

Impact of mepolizumab on exacerbations in severe asthma: Results from a U.S. insurance claims data base

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ABSTRACT

Background: In controlled clinical studies, mepolizumab has been shown to reduce exacerbation rates and the use of oral corticosteroids as well as improve asthma control and health-related quality of life compared with placebo in patients with severe eosinophilic asthma. However, real-world data on the impact of mepolizumab on clinical outcomes are limited.

Objective: To evaluate the effect of mepolizumab on asthma exacerbations and asthma exacerbation-related costs in patients with severe asthma in U.S. clinical practice.

Methods: This retrospective cohort study used U.S. administrative claims data from patients ages ≥ 12 years and with severe asthma at mepolizumab treatment initiation (index date; identification period, January 2015–June 2017) who had received two or more mepolizumab administrations within 180 days of the index date and had no evidence of treatment with another asthma biologic. The exacerbation rate and exacerbation-related costs were assessed in both the 12 months before mepolizumab initiation (baseline period) and the following 12 months (follow-up period). A clinical trial-like cohort was identified, defined as patients with two or more baseline exacerbations and ≥ 10 administrations during follow-up.

Results: A total of 201 patients were included in the overall population and 74 patients in the clinical trial-like cohort. Mepolizumab significantly reduced the exacerbation rate between the baseline and follow-up periods in both the overall population and the clinical trial-like cohort ($p < 0.001$), which corresponded to 33.6% and 48.6% reductions, respectively. The rate of exacerbations in patients who required hospitalization between the baseline and follow-up periods was also reduced by 35.3% ($p = 0.080$) and 68.2% ($p = 0.015$) in the overall population and in the clinical trial-like cohort, respectively. Cost data were inconclusive.

Conclusion: This study, which used real-world data, demonstrated that mepolizumab is associated with reductions in asthma exacerbations, in line with the findings from controlled clinical studies. These results provided further evidence of the effectiveness of mepolizumab in a real-world setting.

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Severe asthma, defined as asthma that requires regular use of high-dose maintenance therapies and additional controllers or that remains uncontrolled despite this treatment,^{1,2} is estimated to affect up to 10% of patients with asthma.² Quality of life is significantly

reduced and health care resource utilization and costs are higher in patients with severe asthma compared with those with nonsevere asthma.^{3–5} Asthma comprises several distinct phenotypes⁶; one such phenotype is severe eosinophilic asthma, which is characterized by increased eosinophil levels in blood and/or sputum, frequent exacerbations, and oral corticosteroid (OCS) dependence to achieve asthma control.⁷

Several biologic therapies have been approved to treat severe asthma in the United States.⁸ In particular, mepolizumab, an anti-interleukin-5 monoclonal antibody,⁹ is approved as an add-on maintenance treatment for patients six or more years of age and with severe eosinophilic asthma.¹⁰ Results from clinical trials show that mepolizumab treatment is associated with reductions in exacerbations and use of OCS as well as improvements in lung function, asthma control, and health-related quality of life compared with placebo.^{11–14} There is also evidence that mepolizumab treatment reduces the rate of exacerbations and improves asthma control in the longer term (up to 3.5 years) and that stopping treatment leads to a rise in blood eosinophil counts and loss of asthma control.^{15,16} However, to date, there

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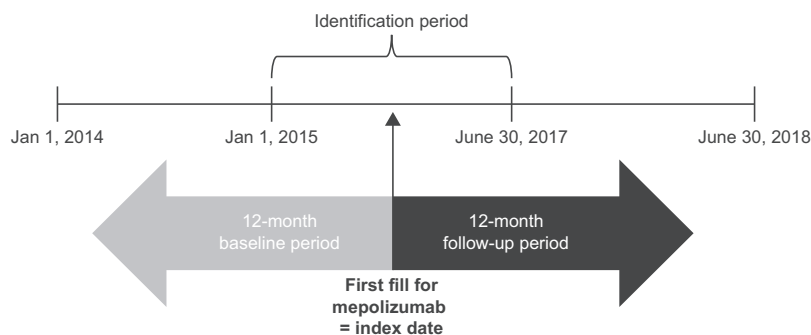


Figure 1. Study design.

are limited data available on the impact of mepolizumab on clinical outcomes in a real-world setting.

The benefits of real-world evidence in describing the effectiveness of a particular treatment in a heterogeneous patient population are well documented, with physicians looking to such evidence to help determine the link between clinical trial data and real-world clinical practice.^{17,18} Given the importance of real-world data in this regard, the main objective of this analysis was to evaluate the impact of mepolizumab on the rate of asthma exacerbations in patients with severe asthma by using data from a U.S. health care claims data base.

METHODS

Study Design

This was a retrospective cohort study (GSK ID: 209032; HO-18-19177) that used administrative claims data from the Optum (Eden Prairie, MN) Research Database. In 2016, this data base contained data on ~14.6 million commercially enrolled individuals and ~3.2 million individuals enrolled in Medicare Advantage from geographically diverse areas across the United States who were enrolled for one or more days between January 1 and December 31, 2016. Patients were identified based on mepolizumab use between January 1, 2015, and June 30, 2017 (identification period). Evidence of mepolizumab treatment was determined by using Healthcare Common Procedure Coding System codes (C9473 or J2182), or National Drug Code (00173-0881-01) listed on a medical or pharmacy claim. Data for each patient were assessed from the baseline period, defined as the 12 months before and including the index date (the first mepolizumab administration), and the follow-up period, defined as the 12 months after the index date (up to June 30, 2018) (Fig. 1).

This study used fully de-identified retrospective claims data and, as such, was not classified as research that involved human participants; therefore, institutional review board approval and informed consent were not required. B. Hahn, H. Ortega, C.F. Bell, M. Bogart, J.-P. Llanos, and T. Bancroft contributed to the conception and design of the study. B. Hahn, T. Bancroft, and B. Chastek contributed to the acquisition

of data. All the authors contributed to the analysis and interpretation of the data and to the development of the manuscript, and approved the final version for submission.

Study Population

Eligible patients received mepolizumab during the identification period and were diagnosed with asthma (defined as one or more nondiagnostic medical claim with an *International Classification of Diseases, Ninth Revision, Clinical Modification* or *International Classification of Diseases, Tenth Revision, Clinical Modification* diagnosis code for asthma in the primary position [Online Supplemental Material]) during the baseline period. Patients also had to be commercial or Medicare Advantage enrollees, ages ≥ 12 years at the index date, with continuous enrollment with medical and pharmacy benefits during the baseline and follow-up periods, and had received two or more doses of mepolizumab in the first 180 days of the 12-month follow-up period (including the index date). Patients who received mepolizumab during the baseline period (excluding the index date) or another asthma-related biologic, such as omalizumab, reslizumab, or benralizumab, during the baseline or follow-up periods were excluded from the analysis, as were patients with a diagnosis of chronic idiopathic urticaria during the baseline period, and those missing demographic information.

Patients were stratified into two cohorts: the all patients cohort, which comprised all patients who met the inclusion/exclusion criteria, and the clinical trial–like cohort. The clinical trial–like cohort included only patients with two or more exacerbations during the baseline period and ≥ 10 mepolizumab administrations during the follow-up (including the index date), which reflected similar criteria used in the design of the mepolizumab clinical trials.

End Points and Assessments

The primary end point was to compare the rate of asthma exacerbations among patients who received mepolizumab in the year before initiating mepolizumab with the year after initiating mepolizumab. The secondary end point was to compare the asthma exacerbation-

related expenditure between the baseline and follow-up periods. Asthma exacerbations were defined as an outpatient or emergency department (ED) visit with a diagnosis of asthma in the primary position and one or more dispensing of systemic corticosteroids (intramuscular, intravenous, or oral) ± 5 days after the encounter. Asthma exacerbations that resulted in hospitalization were defined as inpatient hospital admissions, with asthma as a primary diagnosis any time during the stay. Claims for scheduled administration of mepolizumab (see Online Supplemental Table 1) were not included as exacerbations. Exacerbations that occurred in the 14 days after the exacerbation start date for outpatient exacerbations or the discharge date for hospitalizations were considered a single episode and classified according to the contributing event with the highest severity (exacerbation start and end dates are described in the Online Supplemental Material).

Asthma exacerbation-related costs were measured in the follow-up period and computed as the combined health plan and the patient paid amounts (copayment, deductible, and co-insurance) on adjudicated claims. Costs were adjusted by using the annual medical care component of the Consumer Price Index to reflect inflation to year 2017 and were adjusted by using a coordination of benefits to account for costs from multiple payers.¹⁹ Claims with asthma exacerbation-related costs were identified as the following: inpatient stays with a primary diagnosis of asthma during the stay; ED visits with a primary diagnosis of asthma associated with an asthma-related hospitalization within ± 1 day; ED visit (without an asthma-related hospitalization within ± 1 day), urgent care, or ambulatory visits with an asthma-related diagnosis code in the primary position and the presence of a systemic corticosteroid prescription within ± 5 days of the visit. Costs associated with mepolizumab administration or acquisition, and maintenance medications were excluded.

Data on demographic characteristics and insurance plan type on the index date were collected. General comorbid conditions were defined by using the Clinical Classifications Software managed by the Agency for Healthcare Research and Quality.²⁰ Baseline Quan-Charlson comorbidity scores²¹ were calculated based on the presence of diagnostic codes on medical claims during the baseline period, and the baseline blood eosinophil count was based on the latest measurement during the baseline period.

Statistical Analyses

The rate of asthma exacerbations and the asthma exacerbations that required hospitalization per patient during the 12-month baseline and 12-month follow-up periods were calculated, as were related overall mean total costs per patient within these periods. McNemar tests were

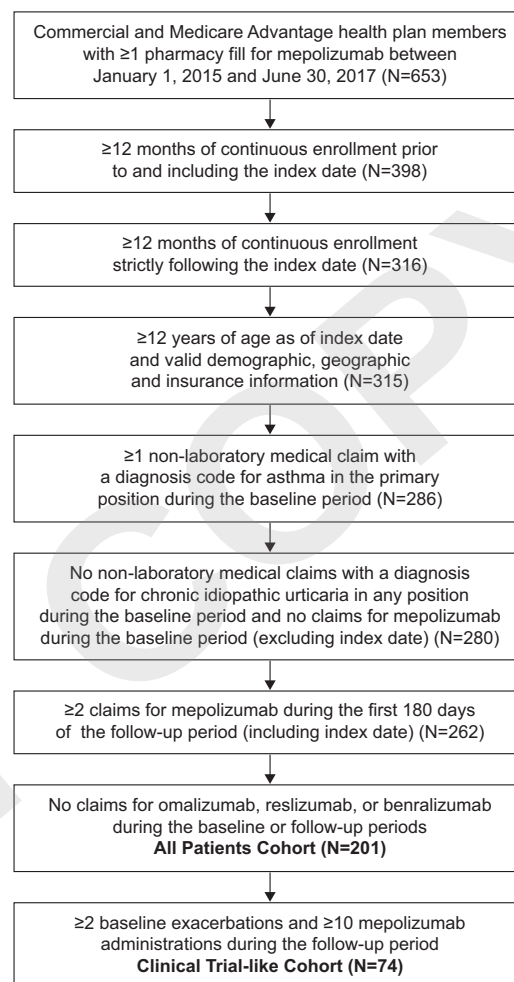


Figure 2. Patient inclusion. In total, 40 patients had two or more baseline exacerbations but did not meet the criteria of ≥ 10 mepolizumab administrations during the follow-up period for inclusion in the clinical trial-like cohort.

used to evaluate the differences for dichotomous or categorical variables, and paired *t*-tests were used for comparison of continuous variables. Differences were considered statistically significant when $p < 0.05$. A *post hoc* sensitivity analysis of the exacerbation cost data was also carried out (owing to the skewed nature of the data) in which data for patients with the 10 largest cost increases and the 10 largest cost decreases between the baseline and follow-up periods were excluded.

RESULTS

Patient Population

In total, 201 patients met the study criteria and were included in the all patients cohort; of these, 74 patients were included in the clinical trial-like cohort (Fig. 2). The mean age in the all patients cohort was 55.9 years, most (67.7%) were female and had commercial insurance (68.2%) (Table 1). Demographics were similar in the

Table 1 Patient baseline demographics and clinical characteristics*

	All Patients Cohort (N = 201)	Clinical Trial–Like Cohort (n = 74)
Age, mean $\pm$ SD, y	55.9 $\pm$ 13.71	56.3 $\pm$ 11.92
Age categories, n (%)		
12–17 y	2 (1.0)	0 (0.0)
18–44 y	38 (18.9)	12 (16.2)
45–64 y	106 (52.7)	43 (58.1)
$\geq$ 65 y	55 (27.4)	19 (25.7)
Gender, n (%)		
Female	136 (67.7)	47 (63.5)
Male	65 (32.3)	27 (36.5)
Region, n (%)		
Northeast	23 (11.4)	8 (10.8)
Midwest	51 (25.4)	20 (27.0)
South	93 (46.3)	33 (44.6)
West	34 (16.9)	13 (17.6)
Insurance plan type, n (%)		
Commercial	137 (68.2)	57 (77.0)
Medicare	64 (31.8)	17 (23.0)
Top 12 AHRQ comorbidities, n (%)		
Other lower respiratory disease	173 (86.1)	65 (87.8)
Other upper respiratory disease	160 (79.6)	65 (87.8)
Respiratory infections	157 (78.1)	59 (79.7)
Hypertension	102 (50.8)	38 (51.4)
Disorders of lipid metabolism	88 (43.8)	33 (44.6)
Other connective tissue disease	86 (42.8)	32 (43.2)
Diseases of the heart	84 (41.8)	33 (44.6)
Other skin disorders	82 (40.8)	32 (43.2)
Upper gastrointestinal disorders	81 (40.3)	33 (44.6)
Eye disorders	80 (39.8)	26 (35.1)
COPD and bronchiectasis	80 (39.8)	30 (40.5)
Nontraumatic joint disorders	75 (37.3)	30 (40.5)
Other comorbid conditions, n (%)		
Allergic rhinitis	136 (67.7)	55 (74.3)
Sinusitis	115 (57.2)	49 (66.2)
COPD	65 (32.3)	26 (35.1)
Nasal polyps	45 (22.4)	19 (25.7)
Autoimmune disorders	17 (8.5)	7 (9.5)
Cancers accompanied by metastasis codes	15 (7.5)	4 (5.4)
Atopic dermatitis	7 (3.5)	4 (5.4)
Eosinophilic esophagitis	4 (2.0)	2 (2.7)
Connective tissue disease	4 (2.0)	2 (2.7)
Eosinophilic granulomatosis with polyangiitis	3 (1.5)	1 (1.4)
Cystic fibrosis	1 (0.5)	0 (0.0)
Modified Quan-Charlson comorbidity score, mean $\pm$ SD	1.58 $\pm$ 1.09	1.50 $\pm$ 0.95
Rate of exacerbations during the 12-mo baseline period, mean $\pm$ SD	2.29 $\pm$ 2.06	3.54 $\pm$ 1.83
Frequent OCS use, n (%)#	115 (57.2)	53 (71.6)

Table 1 Continued

	All Patients Cohort (N = 201)	Clinical Trial–Like Cohort (n = 74)
Blood eosinophil count, n (%)		
<150 cells/ μ L	6 (7.3)	2 (6.5)
150 to <300 cells/ μ L	21 (25.6)	6 (19.4)
300 to <400 cells/ μ L	13 (15.9)	3 (9.7)
≥ 400 cells/ μ L	42 (51.2)	20 (64.5)

SD = Standard deviation; AHRQ = Agency for Healthcare Research and Quality; COPD = chronic obstructive pulmonary disease; OCS = oral corticosteroid.
 *Baseline demographics were measured on the index date.
 #Total day's supply on all claims ≥ 56 days.

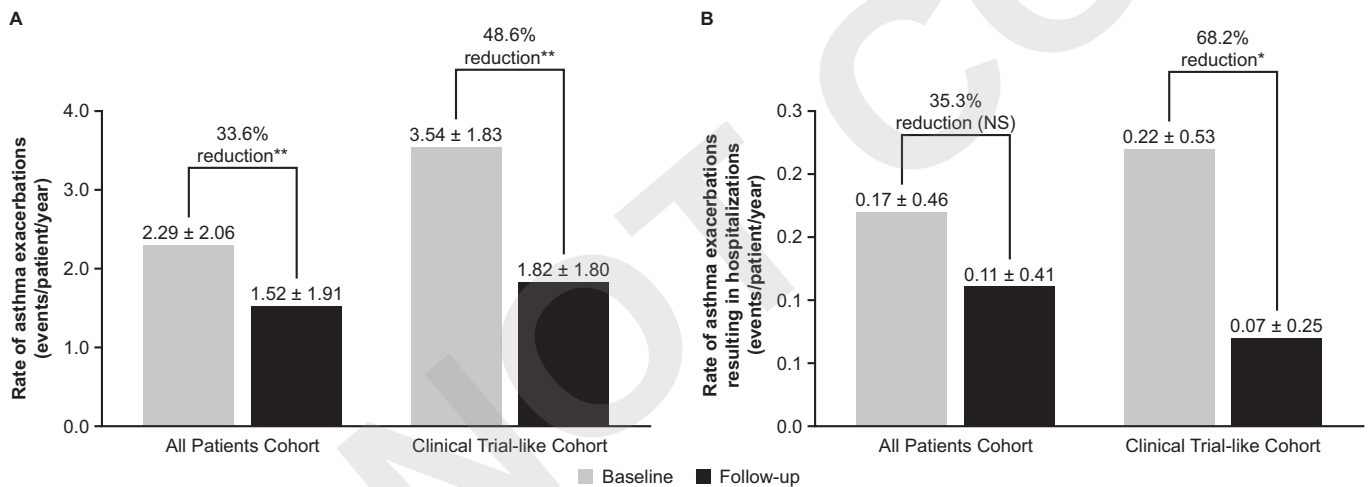


Figure 3. Mean rates of (A) asthma exacerbations and (B) asthma exacerbations that resulted in hospitalization during baseline and follow-up periods. ** $p < 0.001$; * $p < 0.05$. Data labels show mean $\pm$ standard deviation. NS = Not significant.

clinical trial–like cohort, except a higher proportion of patients had commercial insurance (77.0%) (Table 1). During the 12-month baseline period, patients in the all patients cohort experienced a mean of 2.29 exacerbations, whereas those in the clinical trial–like cohort experienced a mean of 3.54 exacerbations. As expected across both cohorts, the most common comorbidities as defined by the Agency for Healthcare Research and Quality²⁰ were respiratory disease and respiratory infections, followed by hypertension, lipid disorders, and other connective tissue disease (Table 1). The mean $\pm$ standard deviation number of mepolizumab administrations in the 12-month follow-up period was 10.7 ± 4.64 in the all patients cohort and 13.3 ± 3.18 in the clinical trial–like cohort. Use of systemic OCS at baseline and during follow-up is detailed in the Online Supplemental Table 2.

Asthma Exacerbations

Mepolizumab significantly reduced the rate of exacerbations from baseline to the follow-up in the all patients cohort (33.6% reduction; $p < 0.001$) and in the

clinical trial–like cohort (48.6% reduction; $p < 0.001$) (Fig. 3). Similarly, mepolizumab reduced the rate of exacerbations that resulted in hospitalization versus the baseline in both cohorts, which corresponded to reductions of 35.3% ($p = 0.080$) and 68.2% ($p = 0.015$) in the all patients cohort and the clinical trial–like cohort, respectively (Fig. 3).

Asthma-Related Costs during Asthma Exacerbations

In the all patients cohort, the mean total asthma-related (medical and pharmacy) costs during asthma exacerbations were found to increase from baseline to follow-up, whereas there was a small decrease in the clinical trial–like cohort (Online Supplemental Table 3). After categorizing asthma-related total costs during exacerbations according to the change from baseline to follow-up, most patients (88.0%) had a change in total cost, ranging from a decrease of up to \$10,000 to an increase of \$10,000, with 12 patients having decreases $> \$10,000$ and 12 patients having increases $> \$10,000$. A *post hoc* sensitivity analysis, in which data from the patients with the

10 largest decreases and 10 largest increases in these total costs were removed, resulted in an overall mean decrease of \$76 between baseline and follow-up.

DISCUSSION

In this retrospective study based on U.S. administrative claims data, treatment with mepolizumab resulted in a reduction in exacerbations and exacerbations that resulted in asthma-related hospitalizations in patients with severe asthma. When data from a cohort of patients with two or more baseline exacerbations and ≥ 10 administrations during follow-up (which reflected study entry criteria and treatment adherence in mepolizumab clinical trials) were assessed, the reductions in the rates of exacerbations and exacerbations that resulted in hospitalization were more pronounced than those seen in the overall study population. Our findings contribute to mounting real-world evidence that demonstrates that the beneficial impact on the exacerbation rate illustrated during the mepolizumab clinical trial program translates into real-world effectiveness in patients treated in clinical practice. This has important clinical implications, as in patients with severe uncontrolled asthma, exacerbations have been shown to contribute substantially to disease burden and clinical data have demonstrated that mepolizumab improves health status by reducing exacerbations.²²

The reductions in the rates of exacerbations and exacerbations that required hospitalization after mepolizumab treatment we observed in the all patients cohort were broadly in line with findings from clinical trials for the licensed dose of mepolizumab (100 mg subcutaneously) in patients with severe eosinophilic asthma. The percentage rate reductions versus placebo of 53–58% for all exacerbations and 61–68% for those exacerbations that required hospitalization were reported.^{12,13} However, to better compare our real-world data with those from previous mepolizumab clinical trials, we identified a clinical trial–like cohort of patients.

Patients in this cohort experienced greater reductions in the rates of exacerbations and exacerbations that resulted in hospitalization than those patients in the full cohort, with the reductions in the clinical trial–like cohort (48.6% and 68.2%, respectively) being closer to those shown in the mepolizumab clinical trials. However, it should be noted that the clinical trial–like cohort excluded patients with one or no exacerbation in the baseline period; therefore, any changes in exacerbations after mepolizumab treatment in these patients would not be detected. Nonetheless, the results from the overall study population showed that outcomes observed during clinical trials can also be seen in a real-world clinical practice setting. This notion is also supported by several smaller real-world studies that showed reductions in exacerbations after mepolizumab initiation.^{23–27}

We also investigated changes in the total asthma exacerbation–related costs between the baseline and follow-up periods; for both the clinical trial–like cohort and the all patients cohort, an increase was observed from baseline to follow-up. This is in contrast to another study based on U.S. insurance claims data (IBM Watson Health MarketScan Commercial Claims Database) (IBM Corporation, Somers, NY) in which a reduction in mean total costs after mepolizumab initiation was observed in patients with severe asthma.²⁸ Likewise, an economic analysis of the phase III MENSA trial²⁹ reported a reduction in mean exacerbation-related medical costs with mepolizumab compared with placebo. In our analysis, the relatively small sample size ($N = 201$) and the large standard deviation of the total costs relative to the means within the periods used did not allow a precise enough estimation of change in costs from baseline to follow-up.

Overall, the proportion of patients who showed a reduction in the mean total asthma exacerbation–related costs was 60.2%, and, indeed, when we conducted a *post hoc* sensitivity analysis, in which data for the 10 patients with the greatest cost increases and the 10 patients with the greatest cost decreases were excluded, a marginal decrease in the mean total costs from baseline to follow-up was seen. Future studies based on data from larger numbers of patients should enable a more thorough investigation of the impact of mepolizumab on exacerbation-related costs. Notably, approximately one-third of the patients in our study had comorbid chronic obstructive pulmonary disease (COPD), which was in line with the IBM Watson Health Database study.²⁸ Asthma–COPD overlap is associated with a greater burden and severity of disease than asthma or COPD alone.³⁰ The substantial proportion of patients in the real world with both asthma and COPD highlights the need for early identification of these individuals and intervention with appropriate tailored therapies.

There were several limitations that should be considered for this study. First, the patient population was restricted to the United States, and a subgroup analysis by insurance type was not possible for this study, owing to the number of patients available. Second, it should be noted that, in some instances, the diagnosis code on a medical encounter or an outside claim may have been coded incorrectly or included as rule-out criterion rather than actual disease, which may have introduced some bias. Third, we also used dispensed medication claims as an indicator of medication use, which does not necessarily indicate that medication was consumed or taken as prescribed. Fourth, the study did not account for other medications or controllers that patients may have been taking during the study period, unlike in clinical trials in which controller medication use and adherence are typically monitored. Despite these limitations, this study provided

further evidence of the effectiveness of mepolizumab treatment in real-world clinical practice.

CONCLUSION

This study of data from a real-world patient population of patients who received mepolizumab demonstrated a reduction in asthma exacerbations, similar to that seen in formal clinical trials. These data provide valuable real-world insights into the impact of mepolizumab treatment for physicians and payers.

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