorts.

METHODS

Data source

Medical, laboratory, and pharmacy US insurance claims data from November 2016 to June 2020 were obtained from the PatientSource and DiagnosticSource databases (stabilized claims data supplied by Symphony Health Solutions Corporation, Blue Bell, PA). These databases contain health care information on approximately 274 million patients annually in the United States, with insurance coverage provided by a range of payers. To comprehensively capture patients' encounters in the health care system, patients were required to have 1 or more claim for benralizumab from November 2017 to June 2019 and 1 or more medical and pharmacy claim for any reason in the 12 months before and the 12 months after their first benralizumab claim (December 2016 through June 2020); have received benralizumab from physicians and pharmacies with regular reporting in greater than or equal to 80% of the months in this 24-month period; and to have been treated at a hospital for any reason within a 100-mile radius of their first benralizumab administration that had 50 or more medical or pharmacy claims per month for 80% of the months in the 24-month period. Because the data were deidentified, ethics approval was not required for this study. The data were used in accordance with the Helsinki Declaration as revised in 2013.

Study design

This retrospective cohort study included patients initiating benralizumab from November 2017 to June 2019, who had 1 or more *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis code for asthma (J45; see Table E1 in this article's Online Repository at www.jaci-inpractice.org), who were 12 years or older at benralizumab initiation, and who had 2 or more asthma exacerbations during the 12-month period before benralizumab initiation. The index date was defined as the day after benralizumab initiation, and the 12-month period before this date was defined as the pre-index period. The post-index period was defined as the 12-month period after the index date for the blood eosinophil count and biologic-experienced cohorts and as the 18- and 24-month periods after the index date for the extended follow-up cohort. A pre-post design was used to compare asthma exacerbations and concomitant asthma medication use between the pre- and post-index periods. Benralizumab dosing was not examined.

Study cohorts

Three nonmutually exclusive cohorts of patients with severe asthma initiating benralizumab were analyzed in this study. No comparisons between cohorts were performed given the overlap between them. The first cohort was classified by blood eosinophil

counts. Patients in this cohort had 2 or more records of benralizumab during the follow-up period, 1 or more blood eosinophil count value during the pre-index period, and were stratified into 5 subgroups by pre-index blood eosinophil count closest to the index date (<150, ≥150, 150-<300, <300, and ≥300 cells/μL). A second biologic-experienced cohort comprised patients with 2 or more records of benralizumab during the follow-up period and 1 or more record of mepolizumab or omalizumab use during the pre-index period with no other biologic use during the post-index period. This cohort was stratified into 2 mutually exclusive subgroups on the basis of pre-index biologic use (mepolizumab or omalizumab) closest to the index date. A third cohort comprised patients with at least 18 or 24 months of follow-up post index. This extended follow-up cohort was stratified into 2 subgroups, one with at least 18 months of follow-up data with 1 or more medical or pharmacy claim between 18 and 24 months and 9 or more records of benralizumab during the follow-up period, and the other with at least 24 months of follow-up data with 1 or more medical or pharmacy claim between 24 and 30 months and 11 or more records of benralizumab during the follow-up period.

Definition of asthma exacerbation

Asthma exacerbations were defined according to the European Respiratory Society/American Thoracic Society guidelines.[23] The definitions were modified to account for any differences in treatment across health care encounter settings. An exacerbation episode associated with a hospitalization was defined as an *ICD-10* code for asthma exacerbation or asthma as the primary diagnosis for an inpatient stay. An exacerbation associated with an emergency department or urgent care visit was defined as asthma exacerbation or an asthma diagnosis code for the emergency department visit and at least 1 claim for a systemic CS (with 3 to <30 days of supply or as a single injection) within 5 or more days of the visit and no diagnosis codes for chronic obstructive pulmonary disease (COPD), acute myocardial infarction, congestive heart failure, or autoimmune diseases during the visit. An exacerbation associated with an outpatient visit was defined as an asthma exacerbation or an asthma diagnosis code for an outpatient visit and 1 or more claim for a systemic CS (with 3 to <30 days of supply or as a single injection) within 5 or more days of the visit and no diagnosis codes for COPD or autoimmune diseases during the visit. Separate episodes of exacerbation were defined as those occurring 14 or more days apart.

Study measures and outcomes

Patient demographic characteristics and comorbidities (identified using *ICD-10* codes; Table E1) were described during the pre-index period. Asthma exacerbation rates pre and post index were evaluated in all cohorts, and rates at 18 and 24 months post index were evaluated in the extended follow-up cohorts. Medications taken concomitantly with benralizumab including systemic CSs (injected CSs and OCSs), quick-relief medications (short-acting β-agonist), controllers (inhaled CS [ICS] + long-acting β-agonist [LABA], ICS + LABA + long-acting muscarinic antagonist, or leukotriene modifiers), and antibiotics (see Table E2 in this article's Online Repository at www.jaci-inpractice.org) were also described for all 3 cohorts. Benralizumab dosing was not examined in this study.

Statistical analysis

Continuous variables were described using mean ± SD and were compared between the pre- and post-index periods using the Wilcoxon signed-rank test. Categorical variables were described using counts and percentages and were compared between the pre- and post-index periods using the McNemar test. Rates of asthma exacerbation were annualized and summarized per patient-year (PPY), and were compared between the pre- and post-index periods using generalized estimating equations. Statistical analyses were performed using the R software, version 3.6.2 (r-project.org). A P value less than .05 was considered statistically significant for all tests.

RESULTS

Sample selection

A total of 429 patients were included in the cohort classified by blood eosinophil counts; of these patients, 114 had blood eosinophil counts of less than 150 cells/μL, 315 had greater than or equal to 150 cells/μL, 80 had 150 to <300 cells/μL, 194 had less than 300 cells/μL, and 235 had greater than or equal to 300 cells/μL (Figure 1). In the overall eosinophil cohort, the mean number of days between the pre-index blood eosinophil level and the first prescription of benralizumab was 107.29 ± 83.04 days (median, 79.00 days). There were 349 patients who switched to benralizumab in the biologic-experienced cohort, including 205 patients with a record of omalizumab and 144 patients with a record of mepolizumab during the pre-index period. The extended follow-up cohort comprised patients who were followed up for 18 months (N = 419) and a subset of these patients who were followed up for 24 months (N = 156).

There were 227 overlapping patients among the eosinophil, biologic-experienced, and extended follow-up cohorts (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Among these 227 patients, 32 were in all 3 cohorts, 50 were in both the eosinophil and the biologic-experienced cohorts, 81 were in both the biologic-experienced and the extended follow-up cohorts, and 64 were in both the eosinophil and the extended follow-up cohorts.

Baseline characteristics of the study population

The baseline characteristics of patients in each cohort are presented in Table I. The mean age was similar across all cohorts and ranged from 51 to 53 years. Most patients were female (67%-69%) and from the southern United States (36%-39%), and nearly one-third had a diagnosis of obesity (32%-33%). The mean Charlson comorbidity index ranged from 1.47 to 1.52. The 3 most common comorbidities were allergic rhinitis (60%-67%), hypertension (41%-44%), and gastroesophageal reflux disease (38%-41%). COPD was present in 26% to 32% of patients, and 14% to 16% of patients had nasal polyps at baseline.

Asthma exacerbation rates with benralizumab

The rate of asthma exacerbations decreased significantly after benralizumab treatment initiation across all cohorts (Figure 2). In the cohort classified by blood eosinophil counts (Figure 2, *A*), the rate of exacerbations decreased from 3.10-3.55 PPY in the pre-index period to 1.11-1.72 PPY in the post-index period, corresponding to a decrease of 52% to 64% ($P < .001$ for all pre-post comparisons).

The rate of asthma exacerbations also decreased significantly after benralizumab treatment initiation in the biologic-experienced cohort (Figure 2, *B*). The rate decreased by 62% (from 3.25 PPY pre index to 1.25 PPY post index) in patients who switched to benralizumab from omalizumab and by 53% (3.81 PPY pre index to 1.78 PPY post index) in those who switched from mepolizumab (both $P < .001$).

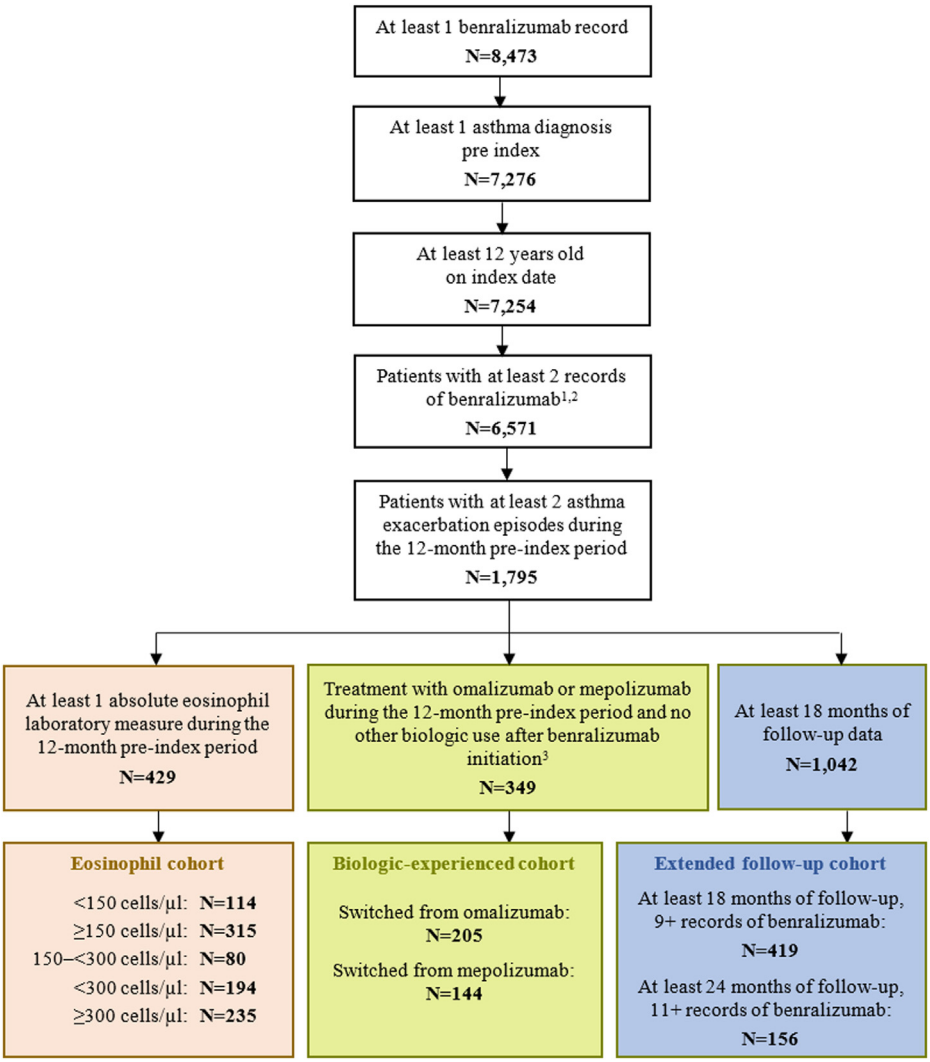

FIGURE 1. Sample selection diagram of patients in the eosinophil cohort, biologic-experienced cohort, and extended follow-up cohort. Patients may overlap between cohorts because the cohort definitions were not mutually exclusive. *The record of benralizumab use occurring the day before the index day was included in the count of benralizumab records. †All patients included in the final sample had at least 1 encounter record every 12 months in the pre- and post-index periods. ‡Patients were considered biologic-experienced if they had a new prescription record for omalizumab or mepolizumab during the 12-month pre-index period or a prescription record before the 12-month pre-index period with days of supply carrying into the pre-index period. They were not allowed to have a prescription for dupilumab, mepolizumab, omalizumab, or reslizumab after benralizumab initiation. The mepolizumab and omalizumab cohorts were mutually exclusive and defined on the basis of the biologic record closest to the index date.

The same trend was observed in the extended follow-up cohorts (Figure 2, *B*). Among patients treated with benralizumab and followed up over a period of 18 months, the pre-index asthma exacerbation rate was 3.38 PPY, declining significantly to 1.34 PPY (60% reduction vs pre index) from 0 to 12 months and to 1.18 PPY (65% reduction) from 12 to 18 months after benralizumab initiation (both $P < .001$). In the 24-month cohort, the pre-index exacerbation rate was 3.38 PPY, decreasing significantly to 1.38 (59% reduction vs pre index) from 0 to 12 months and to 1.08 (68% reduction) from 12 to 24 months post index (both $P < .001$). The proportion of patients with no exacerbations in the first 12-month period after the index date (ie, months 0-12) was 39% and the proportion of patients with no exacerbations in the second 12-month period after the index date (ie, months 12-24) was 49%.

Concomitant asthma medication use before and after benralizumab treatment

After initiating benralizumab treatment, all cohorts experienced significant reductions in the use of OCSs. In the eosinophil cohort, the proportion of patients using OCSs decreased significantly from 98% pre index to 79% post index in patients with greater than or equal to 150 cells/µL, and from 98% to 78% in patients with greater than or equal to 300 cells/µL (both $P < .001$) (Table II). The median cumulative dose of OCSs decreased from 1817 to 1156 mg in patients

TABLE I. Baseline characteristics* of patients stratified by cohort

Characteristic	Eosinophil cohort (N = 429)	Biologic-experienced cohort (N = 349)	18-mo follow-up cohort† (N = 419)
Age on index date (y), mean ± SD	51.99 ± 14.50	51.26 ± 15.71	52.80 ± 14.53
Sex, female, n (%)	296 (69.0)	241 (69.1)	281 (67.1)
Region, n (%)			
Midwest	44 (10.3)	95 (27.2)	108 (25.8)
Northeast	137 (31.9)	79 (22.6)	105 (25.1)
South	167 (38.9)	125 (35.8)	159 (37.9)
West	81 (18.9)	50 (14.3)	47 (11.2)
Charlson comorbidity index, mean ± SD	1.52 ± 1.07	1.47 ± 1.12	1.51 ± 1.15
Comorbidities, n (%)‡			
Allergic rhinitis	277 (64.6)	233 (66.8)	252 (60.1)
Hypertension	175 (40.8)	150 (43.0)	186 (44.4)
Gastroesophageal reflux disease	162 (37.8)	142 (40.7)	171 (40.8)
Sinusitis, chronic	146 (34.0)	110 (31.5)	135 (32.2)
Hyperlipidemia	140 (32.6)	99 (28.4)	124 (29.6)
COPD	138 (32.2)	106 (30.4)	110 (26.3)
Obesity	137 (31.9)	110 (31.5)	138 (32.9)
Obstructive sleep apnea	114 (26.6)	91 (26.1)	111 (26.5)
Sinusitis, acute	106 (24.7)	78 (22.3)	113 (27.0)
Nasal polyps	67 (15.6)	49 (14.0)	57 (13.6)
Pneumonia	66 (15.4)	45 (12.9)	65 (15.5)
Autoimmune diseases	41 (9.6)	39 (11.2)	39 (9.3)
Any eosinophil laboratory value, n (%)	429 (100.0)	82 (23.5)	96 (22.9)
Eosinophil count (cells/μL) closest to index			
Mean ± SD	510.63 ± 622.83	491.65 ± 689.92	482.93 ± 494.78
Median (IQR)	350.00 (130.00-667.00)	244.00 (75.50-681.00)	407.50 (124.75-638.50)
Prior biologic agent use, n (%)§			
Dupilumab	3 (0.7)	0 (0.0)	1 (0.2)
Mepolizumab	44 (10.3)	149 (42.7)	62 (14.8)
Omalizumab	74 (17.2)	217 (62.2)	80 (19.1)
Reslizumab	3 (0.7)	2 (0.6)	4 (1.0)

IQR, Interquartile range.
*Baseline patient characteristics are summarized during the 12-mo pre-index period, with index date defined as the day after the first record of benralizumab.
†A subset of these patients (N = 156) was followed up for ≥24 mo; together, the 18- and 24-mo follow-up groups constituted the extended follow-up cohort.
‡Comorbidities of interest were reported on the basis of relevance in the literature and clinical input.
§In the biologic-experienced cohort, any previous biologic use is reported. In subsequent analyses, the treatment closest to benralizumab initiation (index) was used to categorize patients and is the reason for which the numbers differ slightly from those in this table.

with greater than or equal to 150 cells/μL, and from 1768 to 962 mg in patients with greater than or equal to 300 cells/μL (both $P < .001$). Similarly, in the biologic-experienced cohort, there were significant reductions in the use of OCSs following the switch to benralizumab in patients who were previously treated with omalizumab (from 98% pre index to 86% post index; $P < .001$) or mepolizumab (from 95% to 83%; $P < .01$) (Table III). The median cumulative dose of OCSs decreased from 2183 to 1349 mg in patients previously treated with omalizumab, and from 2493 to 1553 mg in patients previously treated with mepolizumab (both $P < .001$). OCS use also declined in patients treated with benralizumab over a period of 18 and 24 months (Table IV).

The proportion of patients who were OCS-dependent also decreased after benralizumab initiation in all cohorts (Tables II-IV). In the eosinophil cohort, the proportion of OCS-dependent patients decreased significantly from 82% pre index to 49% post index ($P < .001$) in patients with greater than or equal to 150 cells/μL, and from 83% to 46% in patients with greater than or equal to 300 cells/μL ($P < .001$). Similarly, in the biologic-experienced cohort, the proportion of OCS-dependent patients decreased significantly from 82% to 52% in patients who were previously treated with omalizumab ($P < .001$) and from 86% to 60% in patients who were previously treated with mepolizumab ($P < .001$).

The use of other medications was also decreased in many cohorts. Across all cohorts, there was a significant 13% to 21% reduction in the use of short-acting β-agonists after the initiation of benralizumab (all $P < .01$) (Tables II-IV). A reduction in the use of leukotriene modifiers after benralizumab initiation was seen in most, but not all, cohorts. Reductions in combination therapy were also frequently observed: in the eosinophil and extended follow-up cohorts, the proportion of patients using combination therapy decreased significantly from 64%-70% pre index to 53%-58% post index (all $P < .05$) (Tables II and IV).

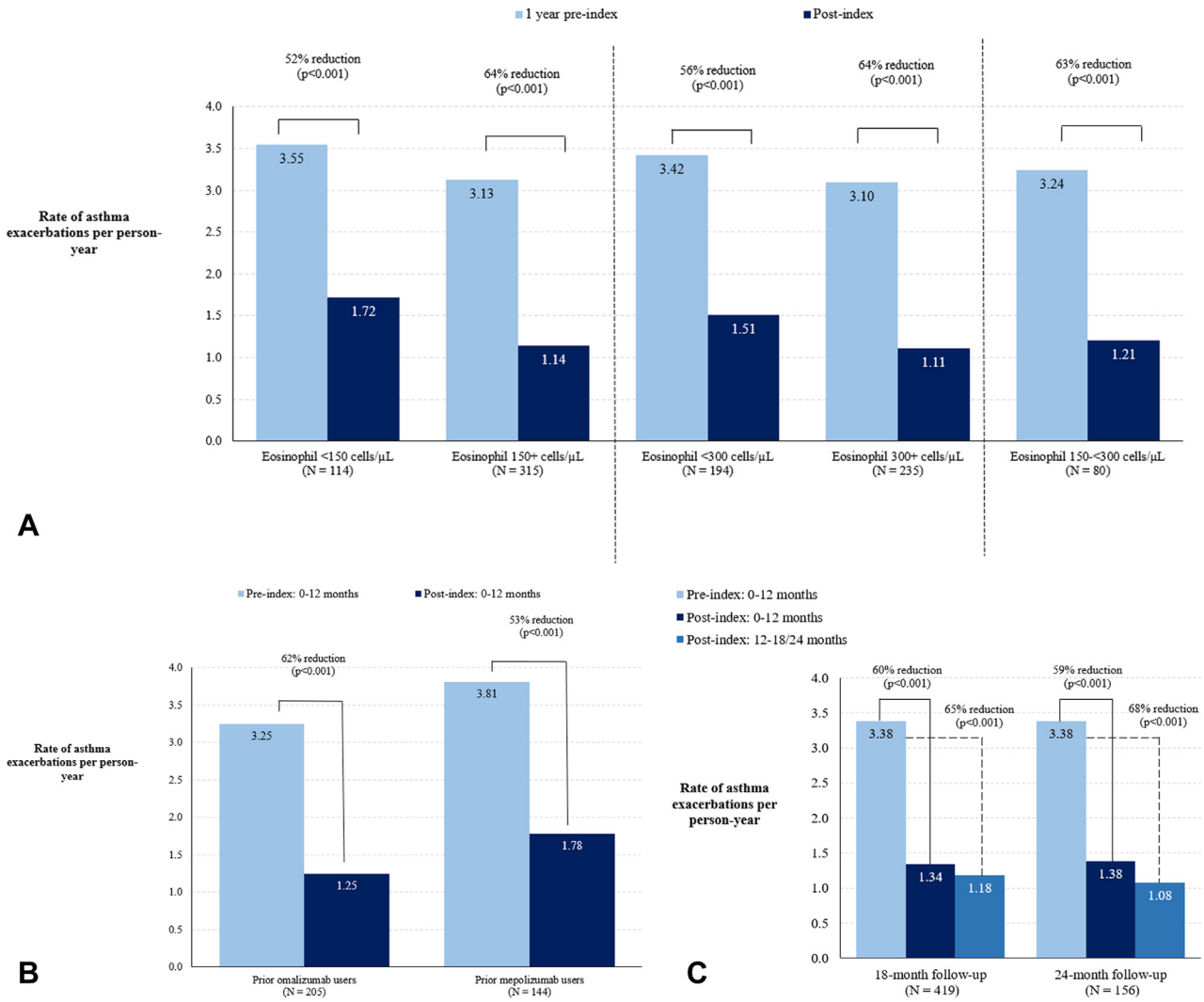

FIGURE 2. Asthma exacerbation rates before and after benralizumab initiation for the (**A**) eosinophil cohort, (**B**) biologic-experienced cohort, and (**C**) extended follow-up cohort.

In the biologic-experienced cohort, the use of combination therapy was similar before and after the switch to benralizumab (Table III).

DISCUSSION

Severe eosinophilic asthma accounts for a relatively small proportion of asthma cases but imposes a disproportionately high disease burden,[24] which has been greatly alleviated by the introduction of biologics targeting the underlying pathogenic mechanisms. Recurrent severe asthma exacerbations are associated with reduced lung function in patients[25]; therefore, preventing exacerbations is an important treatment goal. In the present study—the largest real-world sample of patients with severe eosinophilic asthma analyzed to date—the rate of asthma exacerbations decreased by 52% to 64% with benralizumab treatment in a heterogeneous population of patients, including those with different blood eosinophil counts or who were previously treated with biologics. These results add to the body of evidence supporting the use of benralizumab for the treatment of severe eosinophilic asthma, by demonstrating its effectiveness in specific patient subsets that are not always represented in clinical trials and have not been analyzed in detail in previous real-world studies. For example, the trials restricted their population to patients with blood eosinophil values greater than 150 cells/µL, whereas this study included patients with a wider range of values that are seen in clinical practice including values less than 150 cells/µL.

The clinical benefits of benralizumab in the treatment of severe asthma are well documented. In the pivotal clinical trials, benralizumab reduced the yearly asthma exacerbation rate by 51% (SIROCCO trial) and 28% (CALIMA trial) versus placebo and improved lung function at 48 and 56 weeks.[12,14] Similar findings have been reported in real-world studies[19-21,26-30] with effect sizes comparable with those seen in clinical trials.[19] In the ZEPHYR 1 study, which included patients older than 12 years with severe eosinophilic asthma in the United States, benralizumab initiation was associated with a significant decrease (by

TABLE II. Concomitant asthma medications before and after benralizumab initiation in the eosinophil cohort

	≥150 cells/μL				≥300 cells/μL			
Medication	**Pre index (N = 315)**	**Post index (N = 315)**	**Relative reduction (%)**	***P* value***	**Pre index (N = 235)**	**Post index (N = 235)**	**Relative reduction (%)**	***P* value***
Systemic CSs								
Injected CSs	133 (42.2)	68 (21.6)	48.9	<.001	96 (40.9)	49 (20.9)	49.0	<.001
OCSs	308 (97.8)	250 (79.4)	18.8	<.001	230 (97.9)	184 (78.3)	20.0	<.001
Cumulative OCS dosage (mg)	1500 (800-2415)	600 (129-1365)	—	<.001	1500 (816-2347)	480 (105-1310)	—	<.001
Daily average OCS dosage (mg)	28.14 (22.65-35.61)	25.72 (13.74-37.23)	—	<.001	29.70 (23.10-36.54)	25.31 (11.50-37.88)	—	<.001
OCS-dependent use	258 (81.9)	154 (48.9)	—	<.001	196 (83.4)	107 (45.5)	—	<.001
Quick-relief medications								
SABA	283 (89.8)	231 (73.3)	18.4	<.001	213 (90.6)	168 (71.5)	21.1	<.001
SAMA	49 (15.6)	32 (10.2)	34.7	<.05	35 (14.9)	21 (8.9)	40.0	<.05
Controllers								
ICS monotherapy	65 (20.6)	49 (15.6)	24.6	.07	50 (21.3)	35 (14.9)	30.0	.05
LAMA monotherapy	47 (14.9)	49 (15.6)	−4.3	.89	36 (15.3)	36 (15.3)	0.0	>.99
Combination therapy (ICS + LABA)	211 (67.0)	173 (54.9)	18.0	<.001	165 (70.2)	134 (57.0)	18.8	<.001
Triple therapy (ICS + LABA + LAMA)	127 (40.3)	111 (35.2)	12.6	<.05	92 (39.1)	76 (32.3)	17.4	<.05
Leukotriene modifiers	243 (77.1)	221 (70.2)	9.1	<.01	177 (75.3)	163 (69.4)	7.9	.06
Antibiotics	269 (85.4)	207 (65.7)	23.0	<.001	201 (85.5)	145 (61.7)	27.9	<.001

LAMA, Long-acting muscarinic antagonist; *SABA*, short-acting β-agonist; *SAMA*, short-acting muscarinic antagonist.
Data are presented as n (%) or median (IQR).
*Statistically significant at $P < .05$ (Wilcoxon signed-rank test for continuous variables and McNemar test for categorical variables).

TABLE III. Concomitant asthma medications before and after benralizumab initiation in the biologic-experienced cohort

	Previous omalizumab users				Previous mepolizumab users			
Medication	**Pre index (N = 205)**	**Post index (N = 205)**	**Relative reduction (%)**	***P* value***	**Pre index (N = 144)**	**Post index (N = 144)**	**Relative reduction (%)**	***P* value***
Systemic CSs								
Injected CSs	75 (36.6)	53 (25.9)	29.3	<.01	62 (43.1)	48 (33.3)	22.6	.07
OCSs	201 (98.0)	176 (85.9)	12.4	<.001	137 (95.1)	120 (83.3)	12.4	<.01
Cumulative OCS dosage (mg)	1705 (880-3000)	800 (300-1900)	—	<.001	2133 (1071-3526)	953 (247-2091)	—	<.001
Daily average OCS dosage (mg)	28.18 (20.38-34.53)	24.00 (13.30-33.33)	—	<.001	25.05 (18.63-33.83)	20.18 (9.93-31.94)	—	<.01
OCS-dependent use	168 (82.0)	107 (52.2)	—	<.001	124 (86.1)	86 (59.7)	—	<.001
Quick-relief medications								
SABA	187 (91.2)	158 (77.1)	15.5	<.001	125 (86.8)	109 (75.7)	12.8	<.01
SAMA	19 (9.3)	10 (4.9)	47.4	.08	17 (11.8)	15 (10.4)	11.8	.80
Controllers								
ICS monotherapy	33 (16.1)	31 (15.1)	6.1	.87	30 (20.8)	23 (16.0)	23.3	.21
LAMA monotherapy	34 (16.6)	28 (13.7)	17.6	.36	26 (18.1)	23 (16.0)	11.5	.72
Combination therapy (ICS + LABA)	118 (57.6)	108 (52.7)	8.5	.23	79 (54.9)	77 (53.5)	2.5	.86
Triple therapy (ICS + LABA + LAMA)	84 (41.0)	76 (37.1)	9.5	.30	56 (38.9)	47 (32.6)	16.1	.18
Leukotriene modifiers	147 (71.7)	135 (65.9)	8.2	.06	97 (67.4)	86 (59.7)	11.3	.06
Antibiotics	177 (86.3)	136 (66.3)	23.2	<.001	113 (78.5)	100 (69.4)	11.5	.05

LAMA, Long-acting muscarinic antagonist; *SABA*, short-acting β-agonist; *SAMA*, short-acting muscarinic antagonist.
Data are presented as n (%) or median (IQR).
*Statistically significant at $P < .05$ (Wilcoxon signed-rank test for continuous variables and McNemar test for categorical variables).

TABLE IV. Concomitant asthma medications before and after benralizumab initiation in the extended follow-up cohort

	18-mo follow-up cohort				24-mo follow-up cohort			
Medication	**Pre index (N = 419)**	**Post index (N = 419)**	**Relative reduction (%)**	***P* value*,†**	**Pre index (N = 156)**	**Post index (N = 156)**	**Relative reduction (%)**	***P* value*,†**
Systemic CSs								
Injected CSs (0-12 mo)	180 (43.0)	110 (26.3)	38.9	<.001	77 (49.4)	50 (32.1)	35.1	<.001
OCSs (0-12 mo)	412 (98.3)	317 (75.7)	23.1	<.001	152 (97.4)	117 (75.0)	23.0	<.001
Cumulative OCS dosage (mg)								
0-12 mo	1700 (964-2782)	600 (113-1790)	—	<.001	1926 (1077-3142)	709 (188-2048)	—	<.001
12-18/24 mo		400 (0-1425)	—	<.001		573 (139-1318)	—	<.001
Daily average OCS dosage (mg)								
0-12 mo	27.72 (21.19-34.62)	21.43 (7.08-33.25)	—	<.001	27.65 (19.94-34.52)	20.00 (6.92-32.94)	—	<.001
12-18/24 mo		12.19 (0.00-29.14)	—	<.001		22.44 (8.12-32.54)	—	<.001
OCS-dependent use (0-12 mo)	352 (84.0)	210 (50.1)	—	<.001	135 (86.5)	82 (52.6)	—	<.001
Quick-relief medications (0-12 mo)								
SABA	373 (89.0)	301 (71.8)	19.3	<.001	137 (87.8)	113 (72.4)	17.5	<.001
SAMA	45 (10.7)	29 (6.9)	35.6	<.05	19 (12.2)	12 (7.7)	36.8	.17
Controllers (0-12 mo)								
ICS monotherapy	74 (17.7)	45 (10.7)	39.2	<.01	34 (21.8)	19 (12.2)	44.1	<.05
LAMA monotherapy	65 (15.5)	51 (12.2)	21.5	.11	27 (17.3)	22 (14.1)	18.5	.38
Combination therapy (ICS + LABA)	287 (68.5)	242 (57.8)	15.7	<.001	99 (63.5)	82 (52.6)	17.2	<.05
Triple therapy (ICS + LABA + LAMA)	173 (41.3)	143 (34.1)	17.3	<.01	63 (40.4)	54 (34.6)	14.3	.15
Leukotriene modifiers	308 (73.5)	268 (64.0)	13.0	<.001	109 (69.9)	92 (59.0)	15.6	<.05
Antibiotics (0-12 mo)	356 (85.0)	262 (62.5)	26.4	<.001	138 (88.5)	104 (66.7)	24.6	<.001

IQR, Interquartile range; *LAMA*, long-acting muscarinic antagonist; *SABA*, short-acting β-agonist; *SAMA*, short-acting muscarinic antagonist.
Data are presented as n (%) or median (IQR).
*Statistically significant at $P < .05$ (Wilcoxon signed-rank test for continuous variables and McNemar test for categorical variables).
†Results from the 12- to 18-mo and the 12- to 24-mo post index were compared with the 12-mo pre index results. For comparability, the 12- to 18-mo results were annualized.

55%) in the rate of exacerbations.[22] The present study corroborates this earlier work and further demonstrates the effectiveness of benralizumab in a patient population that was larger than and clinically distinct from that of ZEPHYR 1, and more heterogeneous in terms of baseline characteristics, medication adherence, and treatment history than the cohorts in clinical trials and previous real-world studies.

Although differences in patient populations across studies preclude direct comparisons (eg, different practice and treatment patterns), the present results are also consistent with those seen in patients receiving other biologics such as mepolizumab in the REALITI-A study (71% reduction in clinically significant exacerbations)[31] or omalizumab in the PROSPERO study (exacerbation rate of 3.00 at 12 months before omalizumab treatment to 0.78 at 12 months after -omalizumab treatment).[32] Importantly, in the present study, even greater decreases in the rate of exacerbations were observed at 18 months (65%) and 24 months (68%) post index, and substantial proportions of patients in the eosinophil and extended follow-up cohorts achieved zero exacerbations, demonstrating the effectiveness of benralizumab for long-term asthma control. These findings indicate that benralizumab is effective in reducing the disease burden of real-world patients with severe eosinophilic asthma with diverse clinical profiles. It is worth noting that the high rates of exacerbation before benralizumab treatment observed here and also reported in other real-world studies evaluating the use of biologics in patients with severe asthma[31,33-35] may reflect a delay in referral for biologic therapy by primary care physicians or specialists, suggesting that biologics are not being used to their full potential in clinical practice. The real-world evidence from the present study could encourage a more timely uptake of benralizumab, with patients achieving asthma control sooner in their treatment course.

Blood eosinophil counts are elevated in patients with severe eosinophilic asthma and are therefore a useful biomarker for identifying patients who may benefit from treatment with anti−IL-5 or anti−IL-5 receptor alpha chain therapy and monitoring treatment response.[36-38] Benralizumab has been shown to deplete blood eosinophils in clinical trials[12,14] and real-world patient populations[29,39-42] across a range of eosinophil thresholds.[13,18,43,44] Consistent with the results seen in clinical trials, benralizumab had positive effects on efficacy outcomes in all of these subgroups, suggesting that it is effective in patients with varying eosinophil thresholds and low eosinophil counts.

The disease burden of severe asthma includes not only symptoms but also exacerbations and side effects of medications.[9] In particular, OCSs used to manage exacerbations have adverse effects such as increased risk of infection, fracture, and thromboembolism even in the short term.[45] In the ZONDA[18] and PONENTE[17] trials of patients with severe asthma treated with high-dosage ICS + LABA and OCSs, add-on benralizumab eliminated or reduced OCS dependence. This effect has been reported with other biologics, although the results cannot be directly compared because of differences in study design: in the REALITI-A study, 43% of patients discontinued OCSs and 64% reduced their OCS dose after initiating mepolizumab.[31] In the present work, OCS use, cumulative and daily average OCS dosage, and OCS-dependent use were all significantly reduced by benralizumab treatment across all cohorts. This confirms the results of other real-world studies[21,26,42,46-48] showing that CSs were discontinued altogether or their use diminished on initiation of benralizumab, including in patients with severe eosinophilic asthma who had ongoing symptoms despite therapy with other IL-5 biologics (mepolizumab or reslizumab).[27] Furthermore, consistent with a previous report,[42] we observed that in the eosinophil and extended follow-up cohorts, the use of quick-relief medications and controllers decreased post index. However, the proportion of patients using controllers in the biologic-experienced cohort was unchanged after benralizumab initiation. This may be because patients who received biologic treatment previously had harder-to-control asthma that required ongoing management with controller medication, although further study is needed to evaluate this possibility.

The presentation of severe asthma is heterogeneous, requiring multiple therapeutic options; therefore, patients may need to switch between treatments if their exacerbations are not adequately controlled.[9] Because clinical trials have mostly excluded patients with previous biologic treatment, clinical outcomes of patients who experienced 2 or more exacerbations while on omalizumab or mepolizumab were examined in the present study to assess the impact of previous biologic use on the response to benralizumab. A recent multicountry study found that switching between biologics was uncommon and that patients who switched were more likely to have a higher exacerbation rate.[49] Treatment with benralizumab decreased the rate of exacerbations in the omalizumab- and the mepolizumab-to-benralizumab switch groups by 62% and 53%, respectively, as well as OCS use. This is in agreement with the results of a real-world study of patients in the United Kingdom who switched to benralizumab from other biologics (mepolizumab, omalizumab, or reslizumab)[50]; regardless of previous biologic use, 85% of these patients remained on benralizumab after 48 weeks, exacerbation rates were decreased, and more than half the patients had discontinued OCSs. Similarly, in a small cohort of patients with severe eosinophilic asthma in Japan, benralizumab significantly reduced blood eosinophil counts irrespective of previous treatment with mepolizumab.[41] Although not all possible reasons for the switch from omalizumab or mepolizumab to benralizumab in this cohort were available in the claims data, benralizumab has been shown to be effective in patients who failed to achieve asthma control with other biologics. For example, in the aforementioned UK study, most biologic-experienced patients had discontinued their previous therapy because of a lack of efficacy (ie, a requirement for OCSs, frequent exacerbations, and poor control of symptoms).[50] These results provide supporting evidence that the response to benralizumab is not affected by previous biologic use and that benralizumab is a viable treatment option for biologic-experienced patients.

Strengths and limitations

This study builds on previous real-world evidence[22] of the benefits of benralizumab for the treatment of severe eosinophilic asthma. The consistency of the current results with those of clinical trials and previous real-world studies validates this conclusion. Moreover, by evaluating the impact of benralizumab in different subgroups of patients stratified according to baseline eosinophil counts and previous biologic use as well as the long-term effectiveness of benralizumab treatment, the present work fills a gap in the literature by providing real-world evidence supporting the clinical applicability of benralizumab across a broad patient population. Another strength of this study is that it analyzed data from a claims database containing a large sample of

patients that is likely to be rep-resentative of all patients with severe eosinophilic asthma treated with benralizumab in the United States. Furthermore, specific criteria were applied to select ,patients who were active in the data (eg, requiring patients to have ≥1 medical or pharmacy encounter of any type every 12 months) to capture detailed information on patients' encounters.

This study also had certain limitations. First, because there was no control population (ie, with no benralizumab treatment), the pre-post analysis did not control for changes that may have occurred over time in the absence of benralizumab. Second, the current findings may only be generalizable to patients on therapy for 12 or 24 months on the basis of individual cohorts. Third, the use of *ICD* codes to identify diagnoses may result in misclassification because there may be inaccuracies in the recording of *ICD* codes by physicians. However, to avoid misclassification in the study population, patients were required to have a record of use of an asthma-specific treatment and multiple asthma exacerbations before benralizumab initiation. Fourth, some variables of interest such as eosinophil laboratory values or IgE levels were not available for all patients, and others such as reasons for switching treatments and smoking history were not available for any patient. Additional studies examining the impact of benralizumab on these variables in the real world would be beneficial. Finally, claims data do not capture first-dose samples of benralizumab provided to patients that may have influenced asthma exacerbation rates and other outcomes before and after benralizumab.

CONCLUSIONS

The results of this study in a large population of patients with severe eosinophilic asthma in the United States confirm the effectiveness of benralizumab in achieving asthma control in a real-world practice setting. Specifically, benralizumab treatment significantly reduced the rate of asthma exacerbations in all analyzed cohorts, including across various eosinophil thresholds (<150, ≥150, 150-<300, <300, and ≥300 cells/μL), after a switch from mepolizumab or omalizumab to benralizumab, and for up to 24 months of follow-up. Benralizumab treatment also reduced patients' use of systemic CSs. These findings support benralizumab as a valuable therapeutic option in the management of severe eosinophilic asthma.

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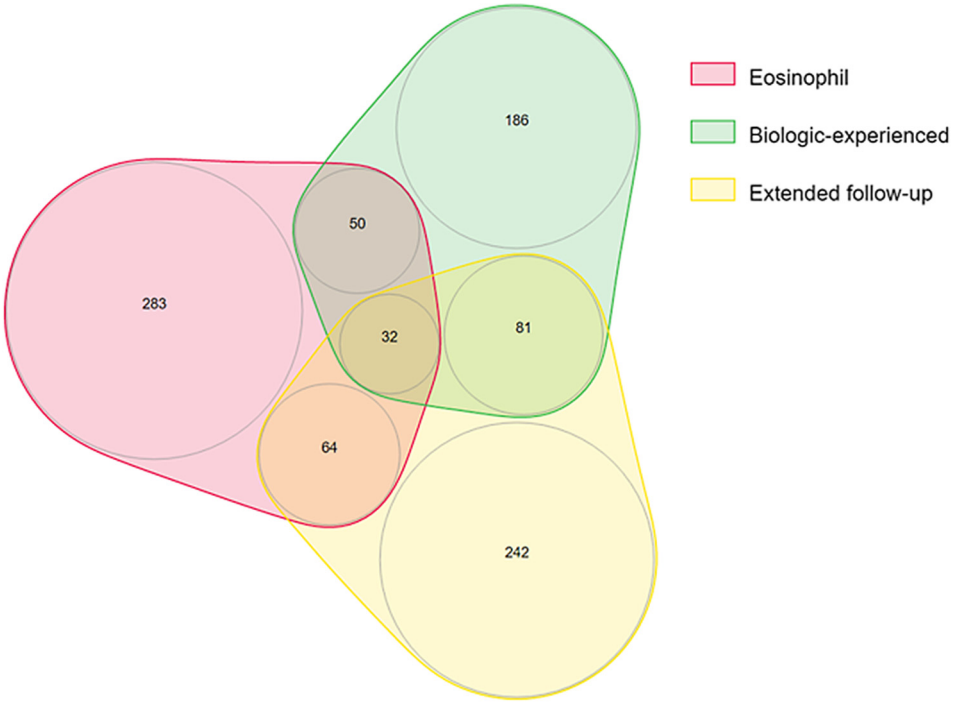

FIGURE E1. Overlap in number of patients between the 3 patient cohorts.

TABLE E1. *ICD-10* codes to identify diagnoses

Diagnosis	*ICD-10* code[E1,E2]
Asthma	J45
Acute asthma exacerbation*	J45.21, J42.22, J45.31, J45.32, J45.41, J45.42, J45.51, J45.52, J45.901, J45.902
Comorbidities	
Cardiovascular	
Acute myocardial infarction	I21
Angina	I20
Hyperlipidemia	E78.0, E78.1, E78.2, E78.3, E78.4, E78.5
Hypertension	I10, I11, I12, I13, I15, I16, I67.4
Pulmonary hypertension	I27.0, I27.2
Infection	
Otitis media	H65-H67
Pneumonia	J12-J18
Sinusitis acute	J01
Sinusitis chronic	J32
Allergy-related	
Eczema	L20-L25
Atopic dermatitis	L20
Allergic conjunctivitis	H10.45
Allergic rhinitis	J30.1, J30.2, J30.5, J30.8, J30.9
Other asthma-related	
Bronchiectasis	J47
Bronchopulmonary dysplasia	P27.1
CIU	L50.1
COPD	J41-J44
Cystic fibrosis	E84
Gastroesophageal reflux disease	K21.9
Interstitial lung disease, including pulmonary fibrosis	J62, J63, J67.9, J70.1-J70.4, J82, J84.0, J84.1, J84.8, J84.9, J99.1, D48.1
Mental disorders	F01-F99
Nasal polyps	J33
Obesity	E66
Obstructive sleep apnea	G47.33
Respiratory tract cancer	C30-C34
Sarcoidosis	D86
Tuberculosis	A15-A19
Autoimmune diseases[E3]†,‡	L63, M45, M08.1, K90.0, N03, L50.8, K50, M31.5, M31.6, E05.0, E06.0, D55, D59, D69.3, G35, K74.3, L40, J84.1, M05, M06, M08.0, M08.2, M08.3, M08.4, M35.0, M32, M34, E10, K51, L80
Additional eosinophilic diseases of interest	
Allergic bronchopulmonary aspergillosis	B44.81
Atopic dermatitis (alternative definition)	L20, L25.9, R21
Bronchiectasis (noncystic fibrosis bronchiectasis)	J47.9, J47.1
Chronic spontaneous urticaria/CIU	L50.1, L50.9, L50.8

(continued)

TABLE E1. *(Continued)*

Diagnosis	*ICD-10* code[E1,E2]
Asthma	See above
COPD	See above
Chronic rhinosinusitis	J31, J32
Nasal polyps	See above
Eosinophilic granulomatosis with polyangiitis	M30.1
Eosinophilic esophagitis	K20.0
Bullous pemphigoid	L12.0
Eosinophilic gastritis or gastroenteritis	K52.81
Charlson comorbidity index[E4]	
Myocardial infarction	I21, I22, I25.2
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43, I50, P29.0
Peripheral vascular disease	I70-I71, I73.1, I73.8-I73.9, I77.1, I79.0, I79.2, K55.1, K55.8-K55.9, Z95.8-Z95.9
Cerebrovascular disease	G45-G46, H34.0, I60-I69
Dementia	F00-F03, F051, G30, G311
Chronic pulmonary disease	I278-I279, J40-J47, J60-J67, J68.4, J70.1, J70.3
Rheumatic disease	M05-M06, M31.5, M32-M34, M35.1, M35.3, M36.0
Peptic ulcer disease	K25-K28
Liver disease, mild	B18, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73-K74, K760, K76.2-K76.4, K76.8-K76.9, Z94.4
Diabetes without chronic complications	E10.0-E10.1, E10.6, E10.8-E11.1, E11.6, E11.8-E12.1, E12.6, E12.8-E13.1, E13.6, E13.8-E14.1, E14.6, E14.8, E14.9
Diabetes with chronic complications	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7
Hemiplegia or paraplegia	G04.1, G11.4, G80.1-G80.2, G81-G82, G83.0-G83.4, G83.9
Renal disease	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18-N19, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Any malignancy including leukemia and lymphoma, except for malignant neoplasm of skin	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97
Liver disease, moderate or severe	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5-K76.7
Metastatic solid tumor	C77-C80
AIDS/HIV	B20-B22, B24

CIU, Chronic idiopathic urticaria.
*Acute asthma exacerbation includes asthma with (acute) exacerbation and asthma with status asthmaticus.
†Psoriasis and psoriatic arthritis were included on the basis of clinical input.
‡Autoimmune diseases include alopecia areata, ankylosing spondylitis, celiac disease, chronic glomerulonephritis, chronic urticaria, Crohn disease, giant cell arteritis, Graves' disease, Hashimoto thyroiditis, hemolytic anemia, immune thrombocytopenia purpura, multiple sclerosis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, pulmonary fibrosis, rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, systemic sclerosis, type 1 diabetes, ulcerative colitis, and vitiligo.

TABLE E2. Codes to identify treatments

Treatment	Generic name*	GPI code	HCPCS code
Fasenra	Benralizumab	4460402000	J0517, C9466†
Biologic agents for asthma			
Dupixent	Dupilumab	9027302000	NA
Nucala	Mepolizumab	4460405500	J2182, C9473
Xolair	Omalizumab	4460306000	J2357
Cinqair	Reslizumab	4460446000	J2786, C9481
Concomitant asthma treatments			
Quick-relief medications			
Short-acting inhaled β_2-agonists (including albuterol)	Albuterol sulfate, bitolterol, epinephrine, isoetharine, isoproterenol, levalbuterol, metaproterenol, pirbuterol, terbutaline	442010xxxx	J0171, J3105, J7607, J7609-J7615, J7620, J7628, J7629, J7647-J7650, J7657-J7660, J7667-J7670, J7680, J7681
Short-acting muscarinic antagonists (ipratropium bromide)‡	Ipratropium bromide	44100030xx	J7644, J7645
Controllers			
ICSs	Beclomethasone dipropionate, budesonide, ciclesonide, dexamethasone, flunisolide, fluticasone furoate, fluticasone propionate, mometasone, triamcinolone	444000xxxx	J7622, J7626, J7627, J7633, J7634, J7637, J7638, J7641, J7683, J7684
LABA	Arformoterol, formoterol fumarate, indacaterol, salmeterol xinafoate	442010xxxx	J7605, J7606, J7640
Combination therapy (ICS + LABA)	Combinations of above ICS and LABA generics	442099xxxx	NA
LAMA	Aclidinium bromide, glycopyrrolate, revefenacin, tiotropium bromide, umeclidinium	441000xxxx	J7642, J7643, J7677
Triple therapy (ICS + LABA + LAMA)	Combinations of above ICS, LABA, and LAMA generics	442099xxxx	NA
Leukotriene modifiers	Montelukast, zafirlukast, zileuton	4450505010, 4450508000, 4450408500	NA
Methylxanthines (theophylline)	Theophylline	44300040xx	J2810
Systemic CSs§			
OCSs	Betamethasone, corticotropin, cortisone, cosyntropin, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone	22xxxxxxxx	J7509, J7510, J7512, J8540
Injected CSs	Dexamethasone, methylprednisolone	22xxxxxxxx	J2920, J2930, J1020, J1030, J1040, J1094, J1100
Antibiotics‖	Amoxicillin clavulanate, azithromycin, ciprofloxacin, clarithromycin, levofloxacin, moxifloxacin	0199000220, 034000xxxx, 05000020xx, 035000xxxx, 05000034xx, 05000037xx	J0456, Q0144, J0744, J1956, J2280

GPI, Generic product identifier; *HCPCS*, Healthcare Common Procedure Coding System; *LAMA*, long-acting muscarinic antagonist; *NA*, not applicable.

*Generic medication names are derived from the American Academy of Allergy Asthma & Immunology Allergy and Asthma Drug Guide and a real-world evidence claims study.[E5] Only medications approved for asthma were included.

†The HCPCS code for benralizumab (J0517) is new as of January 1, 2019; HCPCS code C9466 was terminated on December 31, 2018.

‡The short-acting muscarinic antagonist ipratropium bromide was included on the basis of clinical input.

§Systemic CS medications were categorized by route of administration to differentiate OCSs from injected CSs. HCPCS systemic CS codes were differentiated using http://www.HCPCSData.com/.

‖Antibiotics of interest were included on the basis of clinical input. The listed macrolides and fluoroquinolones encompass antibiotics that are most frequently used for an asthma exacerbation in clinical practice.

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