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ORIGINAL RESEARCH

Benralizumab Reduces Asthma Exacerbations and Costs Among Medicare Beneficiaries with Severe Asthma: The ZEPHYR-5 Study

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Purpose: Clinical trials have demonstrated benralizumab reduces exacerbations among patients with severe asthma. Evidence on the effectiveness of benralizumab among older adults is limited. The objective was to assess the change in the annual asthma exacerbation rate (AAER), exacerbation-related medical costs, and asthma medication utilization 12 months before and after the initiation of benralizumab in Medicare patients, as well as in an all-payer sample, in a subgroup with prior biologic use, and segmented by benralizumab adherence status.

Methods: This was a single-arm, 12-month pre-/post-, within-subjects study using 2017–2023 MORE^2 Registry® and Medicare Fee-For-Service databases. Included patients met the following criteria: 1) prescription for benralizumab (index date) and ≥1 refill within 90 days, 2) 12 months of database enrollment preceding and following the index date, 3) ≥1 inpatient or ≥2 outpatient claims with a diagnosis of asthma during the baseline period, and 4) ≥2 asthma exacerbations during the baseline period. Outcomes included percent change in AAER, exacerbation-related medical costs, and asthma medication utilization.

Results: The study included 4,611 Medicare patients and 7,706 patients in the all-payer sample. Among Medicare patients, there was a 43.5% reduction in AAER (mean [SD], 3.8[2.0] to 2.2[2.2] exacerbations per year; P <0.001). Exacerbation-related medical costs decreased across all cost categories, as did use of corticosteroids and other asthma medications. Reductions in outcomes were also observed in an all-payer sample.

Conclusion: Medicare patients with severe asthma initiating benralizumab demonstrated meaningful reductions in AAER, exacerbation-related medical costs, and corticosteroid use in a real-world setting.

Keywords: asthma, exacerbation, benralizumab, biologics, effectiveness

Introduction

Asthma is a chronic inflammatory disorder of the airways characterized by shortness of breath, wheezing, coughing, chest tightness, variable airflow limitation, and tissue remodeling.[1,2] A subset of asthma, severe eosinophilic asthma, is marked by heightened inflammation and an increased presence of eosinophils in the airways, resulting in more intense symptoms and a higher risk of exacerbations. An exacerbation is progressive worsening of symptoms that is often severe, restricting airflow and lung function.[3,4] Uncontrolled or poorly controlled asthma is costly in the U.S., and costs to the healthcare system and individuals continue to increase over time.[5] Asthma exacerbations, in particular, are especially costly;[5] nearly half of individuals with asthma have had an exacerbation in the past 12 months.[6]

Over the past decade, biologic therapies have changed the treatment landscape for patients with severe asthma, and work by targeting cytokines that are involved in airway inflammation.[7] Omalizumab was the first biologic approved for moderate to severe persistent asthma in 2003. Since then, additional biologics have been approved, including benralizumab, which binds to the interleukin-5 receptor α subunit (IL-5Rα) on eosinophils, triggering antibody-dependent cell-mediated cytotoxicity; mepolizumab and reslizumab, which binds to the IL-5 receptor; dupilumab, which blocks the IL-

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4/IL-13R receptors; and tezepelumab-ekko, which binds to thymic stromal lymphopoietin, a cytokine involved in asthma pathogenesis.[8] These biologics have improved the quality of life for patients by reducing the frequency of asthma exacerbations and decreasing dependence on corticosteroids. According to the Global Initiative for Asthma 2025 guidelines, patients with difficult-to-treat or severe asthma should be on a biologic for at least 4 months to evaluate its effectiveness.[9] Patients who respond positively should be reassessed every 3–6 months, while non-responders are recommended to switch to a different biologic or discontinue biologic therapy.[9]

Benralizumab has been approved by the U.S. Food and Drug Administration as add-on maintenance therapy for patients aged 6 years and older with severe asthma of the eosinophilic phenotype, and for adult patients with eosinophilic granulomatosis with polyangiitis.[10] Clinical trials have demonstrated benralizumab reduces asthma exacerbations, and is not associated with an increased incidence of adverse events,[11–13] The reduction in exacerbations has been demonstrated in multiple retrospective database analyses among patients prescribed benralizumab in a real-world setting, including the ZEPHYR-1 study (55% reduction following treatment initiation),[14] the ZEPHYR-2 study (68% reduction in a biologic naïve cohort),[15] the international XALOC-1 study (84% reduction in a multi-country cohort),[16] and findings from the ZEPHYR-5 study (45% reduction in an adherent, all-payer cohort[17] and 39% reduction in a cohort with concomitant COPD[18]). However, real-world evidence is limited among specific sub-populations typically underrepresented in retrospective studies, including older adult patients.

To address this evidence gap, this real-world study aimed to (1) assess the change in the annualized asthma exacerbations rate (AAER), exacerbation-related medical costs, and asthma medication utilization prior to and following the initiation of benralizumab in a sample of Medicare patients with severe asthma, and (2) replicate these analyses in an all-payer sample, in a subgroup with prior biologic use, and segmented by benralizumab adherence status.

Methods

Study Design and Data Sources

This was a non-interventional, retrospective, single-arm study conducted utilizing administrative claims from the Inovalon MORE^2 Registry® of Closed Claims and the 100% Medicare Fee-For-Service (FFS) databases. The study design was a 12-month pre-post analysis of severe asthma patients treated with benralizumab. The study period began at the time of commercial availability of benralizumab (November 14, 2017) and ended on December 31, 2022 among patients appearing in the 100% Medicare FFS database, and on May 31, 2023 among patients appearing in the MORE^2 Registry® of Closed Claims.

The 100% Medicare FFS database contains enrollment information and claims for Parts A, B, and Part D Prescription Drug Event data for all Part D plans. The Medicare Master Beneficiary Summary File (MBSF) was used to determine beneficiary monthly eligibility for Part A/B services and patient demographics. The MORE^2 Registry® of Closed Claims contains claims from all 50 states and is sourced from over 140 health plans. Access to and use of the 100% Medicare FFS database was granted through a data use agreement with the Centers for Medicare & Medicaid Services (CMS), and access to and use of the MORE^2 Registry® of Closed Claims was provided by Inovalon. These databases contain fully de-identified data in compliance with the United States Health Insurance Portability and Accountability Act (HIPAA) of 1996. Under HIPAA's de-identification provisions (45 CFR §164.514) and corresponding institutional guidelines, analyses of de-identified data are exempt from Institutional Review Board review and patient informed consent requirements.

Study Population

Patients eligible for study inclusion met the following criteria: (1) a prescription claim for benralizumab and at least one refill within 90 days (earliest prescription was the index date), (2) 12 months of database enrollment preceding (pre-index period) and following (post-index period) the index date, (3) one or more inpatient or two or more outpatient claims with a diagnosis code for asthma during the pre-index period, and (4) presence of at least two asthma exacerbations during the pre-index period. Included patients were also required to be 12 years of age or older on the index date.

Two study cohorts were created based on payer. The Medicare cohort included patients with Medicare FFS and Medicare Advantage and an all-payer cohort included patients with Medicare FFS, Medicare Advantage, commercial, and Managed Medicaid payer types. The all-payer cohort was further stratified by benralizumab adherence status and by previous biologic use, overall and by biologic. Patients adherent to benralizumab had six or more claims during the 12-month post-index period, while non-adherent patients had fewer than six claims of benralizumab in the same time period. Patients with previous biologic use had at least one outpatient medical or pharmacy claim for dupilumab, mepolizumab, omalizumab, reslizumab, or tezepelumab during the pre-index period.

Study Outcomes

Study outcomes included the percentage change in the AAER per year and the percentage change in the exacerbation-related healthcare utilization and costs comparing the 12-month pre-index period to the 12-month post-index period.

An asthma exacerbation event was defined based on a previously published study,[19] and was defined as at least one inpatient claim with a diagnosis of asthma as the primary discharge diagnosis; or at least one claim for mechanical ventilation and corresponding asthma diagnosis on the same day; or at least one emergency department visit, urgent care visit, or other outpatient visit claim with an asthma diagnosis treated with short course of systemic corticosteroids within (±) seven days (one administration of injectable steroids or oral corticosteroids for at least three days).

Exacerbation-related medical costs were based on the operational definition of an asthma exacerbation as defined above. The following service categories contributed to sum of medical costs: physician office/clinic visit, emergency department, inpatient hospital costs, and other outpatient costs. For the 100% Medicare FFS analyses, costs were based on the Medicare payment amount reported on the claim plus beneficiary cost-sharing. For the MORE^2 Registry®, standardized costs were defined based on global relative value units and the Medicare fee schedules. All costs were adjusted for inflation using the medical care component of the Consumer Price Index (CPI) obtained from the U.S. Bureau of Labor Statistics and standardized to 2023 U.S. dollars.[20]

Other study outcomes included changes in asthma medication and treatment utilization prior to and following the initiation of benralizumab and included oxygen therapy, nebulizer use, inhaled corticosteroids (ICS), systemic corticosteroids, short-acting β2-agonists (SABA), short-acting muscarinic antagonists (SAMA), long-acting β-agonists (LABA), long-acting muscarinic antagonists (LAMA), ICS/LABA combinations, ICS/LABA/LAMA combinations, leukotriene modifiers, mast cell stabilizers, methylxanthines, PDE-4 inhibitors, and biologic treatments including dupilumab, mepolizumab, omalizumab, reslizumab, and tezepelumab.

Statistical Analysis

Descriptive statistics included means, medians, and standard deviations (SD) for continuous variables and frequencies and percentages for categorical variables. For all descriptive statistics with comparisons between pre-index and post-index periods, percentage change from pre-index to post-index was calculated and statistically significant differences were determined via paired Student's *t*-test or the Wilcoxon signed-rank test for continuous variables, and McNemar's test for categorical variables. The critical alpha level was set to 0.05 for all analyses.

Results

Study Population and Baseline Characteristics

A total of 4,611 patients were included in the Medicare cohort, which was comprised of both Medicare FFS (N=4,213; 91.4%) and Medicare Advantage (N=398; 8.6%) beneficiaries. The Medicare cohort was an older population with a mean (SD) age of 69.3 (10.9) years; 93.1% were aged 50 and older, while 79.6% were aged 65 and older. The majority of patients were female (69.1%) and resided in the South region (40.5%). The mean (SD) Elixhauser Comorbidity Index was 6.8 (7.5) (Table 1). The majority of the Medicare cohort had concomitant COPD (64.6%), and cardiovascular conditions and other comorbidities were also common: dyslipidemia (65.1%), gastroesophageal reflux disease (57.9%), sleep apnea (37.6%), and ischemic heart disease (23.1%).

Table 1 Baseline Patient Characteristics

	Medicare N= 4,611	All-Payer[a] N= 7,706	All-Payer, Prior Biologic Use N= 1,873	Adherence Status[b]	
				Non-Adherent N= 1,639	Adherent N= 6,067
Age, mean (SD)	69.3 (10.9)	59.8 (17.2)	59.6 (16.9)	57.0 (18.2)	60.6 (16.8)
Age group, n (%)					
12–39	116 (2.5%)	1,067 (13.8%)	236 (12.6%)	302 (18.4%)	765 (12.6%)
40–49	203 (4.4%)	911 (11.8%)	261 (13.9%)	238 (14.5%)	673 (11.1%)
50–64	621 (13.5%)	1,896 (24.6%)	470 (25.1%)	402 (24.5%)	1,494 (24.6%)
65–74	2,289 (49.6%)	2,429 (31.5%)	592 (31.6%)	429 (26.2%)	2,000 (33.0%)
75–79	819 (17.8%)	829 (10.8%)	173 (9.2%)	160 (9.8%)	669 (11.0%)
80+	563 (12.2%)	574 (7.4%)	141 (7.5%)	108 (6.6%)	466 (7.7%)
Sex, n (%)					
Male	1,426 (30.9%)	2,356 (30.6%)	602 (32.1%)	450 (27.5%)	1,906 (31.4%)
Female	3,185 (69.1%)	5,350 (69.4%)	1,271 (67.9%)	1,189 (72.5%)	4,161 (68.6%)
Census region, n (%)					
Northeast	1,043 (22.6%)	1,847 (24.0%)	451 (24.1%)	402 (24.5%)	1,445 (23.8%)
Midwest	891 (19.3%)	1,572 (20.4%)	377 (20.1%)	356 (21.7%)	1,216 (20.0%)
South	1,869 (40.5%)	2,991 (38.8%)	695 (37.1%)	627 (38.3%)	2,364 (39.0%)
West/U.S. Territory/Unknown	808 (17.5%)	1,296 (16.8%)	350 (18.7%)	254 (15.5%)	1,042 (17.2%)
Low-income subsidy status, n (%)					
Yes	1,387 (30.1%)	1,399 (18.2%)	395 (21.1%)	322 (19.6%)	1,077 (17.8%)
No	3,175 (68.9%)	3,176 (41.2%)	768 (41.0%)	583 (35.6%)	2,593 (42.7%)
Unknown	49 (1.1%)	3,131 (40.6%)	710 (37.9%)	734 (44.8%)	2,397 (39.5%)
Elixhauser Comorbidity Index, mean (SD)	6.8 (7.5)	5.7 (7.1)	5.5 (7.1)	6.2 (7.3)	5.6 (7.0)
Comorbidities, n (%)					
Allergic rhinitis	2,906 (63.0%)	5,088 (66.0%)	1,349 (72.0%)	1,076 (65.6%)	4,012 (66.1%)
Anxiety	1,425 (30.9%)	2,581 (33.5%)	642 (34.3%)	598 (36.5%)	1,983 (32.7%)
Atopic dermatitis	149 (3.2%)	322 (4.2%)	103 (5.5%)	69 (4.2%)	253 (4.2%)
Chronic sinusitis	1,361 (29.5%)	2,264 (29.4%)	607 (32.4%)	451 (27.5%)	1,813 (29.9%)
Chronic urticaria	169 (3.7%)	355 (4.6%)	129 (6.9%)	84 (5.1%)	271 (4.5%)
Chronic obstructive pulmonary disease (COPD)	2,977 (64.6%)	4,201 (54.5%)	1,008 (53.8%)	874 (53.3%)	3,327 (54.8%)
Dyslipidemia	3,003 (65.1%)	4,045 (52.5%)	1,001 (53.4%)	804 (49.1%)	3,241 (53.4%)
Eosinophilic esophagitis	30 (0.7%)	92 (1.2%)	30 (1.6%)	22 (1.3%)	70 (1.2%)
Gastroesophageal reflux disease	2,671 (57.9%)	4,146 (53.8%)	1,059 (56.5%)	889 (54.2%)	3,257 (53.7%)
Insomnia	193 (4.2%)	310 (4.0%)	84 (4.5%)	78 (4.8%)	232 (3.8%)

(*Continued*)

Table 1 (Continued).

	Medicare N= 4,611	All-Payer[a] N= 7,706	All-Payer, Prior Biologic Use N= 1,873	Adherence Status[b]	
				Non-Adherent N= 1,639	Adherent N= 6,067
Ischemic heart disease	1,065 (23.1%)	1,304 (16.9%)	327 (17.5%)	288 (17.6%)	1,016 (16.7%)
Nasal polyps	400 (8.7%)	730 (9.5%)	244 (13.0%)	153 (9.3%)	577 (9.5%)
Sleep apnea	1,736 (37.6%)	2,761 (35.8%)	717 (38.3%)	611 (37.3%)	2,150 (35.4%)
Tobacco dependence	356 (7.7%)	801 (10.4%)	162 (8.6%)	210 (12.8%)	591 (9.7%)
Vocal cord dysfunction	170 (3.7%)	292 (3.8%)	89 (4.8%)	72 (4.4%)	220 (3.6%)

Notes: [a] All-payer cohort included commercial (N=1,335), Medicare Advantage or Medicare FFS, (N=4,611) and Managed Medicaid (N=1,760) patients. [b] Adherent patients had six or more claims for benralizumab during the 12-month post-index period, while non-adherent patients had fewer than six claims for benralizumab in the same time period.
Abbreviation: AAER, Annual Asthma Exacerbation Rate.

The all-payer cohort included 7,706 patients and was made up of the following payer types: Medicare (N=4,611; 59.8%), commercial (N=1,335; 17.3%), and Managed Medicaid (N=1,760; 22.8%). The mean (SD) age of the all-payer cohort was slightly younger than the Medicare cohort (59.8 (17.2) years), and the mean (SD) Elixhauser Comorbidity Index was 5.7 (7.1) (Table 1). Patients in the all-payer cohort also had a high prevalence of concomitant COPD (54.5%), and slightly lower prevalence of other comorbidities compared to the Medicare cohort: dyslipidemia (52.5%), gastro-esophageal reflux disease (53.8%), sleep apnea (35.8%), and ischemic heart disease (16.9%). The baseline characteristics among patients in the all-payer cohort by payer type are available in eTable 1.

A total of 6,067 (78.7%) patients in the all-payer cohort were adherent to benralizumab, while 1,639 (21.3%) were non-adherent to benralizumab. In the all-payer cohort, 1,873 (24.3%) had previous use of a biologic medication for asthma prior to the index date, meaning approximately a quarter of the sample switched to benralizumab from a different biologic asthma medication. Of those patients with prior biologic use, 197 (10.5%) received dupilumab, 730 (39.0%) received mepolizumab, 1,006 (53.7%) received omalizumab, and 76 (4.1%) received reslizumab (Table 2).

Changes in AAER, Exacerbation-Related Costs, and Asthma Medication Utilization – Medicare Cohort

There was a 43.5% reduction in the mean (SD) AAER after the initiation of benralizumab from 3.8 (2.0) to 2.2 (2.2) asthma exacerbations per year (P <0.001) (Figure 1). The mean (SD) exacerbation-related medical costs decreased by 39.7% from $1,998 ($4,764) to $1,205 ($3,726) (P <0.001) (Figure 2). Likewise, the exacerbation-related medical costs decreased across all cost categories after initiation of benralizumab: inpatient (59.0%; P <0.001), emergency department (60.2%; P < 0.001), physician/clinic visit (14.7%; P <0.001), and other outpatient costs (24.7%; P <0.001) (Table 3).

Following initiation of benralizumab, Medicare patients experienced reductions in asthma-related medication utilization, as well as nebulizer use (Table 2). Inhaled and systemic corticosteroid use decreased by 16.4% and 14.6%, respectively. Among the asthma-related medications measured in the analyses, only ICS/LABA/LAMA combination treatment and dupilumab use increased (Table 2).

Changes in AAER, Exacerbation-Related Costs, and Asthma Medication Utilization – All-Payer Cohort

Among patients in the all-payer cohort, there was a reduction in the mean (SD) AAER by 42.7% from 3.88 (2.08) to 2.22 (2.31) exacerbations per year (P <0.001) (Figure 1). The mean (SD) exacerbation-related medical costs decreased by 45.4% from $1,808 ($4,607) to $988 ($3,398) (P <0.001) (Figure 2). AAER and exacerbation-related costs among patients in the all-payer cohort by payer type are available in eTable 2.

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Table 2 Asthma Medications by Cohort

	Medicare N = 4,611			All-Payer[a] N = 7,706			All-Payer, Prior Biologic Use N = 1,873			All-Payer, Adherence Status[b]					
										Non-Adherent N= 1,639			Adherent N = 6,067		
	Pre Index, n (%)	Post Index, n (%)	Relative Change, % (*P*)	Pre Index, n (%)	Post Index, n (%)	Relative Change, % (*P*)	Pre Index, n (%)	Post Index, n (%)	Relative Change, % (*P*)	Pre Index, n (%)	Post Index, n (%)	Relative Change, % (*P*)	Pre Index, n (%)	Post Index, n (%)	Relative Change, % (*P*)
Respiratory treatments, n (%)															
Oxygen therapy	730 (15.8%)	771 (16.7%)	5.6% (0.023)	1,021 (13.2%)	1,053 (13.7%)	3.1% (0.133)	303 (16.2%)	291 (15.5%)	−4.0% (0.281)	220 (13.4%)	238 (14.5%)	8.2% (0.072)	801 (13.2%)	815 (13.4%)	1.7% (0.457)
Nebulizer use	2,760 (59.9%)	1,788 (38.8%)	−35.2% (<0.001)	4,528 (58.8%)	2,805 (36.4%)	−38.1% (<0.001)	1,024 (54.7%)	772 (41.2%)	−24.6% (<0.001)	965 (58.9%)	743 (45.3%)	−23.0% (<0.001)	3,563 (58.7%)	2,062 (34.0%)	−42.1% (<0.001)
Non-biologic treatments, n (%)															
Inhaled corticosteroids (ICS)	1,424 (30.9%)	1,191 (25.8%)	−16.4% (<0.001)	2,413 (31.3%)	1,995 (25.9%)	−17.3% (<0.001)	662 (35.3%)	603 (32.2%)	−8.9% (0.001)	508 (31.0%)	442 (27.0%)	−13.0% (<0.001)	1,905 (31.4%)	1,553 (25.6%)	−18.5% (<0.001)
Systemic corticosteroids	4,610 (100.0%)	3,937 (85.4%)	−14.6% (<0.001)	7,704 (100.0%)	6,613 (85.8%)	−14.2% (<0.001)	1,873 (100.0%)	1,693 (90.4%)	−9.6% (<0.001)	1,639 (100.0%)	1,487 (90.7%)	−9.3% (<0.001)	6,065 (100.0%)	5,126 (84.5%)	−15.5% (<0.001)
Short-acting β2-agonists (SABA)	3,884 (84.2%)	3,243 (70.3%)	−16.5% (<0.001)	6,822 (88.5%)	5,932 (77.0%)	−13.0% (<0.001)	1,618 (86.4%)	1,500 (80.1%)	−7.3% (<0.001)	1,474 (89.9%)	1,383 (84.4%)	−6.2% (<0.001)	5,348 (88.1%)	4,549 (75.0%)	−14.9% (<0.001)
Short-acting muscarinic antagonists (SAMA)	116 (2.5%)	98 (2.1%)	−15.5% (0.055)	463 (6.0%)	356 (4.6%)	−23.1% (<0.001)	117 (6.2%)	99 (5.3%)	−15.4% (0.063)	108 (6.6%)	96 (5.9%)	−11.1% (0.185)	355 (5.9%)	260 (4.3%)	−26.8% (<0.001)
Long-acting β-agonists (LABA)	410 (8.9%)	381 (8.3%)	−7.1% (0.044)	500 (6.5%)	461 (6.0%)	−7.8% (0.021)	148 (7.9%)	148 (7.9%)	0.0% (1.000)	93 (5.7%)	104 (6.3%)	11.8% (0.179)	407 (6.7%)	357 (5.9%)	−12.3% (0.001)
Long-acting muscarinic antagonists (LAMA)	1,716 (37.2%)	1,372 (29.8%)	−20.0% (<0.001)	3,168 (41.1%)	2,665 (34.6%)	−15.9% (<0.001)	867 (46.3%)	726 (38.8%)	−16.3% (<0.001)	681 (41.5%)	563 (34.4%)	−17.3% (<0.001)	2,487 (41.0%)	2,102 (34.6%)	−15.5% (<0.001)
ICS/LABA	3,351 (72.7%)	2,862 (62.1%)	−14.6% (<0.001)	5,999 (77.8%)	5,204 (67.5%)	−13.3% (<0.001)	1,435 (76.6%)	1,267 (67.6%)	−11.7% (<0.001)	1,263 (77.1%)	1,090 (66.5%)	−13.7% (<0.001)	4,736 (78.1%)	4,114 (67.8%)	−13.1% (<0.001)
ICS/LABA/LAMA	446 (9.7%)	584 (12.7%)	30.9% (<0.001)	756 (9.8%)	974 (12.6%)	28.8% (<0.001)	148 (7.9%)	228 (12.2%)	54.1% (<0.001)	159 (9.7%)	238 (14.5%)	49.7% (<0.001)	597 (9.8%)	736 (12.1%)	23.3% (<0.001)
Leukotriene modifiers	3,543 (76.8%)	3,266 (70.8%)	−7.8% (<0.001)	6,017 (78.1%)	5,538 (71.9%)	−8.0% (<0.001)	1,420 (75.8%)	1,339 (71.5%)	−5.7% (<0.001)	1,253 (76.4%)	1,140 (69.6%)	−9.0% (<0.001)	4,764 (78.5%)	4,398 (72.5%)	−7.7% (<0.001)
Mast cell stabilizers	15 (0.3%)	15 (0.3%)	0.0% (1.000)	27 (0.4%)	26 (0.3%)	−3.7% (0.866)	11 (0.6%)	N < 11	N/A (N/A)	N < 11 (N/A)	N < 11 (N/A)	N/A (N/A)	24 (0.4%)	22 (0.4%)	−8.3% (0.724)
Methylxanthines	238 (5.2%)	192 (4.2%)	−19.3% (<0.001)	372 (4.8%)	298 (3.9%)	−19.9% (<0.001)	126 (6.7%)	110 (5.9%)	−12.7% (0.021)	88 (5.4%)	69 (4.2%)	−21.6% (0.005)	284 (4.7%)	229 (3.8%)	−19.4% (<0.001)
PDE-4 inhibitors	123 (2.7%)	99 (2.1%)	−19.5% (0.003)	168 (2.2%)	139 (1.8%)	−17.3% (0.003)	48 (2.6%)	46 (2.5%)	−4.2% (0.724)	36 (2.2%)	33 (2.0%)	−8.3% (0.532)	132 (2.2%)	106 (1.7%)	−19.7% (0.002)

Biologic treatments, n (%)															
Dupilumab	80 (1.7%)	108 (2.3%)	35.0% (0.029)	197 (2.6%)	321 (4.2%)	62.9% (<0.001)	197 (10.5%)	108 (5.8%)	−45.2% (<0.001)	51 (3.1%)	186 (11.3%)	264.7% (<0.001)	146 (2.4%)	135 (2.2%)	−7.5% (0.501)
Mepolizumab	469 (10.2%)	97 (2.1%)	−79.3% (<0.001)	730 (9.5%)	175 (2.3%)	−76.0% (<0.001)	730 (39.0%)	74 (4.0%)	−89.9% (<0.001)	166 (10.1%)	114 (7.0%)	−31.3% (<0.001)	564 (9.3%)	61 (1.0%)	−89.2% (<0.001)
Omalizumab	640 (13.9%)	157 (3.4%)	−75.5% (<0.001)	1,006 (13.1%)	282 (3.7%)	−72.0% (<0.001)	1,006 (53.7%)	202 (10.8%)	−79.9% (<0.001)	214 (13.1%)	114 (7.0%)	−46.7% (<0.001)	792 (13.1%)	168 (2.8%)	−78.8% (<0.001)
Reslizumab	54 (1.2%)	14 (0.3%)	−74.1% (<0.001)	76 (1.0%)	23 (0.3%)	−69.7% (<0.001)	76 (4.1%)	15 (0.8%)	−80.3% (<0.001)	20 (1.2%)	17 (1.0%)	−15.0% (0.611)	56 (0.9%)	N < 11 (N/A)	N/A (N/A)
Tezepelumab	0 (0.0%)	18 (0.4%)	N/A (N/A)	0 (0.0%)	45 (0.6%)	N/A (N/A)	0 (0.0%)	21 (1.1%)	N/A (N/A)	0 (0.0%)	23 (1.4%)	N/A (N/A)	0 (0.0%)	22 (0.4%)	N/A (N/A)

Notes: [a] All-payer cohort included commercial (N=1,335), Medicare Advantage or Medicare FFS, (N=4,611) and Managed Medicaid (N=1,760) patients. [b] Adherent patients had six or more claims for benralizumab during the 12-month post-index period, while non-adherent patients had fewer than six claims for benralizumab in the same time period.

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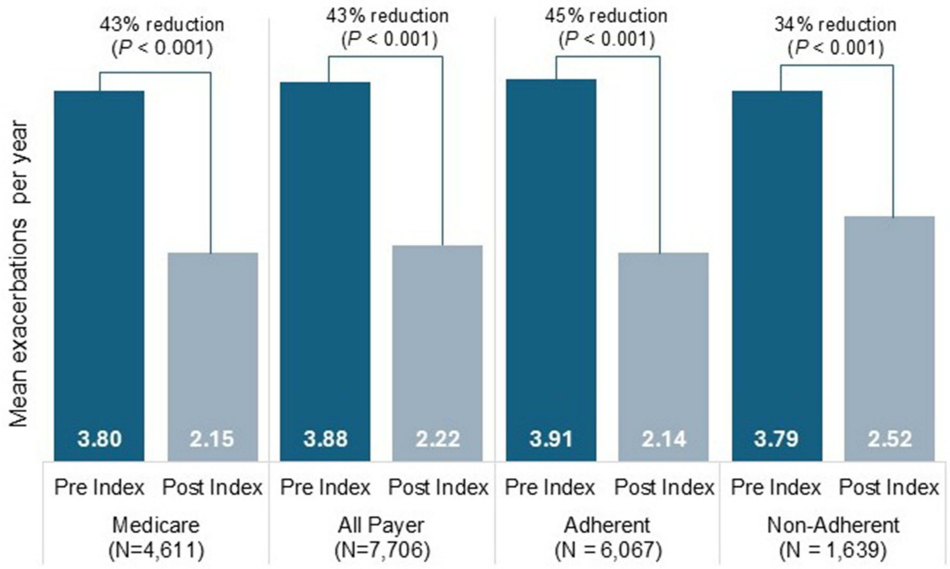

Figure 1 Annual Asthma Exacerbation Rate (AAER) Reduction Among Patients with Severe Asthma by Payer and by Adherence Status.

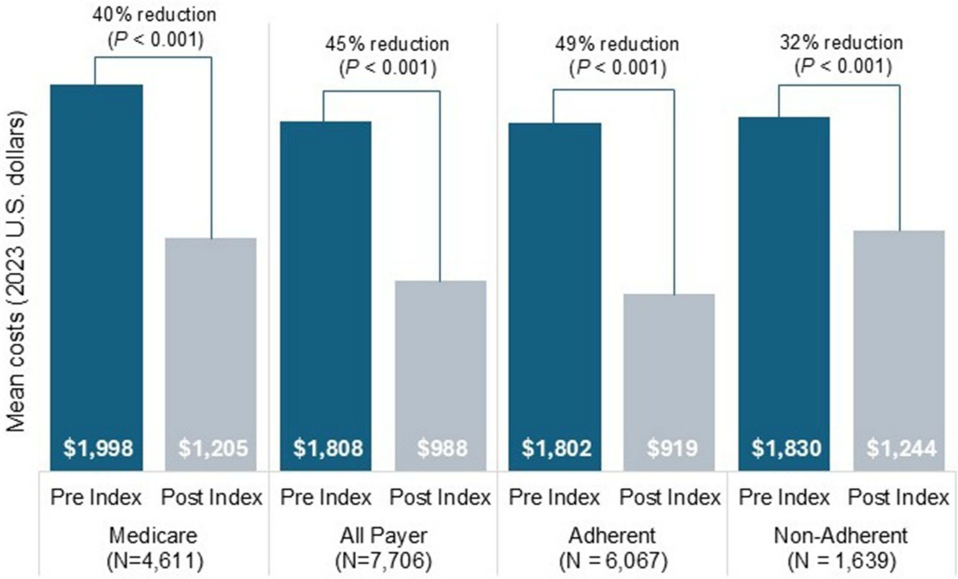

Figure 2 Exacerbation-Related Medical Costs Among Patients with Severe Asthma by Payer and by Adherence Status.

Patients who were adherent to benralizumab experienced greater reductions in both asthma exacerbation rates and exacerbation-related medical costs compared to non-adherent patients. The mean (SD) AAER decreased by 45.2% from 3.91 (2.10) to 2.14 (2.28) exacerbations per year for adherent patients compared to a decrease of 33.5% from 3.79 (1.99) to 2.52 (2.38) exacerbations per year for non-adherent patients (P <0.001) (Figure 1). Exacerbation-related medical costs among patients adherent to benralizumab decreased by 49.0% from mean (SD) costs of $1,802 ($4,760) to $919 ($3,263) (P <0.001), while exacerbation-related medical costs among patients not adherent to benralizumab decreased by 32.0% from $1,830 ($3,994) to $1,244 ($3,846) (P <0.001) (Figure 2 and Table 4).

Among asthma patients with prior biologic experience, the reduction in the AAER was more moderate compared to the all-payer cohort. The mean (SD) AAER decreased by 38.9% from 4.60 (2.43) to 2.81 (2.60) exacerbations per year (P <0.001) (Table 3). The mean (SD) AAER decreased by 37.4% from 4.30 (2.22) to 2.70 (2.59) exacerbations per year

Table 3 Annual Asthma Exacerbation Rate (AAER) Reduction and Exacerbation-Related Medical Costs by Payer and Prior Biologic Use

	Medicare N = 4,611				All-Payer[a] N = 7,706				All-Payer, Prior Biologic Use N = 1,873			
	Pre Index	**Post Index**	**Relative Change (%)**	***P***	**Pre Index**	**Post Index**	**Relative Change (%)**	***P***	**Pre Index**	**Post Index**	**Relative Change (%)**	***P***
Asthma exacerbations												
Presence of ≥ 1 exacerbation, n (%)	4,611 (100%)	3,383 (73%)	−27%		7,706 (100%)	5,711 (74%)	−26%		1,873 (100%)	1,516 (81%)	−19%	
AAER, mean (SD)	3.80 (2.02)	2.15 (2.24)	−43%	<0.001	3.88 (2.08)	2.22 (2.31)	−43%	<0.001	4.60 (2.43)	2.81 (2.60)	−39%	<0.001
Number of exacerbations, n (%)												
1 exacerbation	0 (0.0%)	1,054 (22.9%)	N/A		0 (0.0%)	1,739 (22.6%)	N/A		0 (0%)	348 (19%)	N/A	
2 exacerbations	1,460 (31.7%)	782 (17.0%)	−46%		2,372 (30.8%)	1,328 (17.2%)	−44%		399 (21%)	340 (18%)	−15%	
3 exacerbations	1,160 (25.2%)	562 (12.2%)	−52%		1,877 (24.4%)	905 (11.7%)	−52%		370 (20%)	250 (13%)	−32%	
4+ exacerbations	1,991 (43.2%)	985 (21.4%)	−51%		3,457 (44.9%)	1,739 (22.6%)	−50%		1,104 (59%)	578 (31%)	−48%	
Exacerbation-related medical costs												
Physician office visits, mean (SD)	$553 ($1,221)	$472 ($1,704)	−15%	<0.001	$411 ($966)	$318 ($1,334)	−23%	<0.001	$654 ($1,621)	$455 ($1,755)	−30%	<0.001
Median	$302	$91	−70%		$245	$76	−69%		$232	$106	−54%	
Emergency department, mean (SD)	$48 ($186)	$19 ($132)	−60%	<0.001	$111 ($308)	$49 ($218)	−55%	<0.001	$87 ($271)	$55 ($206)	−37%	<0.001
Median	$0	$0	N/A		$0	$0	N/A		$0	$0	N/A	
Other outpatient, mean (SD)	$411 ($1,649)	$310 ($1,202)	−25%	<0.001	$317 ($2,068)	$210 ($953)	−34%	<0.001	$518 ($1,852)	$294 ($1,235)	−43%	<0.001
Median	$0	$0	N/A		$13	$0	−100%		$51	$0	−100%	
Inpatient, mean (SD)	$986 ($4,323)	$405 ($3,082)	−59%	<0.001	$969 ($3,992)	$411 ($2,941)	−58%	<0.001	$896 ($3,832)	$508 ($3,266)	−43%	<0.001
Median	$0	$0	N/A		$0	$0	N/A		$0	$0	N/A	
Total medical, mean (SD)	$1,998 ($4,764)	$1,205 ($3,726)	−40%	<0.001	$1,808 ($4,607)	$988 ($3,398)	−45%	<0.001	$2,155 ($4,512)	$1,312 ($3,897)	−39%	<0.001
Median	$465	$158	−66%		$434	$134	−69%		$559	$210	−62%	

Notes: [a]All-payer cohort included commercial (N=1,335), Medicare Advantage or Medicare FFS, (N=4,611) and Managed Medicaid (N=1,760) payer groups.
Abbreviation: AAER, Annual Asthma Exacerbation Rate.

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Table 4 Annual Asthma Exacerbation Rate (AAER) Reduction and Exacerbation-Related Medical Costs by Adherence Status

	All-Payer, Adherence Status[a]							
	Adherent N = 6,067				Non-Adherent N = 1,639			
	Pre Index	Post Index	Relative Change (%)	*P*	Pre Index	Post Index	Relative Change (%)	*P*
Asthma exacerbations								
Presence of ≥ 1 exacerbation, n (%)	6,067 (100%)	4,402 (73%)	−27%		1,639 (100%)	1,309 (80%)	−20%	
AAER, mean (SD)	3.91 (2.10)	2.14 (2.28)	−45%	<0.001	3.79 (1.99)	2.52 (2.38)	−34%	<0.001
Number of exacerbations, n (%)								
1 exacerbation	0 (0.0%)	1,382 (22.8%)	N/A		0 (0.0%)	357 (21.8%)	N/A	
2 exacerbations	1,856 (30.6%)	1,045 (17.2%)	−44%		516 (31.5%)	283 (17.3%)	−45%	
3 exacerbations	1,462 (24.1%)	676 (11.1%)	−54%		415 (25.3%)	229 (14.0%)	−45%	
4+ exacerbations	2,749 (45.3%)	1,299 (21.4%)	−53%		708 (43.2%)	440 (26.8%)	−38%	
Exacerbation-related medical costs								
Physician office visits, mean (SD)	$418 ($981)	$328 ($1,389)	−22%	<0.001	$383 ($909)	$280 ($1,105)	−27%	<0.001
Median	$249	$51	−79%		$230	$107	−54%	
Emergency department, mean (SD)	$108 ($312)	$45 ($215)	−58%	<0.001	$121 ($295)	$64 ($226)	−47%	<0.001
Median	$0	$0	N/A		$0	$0	N/A	
Other outpatient, mean (SD)	$307 ($2,136)	$214 ($911)	−31%	<0.001	$354 ($1,793)	$198 ($1,095)	−44%	<0.001
Median	$12	$0	−100%		$14	$0	−100%	
Inpatient, mean (SD)	$969 ($4,120)	$332 ($2,765)	−66%	<0.001	$971 ($3,476)	$702 ($3,503)	−28%	<0.001
Median	$0	$0	N/A		$0	$0	N/A	
Total medical, mean (SD)	$1,802 ($4,760)	$919 ($3,263)	−49%	<0.001	$1,830 ($3,994)	$1,244 ($3,846)	−32%	<0.001
Median	$434	$124	−72%		$434	$189	−56%	

Notes: [a] Adherent patients had six or more claims for benralizumab during the 12-month post-index period, while non-adherent patients had fewer than six claims for benralizumab in the same time period.
Abbreviation: AAER, Annual Asthma Exacerbation Rate.

among individuals who switched from dupilumab, by 33.3% from 4.50 (2.36) to 3.01 (2.69) exacerbations per year among individuals who switched from mepolizumab, by 42.8% from 4.77 (2.53) to 2.73 (2.57) exacerbations per year among individuals who switched from omalizumab, and by 38.8% from 4.58 (2.83) to 2.80 (2.50) exacerbations per year among individuals who switched from reslizumab (Table 5). The mean (SD) exacerbation-related medical costs among biologic experienced patients decreased by 39.1% from $2,155 ($4,512) to $1,312 ($3,897) ($P < 0.001$) (Table 3). Across the four prior biologic cohorts, reductions in mean (SD) exacerbation-related medical costs ranged from 25.6% to 51.3% (all P <0.001) (Table 5).

Within the all-payer cohort, the proportion of patients receiving asthma medications decreased after the initiation of benralizumab, except for ICS/LABA/LAMA combination treatment (Table 2). Notable reductions were seen in inhaled and systemic corticosteroid utilization, with relative reductions of 17.3% and 14.2%, respectively. By adherence status, reductions in inhaled and systemic corticosteroid use were higher among patients adherent to benralizumab, with relative reductions of 18.5% and 15.5%, respectively. In contrast, patients non-adherent to benralizumab showed more modest reductions in inhaled and systemic corticosteroid use, with relative reductions of 13.0% and 9.3%, respectively. Similarly,

Table 5 Annual Asthma Exacerbation Rate (AAER) Reduction and Exacerbation-Related Medical Costs by Prior Biologic

	Dupilumab N = 197				Mepolizumab N = 730				Omalizumab N = 1,006				Reslizumab N = 76			
	Pre Index	Post Index	Relative Change (%)	*P*	Pre Index	Post Index	Relative Change (%)	*P*	Pre Index	Post Index	Relative Change (%)	*P* value	Pre Index	Post Index	Relative Change (%)	*P*
Asthma exacerbations																
Presence of ≥ 1 exacerbation, n (%)	197 (100%)	159 (80.7%)	−19%		730 (100%)	601 (82.3%)	−18%		1,006 (100%)	809 (80.4%)	−20%		76 (100%)	61 (80.3%)	−20%	
AAER, mean (SD)	4.30 (2.22)	2.70 (2.59)	−37%	<0.001	4.50 (2.36)	3.01 (2.69)	−33%	<0.001	4.77 (2.53)	2.73 (2.57)	−43%	<0.001	4.58 (2.83)	2.80 (2.50)	−39%	<0.001
Number of exacerbations, n (%)																
1 exacerbation	0 (0%)	43 (21.8%)	N/A		0 (0%)	117 (16.0%)	N/A		0 (0%)	202 (20.1%)	N/A		0 (0%)	12 (15.8%)	N/A	
2 exacerbations	49 (24.9%)	38 (19.3%)	−22%		160 (21.9%)	144 (19.7%)	−10%		202 (20.1%)	168 (16.7%)	−17%		16 (21.1%)	14 (18.4%)	−13%	
3 exacerbations	34 (17.3%)	22 (11.2%)	−35%		153 (21.0%)	91 (12.5%)	−41%		189 (18.8%)	146 (14.5%)	−23%		19 (25.0%)	11 (14.5%)	−42%	
4+ exacerbations	114 (57.9%)	56 (28.4%)	−51%		417 (57.1%)	249 (34.1%)	−40%		615 (61.1%)	293 (29.1%)	−52%		41 (53.9%)	24 (31.6%)	−41%	
Exacerbation-related medical costs																
Physician office visits, mean (SD)	$340 ($536)	$285 ($1,326)	−16%	<0.001	$580 ($1,479)	$437 ($1,705)	−25%	<0.001	$738 ($1,799)	$476 ($1,803)	−35%	<0.001	$780 ($1,457)	$384 ($1,086)	−51%	<0.001
Median	$231	$110			$229	$109			$231	$97			$268	$109		
Emergency department, mean (SD)	$117 ($258)	$69 ($232)	−41%	<0.001	$101 ($316)	$68 ($236)	−32%	0.001	$76 ($267)	$46 ($189)	−40%	<0.001	$78 ($205)	$37 ($113)	−52%	0.027
Median	$0	$0			$0	$0			$0	$0			$0	$0		
Other outpatient, mean (SD)	$126 ($303)	$140 ($575)	11%	0.006	$376 ($1,390)	$277 ($920)	−26%	<0.001	$657 ($2,162)	$319 ($1,433)	−52%	<0.001	$590 ($2,061)	$351 ($1,501)	−41%	0.125
Median	$27	$0			$40	$0			$73	$0			$11	$0		
Inpatient, mean (SD)	$838 ($3,205)	$563 ($2,824)	−33%	0.270	$940 ($3,305)	$405 ($2,010)	−57%	<0.001	$877 ($4,192)	$587 ($3,996)	−33%	0.004	$1,103 ($4,421)	$469 ($2,091)	−57%	0.313
Median	$0	$0			$0	$0			$0	$0			$0	$0		
Total medical, mean (SD)	$1,421 ($3,308)	$1,057 ($3,328)	−26%	<0.001	$1,997 ($3,806)	$1,187 ($2,841)	−41%	<0.001	$2,349 ($5,000)	$1,428 ($4,572)	−39%	<0.001	$2,550 ($5,023)	$1,241 ($2,736)	−51%	<0.001
Median	$425	$145			$546	$237			$600	$197			$499	$228		

Abbreviation: AAER, Annual Asthma Exacerbation Rate.

among patients with prior biologic experience, reductions in the use of inhaled and systemic corticosteroids were also more moderate, with reductions of 8.9% and 9.6%, respectively.

Discussion

This retrospective, single-arm, claims-based study of Medicare patients demonstrated that initiation of benralizumab decreased the frequency of asthma exacerbations, reduced exacerbation-related medical costs, and lowered inhaled and systemic corticosteroid utilization in a cohort of older adults with severe asthma in a real-world setting. In the broader all-payer cohort, patients experienced reductions in asthma exacerbation frequency and exacerbation-related medical costs, further confirming the clinical and economic benefits across payer types. Patients with prior biologic experience showed more moderate reductions in the frequency of asthma exacerbations and exacerbation-related medical costs, while those who were adherent to benralizumab experienced more substantial reductions than non-adherent patients.[17]

This study's finding of a 43.5% reduction in AAER among Medicare patients aligns with previous work reporting a 55% reduction in exacerbations following initiation of benralizumab.[14] The more moderate reduction in AAER in this study may be attributed to an older population with higher comorbidity burden, particularly the high prevalence of concomitant COPD (almost 65% of the Medicare sample) and concurrent use of triple therapy. This study also provides a current estimate of the exacerbation-related medical costs among Medicare patients with severe asthma. Initiation of benralizumab reduced exacerbation-related medical costs across all measured categories. Inpatient admissions were a driver of overall costs in both the pre-index and post-index periods. However, a notable reduction of approximately 60% in medical costs associated with inpatient stays, as well as emergency department visits, suggests that use of benralizumab may prevent hospitalizations in older adults with severe asthma.

Nearly one quarter of the overall study population switched to benralizumab from a different biologic, suggesting that some individuals remain sub-optimally controlled on biologics. These individuals had higher AAER and more frequent use of inhaled corticosteroids at baseline compared to the overall cohort, suggesting more severe disease in this subgroup. Nonetheless, this analysis confirms previous studies reporting that benralizumab can effectively reduce asthma exacerbations, even among individuals with prior biologic experience.[14–18] By directly targeting and depleting eosinophils, benralizumab may further reduce inflammation and prevent exacerbations in patients who have not fully responded to other biologic medications, an effect likely due to its mechanism of action in reducing eosinophilic inflammation. Thus, benralizumab is an important treatment option in the management of severe, eosinophilic asthma, especially among individuals for whom other biologics have been ineffective or insufficient.

The present study also demonstrated notable reductions in both inhaled and systemic corticosteroid utilization. The adverse effects of prolonged steroid use are well-documented, including among individuals with asthma.[21,22] The observed reductions in corticosteroid utilization following initiation of benralizumab are particularly noteworthy within the current study sample, as older patients are at increased risk of many steroid-related complications, such as osteoporosis, cataracts, hypertension, and infections.[23,24] Therefore, reducing systemic corticosteroid use may play a critical role in managing the already elevated comorbidity burden in this population,[23–25] and help to offset the healthcare costs associated with these complications.

A strength of this study is the inclusion of an older adult population with comorbidities, a patient group too often excluded from clinical trials. Eligibility criteria of clinical trials can create study populations that are poorly matched to typical Medicare patients.[26,27] Real-world analyses that include older adults improve the representativeness of asthma-focused research. Another strength was the representativeness of the all-payer cohort. The MORE^2 Registry and 100% Medicare FFS databases span the full continuum of care for a substantial portion of the U.S. population across different payer types and geographical regions of the U.S.

There are several limitations of this study. The single-arm study design without a placebo or control group limits the ability to separate the true treatment effect from natural variations in disease activity, including potential regression to the mean. This is a secondary analysis of administrative healthcare claims data, which are collected for billing purposes and not specifically designed for research. Claims data have the potential for missingness and medical coding errors that could contribute to misclassification of illness or healthcare resource utilization and costs. However, coding errors are thought to be minimal as accurate information is needed for claims to be adjudicated and paid. Despite these limitations,

using claims data for research contributes valuable insights into clinical practice outside of controlled clinical trial environments.

This real-world analysis provides insights into the effectiveness of benralizumab among older adults with severe asthma, demonstrating that the initiation of benralizumab decreased the AAER, exacerbation-related medical costs, and corticosteroid use in a real-world setting. In an all-payer sample, patients with prior biologic experience had more moderate reductions in AAER and exacerbation-related medical costs, while those adherent to benralizumab experienced the most substantial clinical benefit. These findings underscore the potential of biologic therapies to improve asthma management in older or complex patient populations.

Data Sharing Statement

This study utilized data from the following sources: the Centers for Medicare & Medicaid Services (CMS) 100% Medicare Fee-for-Service (FFS) claims database and the Inovalon MORE^2 Registry® of Closed Claims. Restrictions apply to the availability of these data, which were obtained under license and are not publicly available. Researchers may request access to similar data directly from the data providers, subject to applicable licensing and data use agreements.

Ethics Approval and Informed Consent

The CMS 100% Medicare FFS database and MORE^2 Registry® of Closed Claims contain fully de-identified data in compliance with the United States Health Insurance Portability and Accountability Act (HIPAA) of 1996. Under HIPAA's de-identification provisions (45 CFR §164.514) and corresponding institutional guidelines, analyses of de-identified data are exempt from Institutional Review Board review and patient informed consent requirements.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

MA is a paid external clinical consultant of AstraZeneca. JKD, DC, and MJ are employees of AstraZeneca. JS and KW are employees of Inovalon, which received funding from AstraZeneca for this study. JT was an employee of Inovalon at the time the study was conducted. The authors report no other conflicts of interest in this work.

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