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ORIGINAL RESEARCH

Medicare Advantage Population in the United States: Outcomes of Patients with Asthma Treated with ICS/LABA Before and After Initiation with Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI)

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ABSTRACT

Introduction: The clinical benefits of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) have been demonstrated in clinical trials. There is limited evidence regarding the effectiveness and economic outcomes associated with FF/UMEC/VI use in US clinical practice. This real-world study assessed asthma-related exacerbations, healthcare resource utilization (HRU), and healthcare costs among a Medicare Advantage-insured population before and after initiation of FF/UMEC/VI in patients with asthma previously treated with an inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA).

Methods: De-identified data were obtained from the Komodo Health database (01/01/2016–12/31/2023) for adults with asthma who received prior ICS/LABA treatment and had ≥12 months of continuous Medicare Advantage coverage both pre- and post-FF/UMEC/VI initiation (index date). Rates of asthma-related exacerbations and HRU were compared using rate ratios (RR) from Poisson regressions. Healthcare costs were calculated per patient per year (PPPY) and compared using mean cost differences from generalized linear models.

Results: In total, 2598 Medicare Advantage-insured patients who initiated FF/UMEC/VI for asthma were included. The mean ± SD age was 67.9 ± 12.3 years; 75.5% were female. The rate of

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overall asthma-related exacerbations was 31% lower in the post- versus pre-initiation period (RR 0.69; 95% CI 0.65, 0.73; $p<0.001$) and included a 24% lower rate of inpatient/emergency department (IP/ED)-defined exacerbations (RR 0.76; 95% CI 0.68, 0.85; $p<0.001$) and a 34% lower rate of systemic corticosteroid (SCS)-defined exacerbations (RR 0.66; 95% CI 0.61, 0.71; $p<0.001$). Asthma-related ED visits (RR 0.69; 95% CI 0.60, 0.80; $p<0.001$) and asthma-related outpatient (OP) visits (RR 0.77; 95% CI 0.71, 0.84; $p<0.001$) were both lower, and the mean reduction in cost was $411 PPPY (95% CI $575, $248; $p<0.001$), after FF/UMEC/VI initiation.

***Conclusions*:** Initiation of FF/UMEC/VI after ICS/LABA treatment among Medicare Advantage-insured patients with asthma was associated with reduced rates of asthma-related exacerbations, ED and OP visits, and healthcare costs, highlighting the benefits of therapy escalation among this patient population.

Keywords: Medicare advantage; FF/UMEC/VI; Real-world evidence; Single-inhaler triple therapy

Key Summary Points

Why carry out the study?

Although the benefit of FF/UMEC/VI use has been demonstrated in clinical trials, its effectiveness in a Medicare Advantage-insured population previously on an ICS/LABA medication has not been evaluated.

This real-world study assessed asthma-related exacerbations, healthcare resource utilization, and healthcare costs before and after FF/UMEC/VI initiation.

What was learned from the study?

Patients experienced a decline in asthma-related exacerbations, ED visits, OP visits, and healthcare costs after FF/UMEC/VI initiation relative to the pre-initiation period.

Escalating from ICS/LABA to FF/UMEC/VI was associated with a reduced burden of asthma in this cohort of Medicare Advantage patients.

INTRODUCTION

An estimated 20.2 million adults live with asthma in the USA [1]. Of all patients with asthma in the USA, approximately 80% are adults, and asthma control tends to be poorest among those aged ≥ 65 years [1, 2]. The prevalence of asthma has been estimated to be 5% within Medicare patients, a population that is older than the broader US asthma population as eligibility is largely age-based (i.e., ≥ 65 years) [3].

Patients with asthma are frequently treated with inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) maintenance therapy, particularly if asthma symptoms or exacerbations are uncontrolled using ICS therapy alone [4]. Current guidelines by both the Global Initiative for Asthma (GINA; Track 1 and 2, step 5) and the National Heart, Lung, and Blood Institute (NHLBI) recommend the inclusion of long-acting muscarinic antagonist (LAMA) add-on therapy if asthma remains uncontrolled despite ICS/LABA treatment, as occurs in up to approximately 50% of patients [4–7]. Among patients with uncontrolled asthma, the addition of a LAMA to ICS/LABA therapy improves lung function and reduces exacerbations [8]. When prescribed as a multiple-inhaler triple therapy (MITT) formulation, adherence rates are low, with only approximately 20% of patients remaining on ICS/LAMA/LABA therapy 6 months after initiation [9, 10]. The recent development of single-inhaler triple therapy (SITT) allows for the administration of ICS/LAMA/LABA in one inhaler once daily, offering a less cumbersome treatment option for patients with uncontrolled asthma [11].

The SITT fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) received US Food and Drug Administration (FDA) approval for the treatment of asthma in September 2020 based on results of the pivotal CAPTAIN study, whereby

patients with asthma demonstrated improved lung function when treated with FF/UMEC/VI triple therapy versus FF/VI dual therapy, including greater asthma control and numerical reductions in asthma-related exacerbations [12, 13].

Although the benefits of FF/UMEC/VI have been demonstrated in clinical trials, real-world data on clinical effectiveness and economic outcomes associated with FF/UMEC/VI treatment are sparse. Understanding the real-world clinical and economic impact of FF/UMEC/VI initiation in adults with asthma can provide valuable insights into optimized treatment strategies that benefit both patients and the healthcare system. Therefore, this study aimed to evaluate asthma-related exacerbations, healthcare resource utilization (HRU), healthcare costs, and oral corticosteroid (OCS) and short-acting beta-agonist (SABA) use before and after FF/UMEC/VI initiation among Medicare Advantage-insured patients with asthma previously treated with ICS/LABA in US clinical practice.

METHODS

Data Source

Data from January 1, 2016 to December 31, 2023, were obtained from the Komodo Health database, composed of de-identified healthcare encounters (i.e., any interaction between a patient and provider) for more than 330 million individual patients. The database includes over 65 billion clinical, pharmacy, and laboratory encounters from 2016 to present, captured through a wide range of partnerships with more than 500 payers across the USA, and displays census-level representation across patient populations (e.g., age, geography, risk pools), including hospital networks, physician networks, healthcare claims processing companies, pharmacies, and health insurers. The study was considered exempt research under 45 CFR § 46.104(d)(4) as it involved only the secondary use of data that were de-identified in compliance with the Health Insurance Portability and Accountability Act (HIPAA): specifically, 45 CFR § 164.514.

Study Design

This study used a retrospective longitudinal pre–post design, with the index date defined as the first pharmacy claim for FF/UMEC/VI (Fig. S1). The patient identification period spanned from September 9, 2020 (i.e., date of US FDA approval of FF/UMEC/VI for asthma) to December 31, 2022, allowing for a 12-month follow-up period for all patients. The pre-initiation baseline period comprised either the 12 months before and including the index date or the date of the first asthma diagnosis to the index date, whichever occurred latest. The post-initiation follow-up period included the day after the index date to the earliest of 12 months post-index, the end of patient eligibility, the end of data availability, death, or the initiation of a biologic therapy for asthma.

Study Population

Adult patients were eligible for study inclusion if they had ≥ 1 pharmacy claim for SITT FF/UMEC/VI during the patient identification period (i.e., September 9, 2020 to December 31, 2022). Additionally, patients were required to have ≥ 12 months of continuous insurance coverage both pre- and post-index, ≥ 30 consecutive days' supply of ICS/LABA within the pre-initiation period (National Drug Codes [NDC] listed in Table S1), and ≥ 2 medical claims with a diagnosis code for asthma on separate dates during the pre-initiation period.

Patients were excluded if they had ≥ 1 pharmacy claim for a SITT (i.e., FF/UMEC/VI or budesonide/glycopyrrolate/formoterol [BGF]) before the index date or were not enrolled in Medicare Advantage. Patients were also ineligible if, during the pre-initiation period, they had ≥ 1 pharmacy claim for a MITT (defined as ≥ 30 consecutive days of overlap in the supply of ICS, LABA, LAMA), ≥ 1 medical claim with a diagnosis code for cystic fibrosis, interstitial lung disease, alpha-1 antitrypsin deficiency, or lung cancer, ≥ 2 medical claims with a diagnosis code for chronic obstructive pulmonary disease (COPD) on separate dates, ≥ 1 medical or pharmacy

claim for biologic asthma therapy, whether used to treat asthma or any other indication (i.e., mepolizumab, omalizumab, reslizumab, benralizumab, dupilumab, or tezepelumab), or ≥ 1 medical claim for eosinophilic granulomatosis with polyangiitis (EGPA).

Study Outcomes

Baseline demographic and clinical characteristics were evaluated during the pre-initiation period, with demographic characteristics including age, sex, geographic region, race, ethnicity, and index year and quarter, and clinical characteristics including prescribing physician specialty, respiratory medication use during the baseline period, Quan-Charlson Comorbidity Index (Quan-CCI), asthma-related comorbidities, and Elixhauser comorbidities.

The primary study objective was to evaluate the rates of overall asthma-related exacerbations, including inpatient/emergency department (IP/ED) and systemic corticosteroid (SCS)-defined exacerbations, during the pre- versus post-initiation periods. Asthma-related IP/ED-defined exacerbations incorporated (1) asthma-related IP visits that resulted in an IP visit within 1 day, (2) asthma-related urgent care-defined exacerbations (i.e., asthma-related ED visits that resulted in an IP visit within 1 day), and (3) asthma-related ED visits. Asthma-related SCS-defined exacerbations were asthma-related ED visits or asthma-related outpatient (OP) visits with an SCS (i.e., parenteral or OCS) claim within 5 days pre- or post-visit.

Secondary study objectives aimed to evaluate the rates of asthma-related HRU and asthma-related healthcare costs, defined as any claim with a primary diagnosis of asthma (ICD-10-CM: J45.x), as well as rates of OCS and SABA use within the pre- versus post-initiation periods. Both HRU and healthcare costs were stratified by IP, ED, and OP visits, with overall healthcare costs additionally reported.

Statistical Analyses

Continuous variables were evaluated using means, standard deviations (SDs), medians, and interquartile ranges (IQRs), and categorical variables were evaluated using relative frequencies and proportions.

Rates of asthma-related exacerbations and HRU, as well as OCS and SABA use, were calculated as the number of events divided by the patient-years of observation (i.e., per patient year [PPY]), with rates between the pre- and post-initiation periods compared using rate ratios (RRs) from Poisson regressions with accompanying 95% confidence intervals (CI) and p values using robust standard errors (SEs). All regression models accounted for the correlation of observations within the same patient using generalized estimating equations (GEEs). The proportion of patients with ≥ 1 asthma-related exacerbation and the duration of asthma-related exacerbations were reported and compared between the pre- and post-initiation periods using odds ratios (ORs) or mean differences, respectively, 95% CIs, and p values obtained from logistic and linear regression models using robust SEs.

Healthcare costs were calculated as the costs incurred per patient per year (PPPY) with all costs inflation-adjusted to 2024 US dollars (USD) based on the medical care component of the Consumer Price Index. Healthcare costs were compared between the pre- and post-initiation periods using mean cost differences obtained from generalized linear models with a normal distribution and log-link function, with accompanying 95% CIs and p values using robust SEs. For all healthcare costs, regression models accounted for the correlation of observations within the same patient using GEEs. All statistical analyses were conducted using SAS Enterprise Guide Software version 7.15 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

A total of 2598 patients were identified as having initiated FF/UMEC/VI for asthma treatment and met the study selection criteria (Fig. 1). Patients had a mean ± SD age of 67.9 ± 12.3 years, and 75.5% of patients were female (Table 1). Patients were more often from the Northeast geographic region (44.1%) and non-Hispanic White (47.0%) compared with other geographic regions and ethnicities.

Frequent prescribing physicians were primary care physicians (44.2%), pulmonologists (31.8%), and allergists (11.1%). The most common maintenance controller medication used was leukotriene modifiers (60.0%), with rescue medications including SABA (83.3%), SCS (71.9%), SABA/short-acting muscarinic antagonist (SABA/SAMA; 11.5%), and SAMA (3.4%).

Patients had a mean ± SD Quan-CCI of 2.3 ± 1.7, with prevalent asthma-related comorbidities including gastroesophageal reflux disease (47.0%), allergic rhinitis (44.8%), depressive disorders (29.3%), anxiety disorders (28.3%), and obstructive sleep apnea (25.8%) (Table 2). Frequent Elixhauser comorbidities included hypertension (76.6%), obesity (44.4%), diabetes (40.0%), and cardiac arrhythmias (23.7%).

Asthma-Related Exacerbations

The median observation period both pre- and post-initiation was 365 days (Table S2). In total, 53.1% of patients had ≥ 1 overall exacerbation during the pre-initiation period, compared with 39.1% of patients during the post-initiation period (OR 0.57; 95% CI 0.51, 0.62; $p < 0.001$; Fig. 2). During the pre-initiation period, 19.7% of patients had ≥ 1 IP/ED-defined exacerbation, including 3.8% of patients with ≥ 1 urgent care-defined exacerbation, compared with 15.7% (OR 0.76; 95% CI 0.67, 0.85; $p < 0.001$) and 2.1% (OR 0.54; 95% CI 0.40, 0.74; $p < 0.001$) of patients during the post-initiation period, respectively. The proportion of patients with ≥ 1 SCS-defined exacerbation during the pre-initiation period was 43.1%, versus 29.9% of patients during the post-initiation period (OR 0.56; 95% CI 0.51, 0.6; $p < 0.001$).

Patients experienced a 31% lower rate of overall exacerbations reduction during the post-initiation period than in the pre-initiation period (RR 0.69; 95% CI 0.65, 0.73; $p < 0.001$). This included a 24% lower rate of IP/ED-defined exacerbations (RR 0.76; 95% CI 0.68, 0.85; $p < 0.001$) and a 34% lower rate of SCS-defined exacerbations (RR 0.66; 95% CI 0.61, 0.71; $p < 0.001$) after FF/UMEC/VI initiation. The rate of urgent care-defined exacerbations was also significantly lower in the post- versus pre-initiation period (RR 0.52; 95% CI 0.37, 0.72; $p < 0.001$).

There was no significant difference in the mean ± SD duration of asthma exacerbations between the pre- (1.59 ± 3.76 days) and post-initiation (1.82 ± 5.90 days) periods (mean difference 0.23; 95% CI − 0.22, 0.68; $p = 0.309$).

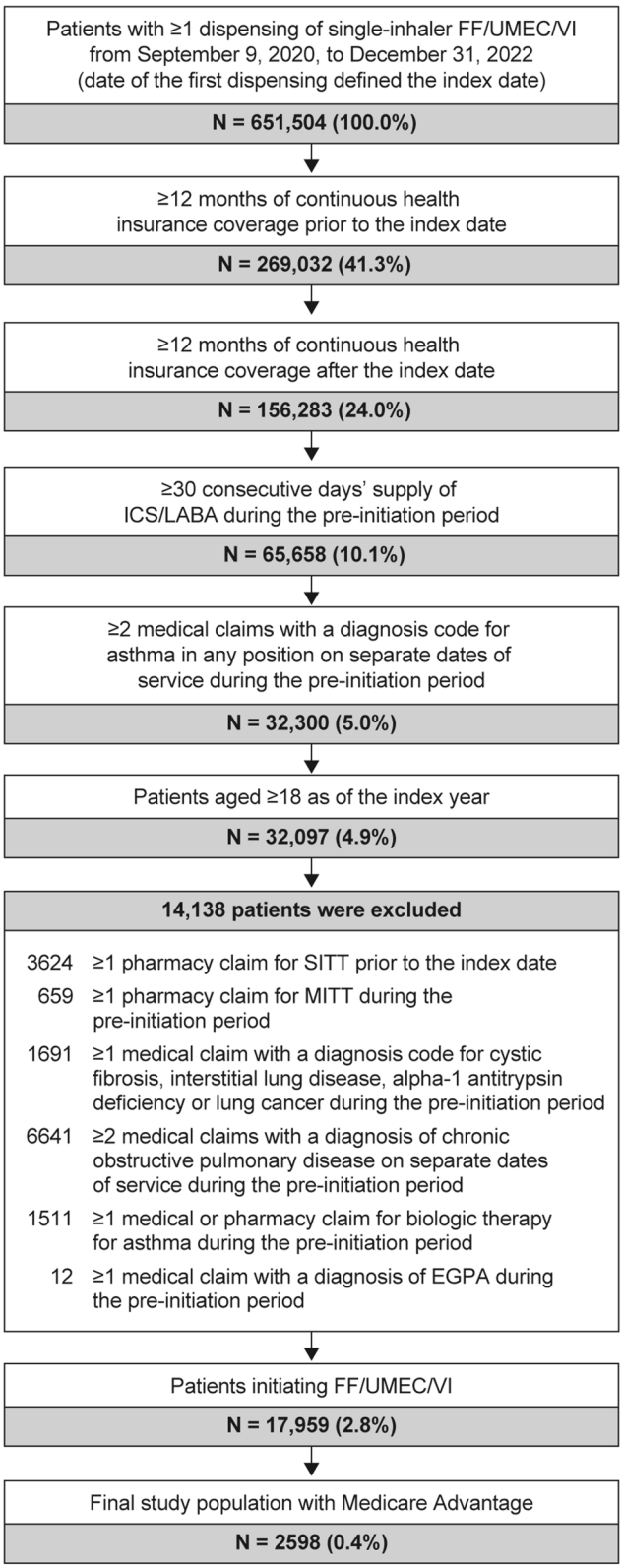
Asthma-Related HRU

The rate of asthma-related hospitalizations did not differ between the pre- and post-initiation periods (RR 1.11; 95% CI 0.89, 1.37; $p = 0.358$; Fig. 3).

The rates of asthma-related ED visits and asthma-related OP visits were 31% lower (RR 0.69; 95% CI 0.60, 0.80; $p < 0.001$) and 23% lower (RR 0.77; 95% CI 0.71, 0.84; $p < 0.001$), respectively, during the post- versus pre-initiation period. Patients also had a 48% lower rate of asthma-related urgent care visits after FF/UMEC/VI initiation (RR 0.52; 95% CI 0.37, 0.74; $p < 0.001$).

Asthma-Related Healthcare Costs

During the pre-initiation period, asthma-related healthcare costs were $1556 PPPY, comprising $1035 PPPY for asthma-related OP visits, $328 PPPY for asthma-related hospitalizations, and $193 PPPY for ED visits (Fig. 4). During the post-initiation period, asthma-related healthcare


Patients with ≥1 dispensing of single-inhaler FF/UMEC/VI from September 9, 2020, to December 31, 2022 (date of the first dispensing defined the index date)
N = 651,504 (100.0%)
≥12 months of continuous health insurance coverage prior to the index date
N = 269,032 (41.3%)
≥12 months of continuous health insurance coverage after the index date
N = 156,283 (24.0%)
≥30 consecutive days' supply of ICS/LABA during the pre-initiation period
N = 65,658 (10.1%)
≥2 medical claims with a diagnosis code for asthma in any position on separate dates of service during the pre-initiation period
N = 32,300 (5.0%)
Patients aged ≥18 as of the index year
N = 32,097 (4.9%)
14,138 patients were excluded
3624 ≥1 pharmacy claim for SITT prior to the index date
659 ≥1 pharmacy claim for MITT during the pre-initiation period
1691 ≥1 medical claim with a diagnosis code for cystic fibrosis, interstitial lung disease, alpha-1 antitrypsin deficiency or lung cancer during the pre-initiation period
6641 ≥2 medical claims with a diagnosis of chronic obstructive pulmonary disease on separate dates of service during the pre-initiation period
1511 ≥1 medical or pharmacy claim for biologic therapy for asthma during the pre-initiation period
12 ≥1 medical claim with a diagnosis of EGPA during the pre-initiation period
Patients initiating FF/UMEC/VI
N = 17,959 (2.8%)
Final study population with Medicare Advantage
N = 2598 (0.4%)

◂**Fig. 1** Patient disposition. *EGPA* eosinophilic granulomatosis with polyangiitis, *FF/UMEC/VI* fluticasone furoate/umeclidinium/vilanterol, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *MITT* multiple-inhaler triple therapy, *SITT* single-inhaler triple therapy. [a]See Table S1 for a complete list of ICS/LABA codes used

costs were $1144 PPPY, comprising $794 PPPY for asthma-related OP visits, $234 PPPY for asthma-related hospitalizations, and $116 PPPY for asthma-related ED visits. Overall, there was a mean reduction in cost of $411 PPPY between the pre- and post-initiation periods (95% CI $575, $248; $p<0.001$).

OCS and SABA Use

The rates of OCS dispensing and SABA canisters were significantly lower during the post- versus pre-initiation period. Patients had a 13% lower rate of OCS dispensing (RR 0.87; 95% CI 0.83, 0.91) and an 8% lower rate of SABA canister (RR 0.92; 95% CI 0.88, 0.95) during the post-initiation relative to the pre-initiation period.

DISCUSSION

This real-world study evaluated asthma-related exacerbations, OCS and SABA use, HRU, and healthcare costs before and after FF/UMEC/VI initiation among Medicare Advantage-insured patients with asthma who previously received treatment with ICS/LABA. Within this study population, initiation of FF/UMEC/VI was associated with a significant reduction in the rate of asthma-related overall exacerbations. This comprised significant reductions in the rates of IP/ED-defined exacerbations, including urgent care-defined exacerbations, and SCS-defined exacerbations after FF/UMEC/VI initiation. Further, the rates of asthma-related ED visits and asthma-related OP visits, as well as asthma-related medical costs, were significantly lower during the post- versus pre-initiation period.

The improved rates of asthma-related exacerbations after FF/UMEC/VI treatment initiation among patients enrolled in Medicare Advantage observed in the present study are in line with the findings of previous research among a broader patient population. In a claims-based study by Bogart et al., real-world asthma-related exacerbations before and after FF/UMEC/VI initiation were evaluated among a primarily commercially insured population aged < 65 years [14]. Therefore, patients were younger and had a lower comorbidity burden than those included in the present analysis. Importantly, patients with asthma evaluated in the Bogart et al. study were early adopters of FF/UMEC/VI, as the study observed only the off-label use of FF/UMEC/VI 100/62.5/25 µg after FDA approval in patients with COPD. Patients therefore may not have been representative of those who initiated either FF/UMEC/VI 100/62.5/25 µg or 200/62.5/25 µg after marketing authorization. Additionally, asthma medication use during the pre-treatment period was not comprehensively evaluated, and therefore, the initiation of FF/UMEC/VI treatment did not necessarily represent therapy escalation from ICS/LABA to FF/UMEC/VI. Thus, the current study extends previous results and more accurately reflects the real-world benefits of therapy escalation as recommended by GINA guidelines within a Medicare Advantage population [4].

The healthcare benefits noted in this study can be instigated by any one (or any combination) of the changes that occur when a patient changes therapy (addition of a LAMA, change in ICS dose, change in device, or change in drug formulation). Although the current study was not designed to quantify the individual effects of these changes, the double-blind, phase 3 CAPTAIN trial was designed to do this. In this study, patients with inadequately controlled asthma despite ICS/LABA use were randomized to one of six treatment groups, FF/VI 100/25 µg or 200/25 µg, or FF/UMEC/VI 100/31.25/25 µg, 100/62.5/25 µg, 200/31.25/25 µg, or 200/62.5/25 µg [13]. Over the variable 24- to 52-week treatment period, there was a nonsignificant 13% reduction in the mean annualized rate of moderate and/or severe asthma-related exacerbations among the pooled FF/UMEC 62.5 µg/VI

Table 1 Baseline demographic and clinical characteristics

Characteristics	Overall $N = 2598$
Pre-initiation observation period, days, mean ± SD [median]	349.8 ± 58.5 [365]
Demographics[a]	
Age, years, mean ± SD [median]	67.9 ± 12.3 [70]
Female, *n* (%)	1961 (75.5)
Region, *n* (%)	
Northeast	1146 (44.1)
South	743 (28.6)
Midwest	358 (13.8)
West	309 (11.9)
Other[b]	42 (1.6)
Race and ethnicity, *n* (%)[c]	
Non-Hispanic White	1221 (47.0)
Hispanic or Latino	677 (26.1)
Black or African American	448 (17.2)
Asian or Pacific Islander	130 (5.0)
Other	36 (1.4)
Unknown	86 (3.3)
Year and quarter of index date,[d] ***n*** **(%)**	
2020	
Q3, 2020	32 (1.2)
Q4, 2020	236 (9.1)
2021	
Q1, 2021	316 (12.2)
Q2, 2021	360 (13.9)
Q3, 2021	280 (10.8)
Q4, 2021	364 (14.0)
2022	
Q1, 2022	398 (15.3)
Q2, 2022	413 (15.9)
Q3, 2022	142 (5.5)
Q4, 2022	57 (2.2)
Physician specialty[e]	
Primary care	1148 (44.2)
Respiratory specialist	1114 (42.9)
Pulmonologist	826 (31.8)
Allergist	288 (11.1)
Other	332 (12.8)
Unknown	7 (0.3)
Respiratory medication,[f] ***n*** **(%)**	
ICS/LABA	
Budesonide/formoterol	859 (33.1)
Fluticasone/vilanterol	841 (32.4)
Fluticasone/salmeterol	823 (31.7)
Mometasone/formoterol	75 (2.9)
Other maintenance controller medications	
Leukotriene modifiers	1560 (60.0)
Methylxanthines	23 (0.9)
Mast cell stabilizers	2 (0.1)
Rescue medications	
SABA	2163 (83.3)
SCS	1867 (71.9)
SABA/SAMA	298 (11.5)
SAMA	88 (3.4)

FF/UMEC/VI fluticasone furoate/umeclidinium/vilanterol, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *SABA* short-acting β_2-agonist, *SAMA* short-acting muscarinic antagonist, *SCS* systemic corticosteroid, *SD* standard deviation

[a]Evaluated on the index date

[b]Other category for region includes Puerto Rico and US Virgin Islands

[c]Race and ethnicity were reported together in Komodo

[d]The index date was defined as the date of first dispensing of FF/UMEC/VI between September 9, 2020 and December 31, 2022

Table 1 continued

[c]Physician specialty was evaluated on the index date; if physician specialty information was missing on the index date, the claim closest to the index date was used to identify physician specialty. Primary care physician included family practice, general medicine practice, nurse practitioner, internal medicine, pediatrician, and geriatrician. Respiratory specialist included pulmonologist, pediatric pulmonology physician, and allergist. Respiratory specialist was prioritized among patients with both primary care and respiratory specialist (i.e., respiratory specialist and primary care are mutually exclusive). Patients with claims with information on provider type, but not elsewhere classified (i.e., not in respiratory specialist nor primary care physician) were classified as other. Common other provider specialties include pharmacy and clinical medical laboratory

[f]Evaluated during the 12-month baseline period, including the index date

treatment group relative to FF/VI ($p=0.15$). Statistically significant increases in forced expiratory volume in 1 s (FEV_1) values at 24 weeks relative to baseline, a measure of improved lung function and the primary study endpoint, were observed among patients treated with either FF/UMEC/VI 100/62.5/25 µg or 200/62.5/25 µg versus FF/VI 100/25 µg (least squares mean change 110 mL; 95% CI 66, 153; $p<0.0001$) or FF/VI 200/25 µg (least squares mean change 92 mL; 95% CI 49, 135; $p<0.0001$), respectively. Additionally, a meta-analysis of 20 randomized control trials assessed clinical outcomes with ICS/LABA/LAMA triple therapy versus ICS/LABA dual therapy among patients with moderate to severe asthma [15]. Treatment with ICS/LABA/LAMA was associated with a 15% lower rate of severe asthma-related exacerbations compared with treatment with ICS/LABA dual therapy (incidence RR 0.85; 95% CI 0.78, 0.92). In line with that study, Yamasaki et al. found that compared with ICS/LABA, triple therapy resulted in an 18% reduction in the risk of severe asthma exacerbations (RR 0.82; 95% CI 0.67, 1.00) and a 24% reduction in the annualized RR (annualized RR 0.76; 95% CI 0.62, 0.92) [16]. Finally, an umbrella review provided evidence that ICS/LAMA/LABA triple therapy may reduce the risk of asthma exacerbations [17]. Thus, the reduced rates of asthma-related exacerbations

Table 2 Baseline comorbidities

Comorbidities[a]	**Overall** *N* = **2598**
Quan-CCI,[b] **mean ± SD [median]**	2.3 ± 1.7 [2]
Select asthma-related comorbidities, *n* (%)	
Gastroesophageal reflux disease	1222 (47.0)
Allergic rhinitis	1163 (44.8)
Depressive disorders	760 (29.3)
Anxiety disorders	735 (28.3)
Obstructive sleep apnea	670 (25.8)
Elixhauser comorbidities,[c] ***n*** **(%)**	
Hypertension	1991 (76.6)
Hypertension, uncomplicated	1449 (55.8)
Hypertension, complicated	542 (20.9)
Obesity	1153 (44.4)
Diabetes	1038 (40.0)
Diabetes, complicated	706 (27.2)
Diabetes, uncomplicated	332 (12.8)
Cardiac arrhythmias	616 (23.7)
Peripheral vascular disease	549 (21.1)
Renal failure	418 (16.1)
Congestive heart failure	348 (13.4)
Rheumatoid arthritis/collagen vascular disease	338 (13.0)
Deficiency anemias	334 (12.9)
Valvular disease	326 (12.5)

Quan-CCI Quan-Charlson Comorbidity Index, *SD* standard deviation

[a]Evaluated during the 12-month baseline period, including the index date

[b]Quan et al. (2005). Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Medical Care, 43(11): 1130–39

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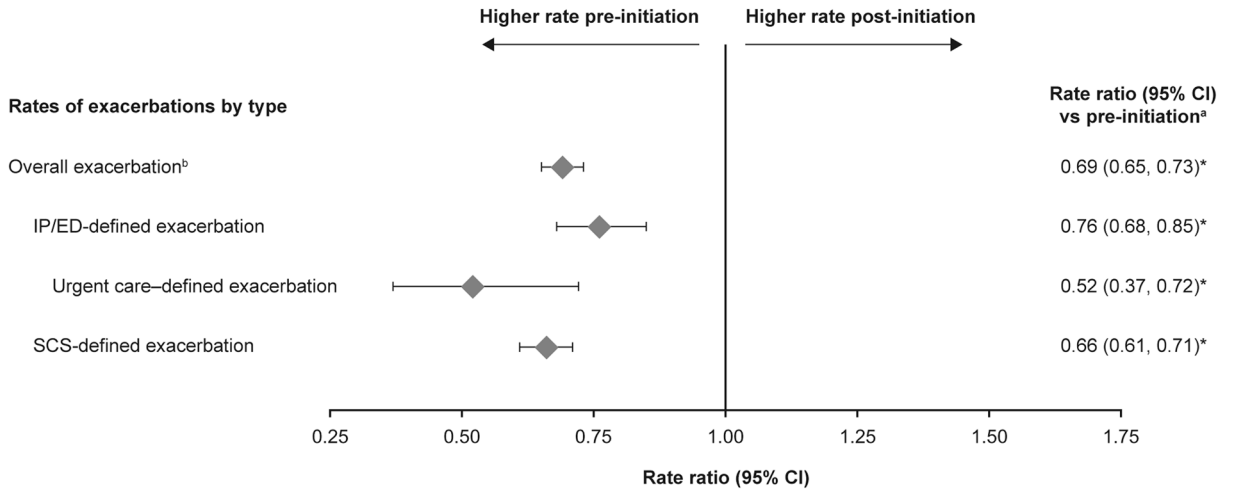

Fig. 2 Rates of asthma-related exacerbations pre- and post-FF/UMEC/VI initiation. *CI* confidence interval, *ED* emergency department, *FF/UMEC/VI* fluticasone furoate/umeclidinium/vilanterol, *GEE* generalized estimating equations, *IP* inpatient, *SCS* systemic corticosteroid. [a]Rate ratios and 95% CIs estimated from GEE Poisson regression models with robust standard errors to account for the correlation of observations within the same patient were used to compare rates of asthma-related exacerbations between the pre-initiation and post-initiation periods. [b]Overall asthma-related exacerbations include both SCS-defined exacerbation and IP/ED-defined exacerbation. Two or more exacerbations within 14 days of each other were considered as one exacerbation and classified according to the highest severity. *Statistically significant

observed in the present real-world study are in line with class-level meta-analyses of triple therapy and are indicative of improved asthma control with FF/UMEC/VI versus ICS/LABA in US clinical practice. As the present study did not control for formulation differences between FF/UMEC/VI and previous ICS/LABA treatment, variations in dosing regimens and strengths during treatment escalation to SITT may account for part of this improvement [13].

Although previous work has demonstrated that uncontrolled asthma is associated with worse economic outcomes that are projected to grow [18, 19], no previous study has evaluated real-world asthma-related HRU or healthcare costs among patients with asthma treated with FF/UMEC/VI in the USA. Findings from the current analysis provide novel evidence that initiation of FF/UMEC/VI is associated with reduced rates of asthma-related ED visits and asthma-related OP visits, as well as lower asthma-related medical costs, in Medicare Advantage-insured patients with asthma previously treated with ICS/LABA. In addition, more than 90% of the patients in this study escalated therapy from fluticasone propionate/salmeterol (FP/SAL), FF/VI, or budesonide/formoterol (BUD/FOR) dual therapies. According to SRR Health, the median annual cost of these therapies ranges from $1200 less expensive to $700 more expensive than FF/UMEC/VI [20]. These differences in treatment cost should be considered in the context of the healthcare savings due to asthma events noted in this study.

In addition, the overuse of SABA and OCS has been linked to an increased risk of hospitalization and death [21]. This study is the first to present real-world evidence showing that, after initiating FF/UMEC/VI, Medicare Advantage patients with asthma experience a reduction in SABA and OCS use. These findings further underscore the potential clinical benefits of FF/UMEC/VI, alongside its positive impact on HRU and healthcare costs.

This study included only patients insured with Medicare Advantage, a population that is older than the general US population given the largely age-based requirements for enrollment (i.e., age ≥ 65 years) [22]. There are several unique factors to consider in the management

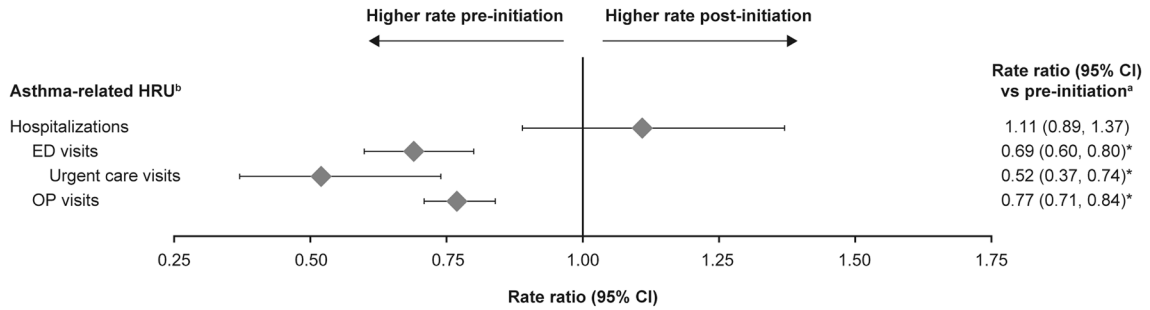

Fig. 3 Rates of asthma-related HRU pre- and post-FF/UMEC/VI initiation. *CI* confidence interval, *ED* emergency department, *FF/UMEC/VI* fluticasone furoate/umeclidinium/vilanterol, *GEE* generalized estimating equations, *HRU* healthcare resource utilization, *ICD-10-CM* International Classification of Diseases, Tenth Revision, Clinical Modifications, *OP* outpatient. [a]Rate ratios and 95% CIs estimated from GEE Poisson regression models with robust standard errors to account for the correlation of observations within the same patient were used to compare rates of asthma-related exacerbations between the pre-initiation and post-initiation periods. [b]Asthma-related HRU was defined as any claims with a primary diagnosis of asthma (ICD-10-CM: J45.x). *Statistically significant

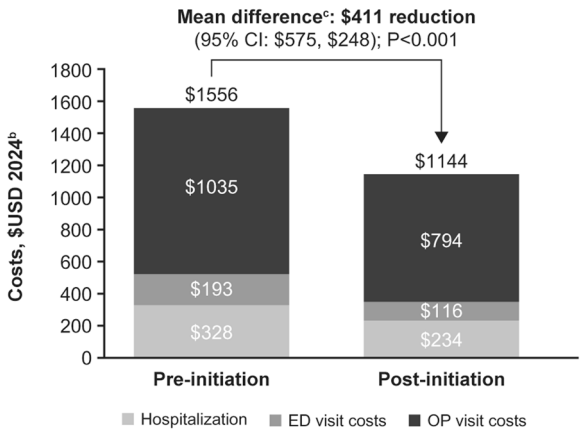

Fig. 4 Asthma-related healthcare costs pre- and post-FF/UMEC/VI initiation[a]. *CI* confidence interval, *ED* emergency department, *FF/UMEC/VI* fluticasone furoate/umeclidinium/vilanterol, *GEE* generalized estimating equation, *ICD-10-CM* International Classification of Diseases, Tenth Revision, Clinical Modifications, *OP* outpatient. [a]Asthma-related costs were defined as any claims with a primary diagnosis of asthma (ICD-10-CM: J45.x). [b]Costs are inflated to $USD 2024 using the US Medical Care consumer price index from the Bureau of Labor Statistics from the US Department of Labor. [c]Cost differences, 95% CIs, and *p* values were estimated from GEE generalized linear models with a normal distribution and identity link function with robust standard errors to account for the correlation of observations within the same patient

of asthma in older adults; for instance, the presence of comorbid conditions and the risk of polypharmacy may impact the safety profile and efficacy of asthma medications, and the prescription of multiple inhaler therapies may reduce medication adherence [23]. The demonstration of significant effect sizes among Medicare Advantage-insured patients in the present study therefore supports the benefits of FF/UMEC/VI for asthma-related exacerbations within older populations.

Limitations

This study was subject to several limitations associated with the use of retrospective claims data. As administrative claims are collected for payment versus research purposes, data are vulnerable to coding inaccuracies and misclassification bias. Missing data are possible, as is a lack of information on specific clinical and patient characteristics that may have influenced study outcomes. Lung function measures and patient-reported outcomes were not available in the Komodo database and as such were not reported. The presence of a pharmacy claim within the database did not ensure that the medication was consumed by the patient or taken as prescribed. As this is not a randomized controlled

trial, a control group of patients who did not change inhaler therapy could not be included. Although the pre–post design allowed patients to act as their own controls, it did not account for changes in prescribing practices or other factors over time that may have influenced study outcomes. As the present analysis only included Medicare Advantage-insured patients with asthma from the Komodo Health database, results may not be generalizable to the entire population of Medicare patients with asthma. Finally, a portion of the study period overlapped with the COVID-19 pandemic, which may have impacted clinical outcomes, HRU, and healthcare costs associated with FF/UMEC/VI initiation.

CONCLUSIONS

In this retrospective cohort study using real-world data from the USA, initiation of FF/UMEC/VI among Medicare Advantage-insured patients with asthma who previously used ICS/LABA was associated with reduced rates of asthma-related exacerbations, OCS and SABA use, HRU, and healthcare costs. These findings highlight the benefits of FF/UMEC/VI therapy escalation in reducing disease burden among Medicare recipients with asthma.

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Data Availability. The data reported in this publication are contained in a database owned by Komodo Health and contain proprietary elements. Therefore, it cannot be broadly disclosed or made publicly available at this time. The disclosure of this data to third-party clients assumes certain data security and privacy protocols are in place and that the third-party client has executed Komodo Health's standard license agreement, which includes restrictive covenants governing the use of the data.

Declarations

Conflict of Interest. Alan P. Baptist reports grant support from GSK, AstraZeneca, and Teva. Guillaume Germain, Jacob Klimek, François

Laliberté, and Robert C. Schell are employees of Analysis Group, a consulting company that has received research funds from GSK to conduct this study. Sergio Forero-Schwanhaeuser, Alison Moore, Stephen G. Noorduyn, and Rosirene Paczkowski are employees of GSK and hold financial equities in GSK. Stephen G. Noorduyn is also a PhD candidate at McMaster University.

Ethical Approval. The study was considered exempt research under 45 CFR § 46.104(d)(4) as it involved only the secondary use of data that were de-identified in compliance with the Health Insurance Portability and Accountability Act (HIPAA): specifically, 45 CFR § 164.514.

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