Original Article

Adherence and Persistence to Single-Inhaler Versus Multiple-Inhaler Triple Therapy for Asthma Management

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What is already known about this topic? Multiple-inhaler triple therapy (MITT) use among patients with asthma has been associated with low adherence and persistence rates. However, real-world data on adherence among patients with asthma initiating once-daily single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) is not available.

What does this article add to our knowledge? Initiation of FF/UMEC/VI compared with initiation of MITT was associated with significantly higher adherence and persistence. However, FF/UMEC/VI adherence and persistence rates reported here are still relatively low and decreased over 12 months.

How does this study impact current management guidelines? Our study shows that single-inhaler triple therapy could improve patient adherence and persistence, highlighting an unmet need for improved patient education on the benefits of treatment and active monitoring of triple-therapy adherence by healthcare professionals.

BACKGROUND: Treatment guidelines recommend triple therapy for patients with asthma who remain uncontrolled on inhaled corticosteroid/long-acting β_2-agonist therapy. Previously, triple therapy was only available via multiple inhalers. Single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) is approved as maintenance treatment for asthma; however, real-world information on adherence and persistence is limited.

OBJECTIVE: To compare adherence and persistence among adult patients with asthma receiving single-inhaler FF/UMEC/VI versus multiple-inhaler triple therapy (MITT) in the United States.

METHODS: This retrospective cohort study used IQVIA PharMetrics Plus data to evaluate patients with asthma who initiated once-daily FF/UMEC/VI 100/62.5/25 mcg or MITT between September 18, 2017, and September 30, 2019. Inverse probability weighting and multivariable regression adjusted for differences in characteristics between the FF/UMEC/VI and MITT cohorts. Adherence was assessed using proportion of days covered (PDC) and proportion of patients achieving PDC ≥0.8 and PDC ≥0.5. Non-persistence was identified as a >45-day gap between fills.

RESULTS: The study included 1396 FF/UMEC/VI and 5115 MITT initiators. Three months after initiation, FF/UMEC/VI users had significantly higher mean PDC versus MITT users (0.68 vs 0.59; $P < .001$) and 31% more likely to be adherent (PDC ≥0.8; 40.6% vs 31.3%; adjusted risk ratio [95% confidence interval (CI)]: 1.31 [1.13-1.54]; $P < .001$). Similar patterns were observed at 6 and 12 months post initiation. In addition, FF/UMEC/VI users were 49% more likely to persist at 12 months than MITT users (25.9% vs 15.1%, adjusted hazard ratio [95% CI]: 1.49 [1.39-1.60]; $P < .001$).

CONCLUSIONS: Patients with asthma initiating triple therapy with FF/UMEC/VI had significantly better adherence and persistence compared with MITT initiators. © 2022 The

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Abbreviations used

aHR- Adjusted hazard ratio
aMD- Adjusted mean difference
aRR- Adjusted risk ratio
CI- Confidence interval
COPD- Chronic obstructive pulmonary disease
ED- Emergency department
FDA- Food and Drug Administration
FF- Fluticasone furoate
GINA- Global Initiative for Asthma
HCP- Healthcare professional
HRU- Healthcare resource utilization
ICD-10-CM- International Classification of Diseases, Tenth Revision, Clinical Modification
ICS- Inhaled corticosteroid
LABA- Long-acting β_2-agonist
LAMA- Long-acting muscarinic antagonist
MITT- Multiple-inhaler triple therapy
NHLBI- The National Institutes of Health National Heart, Lung, and Blood Institute
PDC- Proportion of days covered
Quan-CCI- Quan-Charlson Comorbidity Index
SABA- Short-acting β_2-agonist
SD- Standard deviation
SITT- Single-inhaler triple therapy
std. diff.- Standardized difference
UMEC- Umeclidinium
VI- Vilanterol

Key words: *Multiple-inhaler triple therapy; Single-inhaler triple therapy; Asthma management; Uncontrolled asthma; Adherence; Persistence; Fluticasone furoate; Umeclidinium; Vilanterol*

Asthma is a heterogeneous chronic inflammatory respiratory disease defined by symptoms such as wheeze, shortness of breath, chest tightness, cough, and airflow limitation.[1,2] Poor asthma control represents a significant burden to both patients and society as it is associated with poor quality of life and increased exacerbations, health care costs, and mortality.[3-7] Prevalence rates are increasing globally and, in 2015, over 358 million people worldwide were suffering from asthma and 400,000 died from this disease.[8] In the United States, asthma affected an estimated 25 million people, with approximately 3500 deaths due to asthma according to 2019 data.[9]

The National Institutes of Health National Heart, Lung, and Blood Institute (NHLBI) 2020 asthma guideline update and the Global Initiative for Asthma (GINA) 2021 report highlight the importance of medication adherence in asthma management and control.[1,2] Medication adherence tends to be suboptimal in the real world, and lower adherence has been shown to be associated with increased asthma exacerbation risk, rescue medication use, healthcare resource utilization (HRU), and costs.[10-13] However, conflicting data have been reported which suggest that patients with higher adherence to treatment may actually experience more exacerbations, worse asthma control, and have a higher probability of their treatment being stepped up.[14,15] One potential explanation for this conflicting finding is reverse causality; patients with more severe symptoms may maximize their inhaled controller use and thereby meet requirements for step-up therapy more quickly (therefore characterized with exacerbations or having poor asthma control).

The NHLBI 2020 asthma guidelines and GINA report recommend adding long-acting muscarinic antagonists (LAMA) as an additional controller for patients with uncontrolled asthma on at least medium-dose inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) therapy.[1,2] The addition of a LAMA to ICS/LABA maintenance therapy has been shown to improve lung function and symptoms and reduce exacerbation rates in patients with uncontrolled asthma; furthermore, the addition of LAMA is likely to incur substantially lower costs compared with escalating to biologic therapy.[16-20]

Until recently, the addition of a LAMA to ICS/LABA therapy (ie, triple therapy) for asthma maintenance was only available in the form of multiple-inhaler triple therapy (MITT), usually with different devices or differing dosing regimens.[2] Real-world observational studies in the United States and Japan reported low adherence to, and persistence with MITT among patients with asthma requiring triple therapy.[21,22] The US study also reported a substantial disease burden (high HRU and exacerbation rates) associated with MITT.[22]

A fixed-dose combination of fluticasone furoate (FF), umeclidinium (UMEC), and vilanterol (VI) (FF/UMEC/VI 100/62.5/25 mcg), administered once daily via a single inhaler (ELLIPTA dry-powder inhaler),[23] was approved by the Food and Drug Administration (FDA) for chronic obstructive pulmonary disease (COPD) on September 18, 2017, and September 9, 2020, for adults with asthma.[23,24] FF/UMEC/VI is the first single-inhaler triple therapy (SITT) approved by the FDA for the management of both asthma and COPD, and is the only SITT available in the United States that is administered once daily.[24] SITT introduces a new treatment paradigm for the management of adult patients with asthma who remain symptomatic on dual therapy.[25] However, real-world information on adherence and persistence among patients with asthma initiating SITT is currently limited.

This retrospective cohort study assessed adherence and persistence to once-daily single-inhaler FF/UMEC/VI (100/62.5/25 mcg), relative to MITT among patients with asthma in the United States.

METHODS

Data source

This study used data from the IQVIA PharMetrics Plus database (spanning the period from September 18, 2016, to December 31, 2019), which contains fully adjudicated medical and pharmacy claims data for approximately 40 million patients in any given recent year across all 50 US states, with an average length of health plan enrollment of 36 months. Commercial insurance is the most frequent plan type captured (the database is generally representative of the <65 years of age, commercially insured population in the United States), but other types can also be found, including Medicare, and self-insured employer groups (as managed by health plan). The database contains information on patient demographics, plan enrollment, inpatient and outpatient medical claims, and outpatient pharmacy claims. Data are de-identified and compliant with the Health Insurance Portability and Accountability Act.

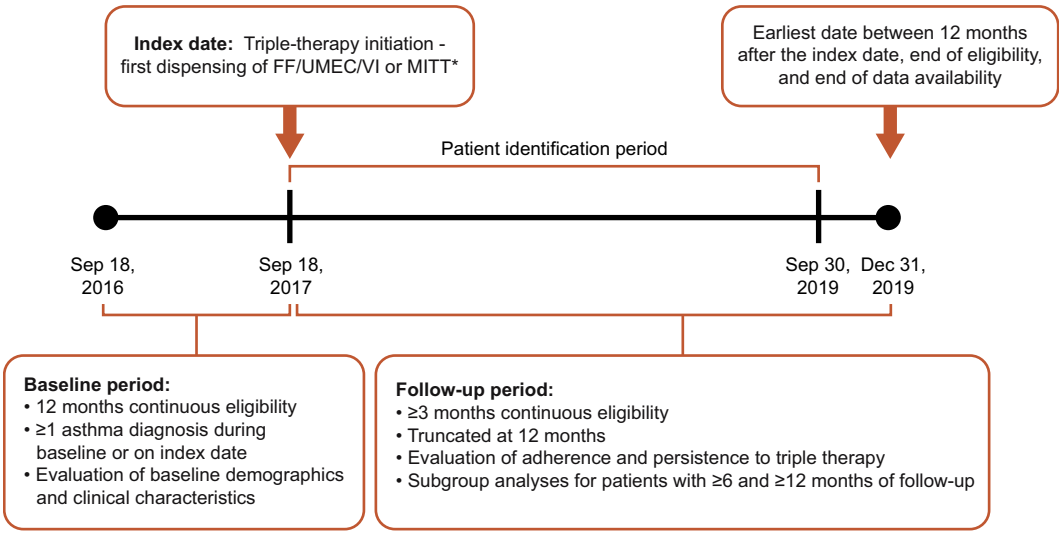

FIGURE 1. Study design. *Index date for MITT was defined as the first overlapping day supply with ICS, LABA, and LAMA. *FF*, Fluticasone furoate; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist; *LAMA*, long-acting muscarinic antagonist; *MITT*, multiple-inhaler triple therapy; *UMEC*, umeclidinium; *VI*, vilanterol.

Study design

This was a retrospective, weighted cohort study of patients with asthma initiating once-daily single-inhaler FF/UMEC/VI (100/62.5/25 mcg) or MITT (once or twice daily) during the patient identification period from September 18, 2017, to September 30, 2019. The index date was defined as the date of the first dispensing of FF/UMEC/VI or MITT (Figure 1). MITT users were identified based on an overlap of ≥1 day of supply of all 3 triple-therapy components (ICS, LABA, and LAMA), which could be via 3 separate inhalers (ICS + LAMA + LABA) or 2 inhalers (ICS/LABA + LAMA or LAMA/LABA + ICS); this algorithm was based on previous studies.[26-28]

The baseline period was defined as the 12 months before the index date and was used to assess patient demographics and clinical characteristics. An intent-to-treat design was used, where adherence and persistence to triple therapy were evaluated during the follow-up period, which spanned from the index date until 12 months after the index date, end of eligibility, or end of data availability (December 31, 2019), whichever occurred first (Figure 1). This study design did not take medication switch from MITT to SITT (or vice versa) during the follow-up period into account.

The protocol for this retrospective study was preregistered with a public registry (GSK study 208189, https://www.gsk-studyregister.com/en/).

Study population

Patients included in this study were aged ≥18 years at the index date and had ≥1 diagnosis of asthma (International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]: J45.xxx) during the baseline period or on the index date. Patients had ≥1 dispensing of FF/UMEC/VI 100/62.5/25 mcg, or, if none, ≥1 overlapping day supply with all 3 components of triple therapy (ICS, LABA, and LAMA) during the patient identification period. All patients had continuous health plan enrollment with medical and pharmacy coverage for ≥12 months before the index date and ≥3 months after the index date.

Patients were excluded if they had a diagnosis of COPD (ICD-10-CM: J41.x, J42, J43.x, J44.x) or acute respiratory failure (ICD-10-CM: J96.0x, J96.2x) during the baseline period or on the index date, had a diagnosis of cystic fibrosis (ICD-10-CM: E84.0-E84.9x) during the baseline or follow-up periods, had dispensing for both FF/UMEC/VI and MITT on the index date, or used MITT during the baseline period. Patients were excluded from the FF/UMEC/VI cohort if they had ≥1 dispensing of FF/UMEC/VI during the baseline period. Subgroups of patients with ≥6 months and ≥12 months of continuous enrollment after index were also identified.

Study outcomes

Study outcomes included adherence and persistence to triple therapy. Adherence was measured as the proportion of days covered (PDC) at 3 months of follow-up in the main analysis, and 6 and 12 months among the subgroups of patients with ≥6 and ≥12 months of follow-up, respectively. PDC was calculated based on the total number of days with FF/UMEC/VI for the FF/UMEC/VI cohort, or the total number of days with all 3 triple-therapy components (ICS, LABA, and LAMA) for the MITT cohort. Days on triple therapy were divided by a fixed time interval (ie, 90 days for the main analysis). Adherent patients were defined as patients achieving PDC ≥0.8 and PDC ≥0.5, based on existing studies and guidelines.[26,29,30]

Treatment persistence was assessed by the time to discontinuation of FF/UMEC/VI or MITT. For the FF/UMEC/VI cohort, nonpersistence (discontinuation) was defined as a gap of >45 days (>60 days and >90 days were considered as sensitivity analyses) between the end of a dispensing and the following fill, or between the end of the last dispensing and the end of follow-up. For the MITT cohort, nonpersistence was defined as noted above, but for any of the 3 components of triple therapy (ICS, LABA, or LAMA). Median time to nonpersistence (time point when the proportion of patients persisting on triple therapy dropped to 50%) was also evaluated.

Statistical analysis

Inverse probability of treatment weighting based on the propensity score was used to adjust for differences in baseline patient

TABLE I. Baseline demographics and clinical characteristics among patients initiating FF/UMEC/VI and MITT with ≥3 months of follow-up

	Unweighted cohorts			Weighted cohorts		
	FF/UMEC/VI (N = 1396)	MITT (N = 5115)	std. diff. (%)*	FF/UMEC/VI (N = 1396)	MITT (N = 5115)	std. diff. (%)*
Post-index follow-up time, mean (SD) (d)	275.4 (90.8)	295.2 (90.6)	21.8	296.2 (90.4)	291.6 (91.1)	5.1
Age, mean (SD) (y)	52.1 (11.3)	49.7 (12.9)	19.3	50.6 (12.2)	50.2 (12.7)	3.1
Female, n (%)	813 (58.2)	3372 (65.9)	15.8	891 (63.8)	3302 (64.5)	1.5
Quan-CCI score,[33] mean (SD)	1.4 (1.2)	1.4 (1.1)	0.8	1.5 (1.1)	1.4 (1.1)	4.7
Physician specialty†, n (%)						
Primary care	606 (43.4)	1620 (31.7)	24.2	429 (30.7)	1733 (33.9)	6.8
Respiratory specialist	554 (39.7)	2625 (51.3)	23.4	777 (55.7)	2537 (49.6)	12.2
Others	236 (16.9)	870 (17.0)	0.3	190 (13.6)	845 (16.5)	8.1
Overall asthma-related exacerbations‡						
Asthma-related exacerbation, mean (SD)	0.7 (1.2)	0.9 (1.2)	18.2	0.9 (1.3)	0.9 (1.2)	0.8
≥1 Asthma-related exacerbation, n (%)	553 (39.6)	2709 (53.0)	26.8	670 (48.0)	2612 (51.1)	6.2
All-cause HCU, n (%)						
≥1 ED visit	512 (36.7)	2054 (40.2)	7.2	516 (37.0)	2015 (39.4)	5.0
≥1 hospitalization	90 (6.4)	480 (9.4)	10.9	131 (9.4)	451 (8.8)	1.9
Asthma-related HCU, n (%)§						
≥1 ED visit	108 (7.7)	516 (10.1)	8.3	128 (9.2)	488 (9.5)	1.2
≥1 hospitalization	26 (1.9)	149 (2.9)	6.9	35 (2.5)	140 (2.7)	1.5
All-cause healthcare costs $US 2019, mean (SD)						
Total costs (medical + pharmacy)	16,113 (25,962)	19,504 (52,190)	8.2	19,696 (28,452)	19,034 (48,142)	1.7
Asthma-related healthcare costs $US 2019, mean (SD)§						
Total costs (medical + pharmacy)	3665 (10,537)	4883 (10,130)	11.8	5332 (10,782)	4701 (10,231)	6.0
Patient-paid cost of index medication fill	92 (164)	67 (120)	17.6	85 (160)	73 (140)	7.9
Comorbidities, n (%)‖						
Hypertension	676 (48.4)	2133 (41.7)	13.5	656 (47.0)	2193 (42.9)	8.2
Obesity	330 (23.6)	1259 (24.6)	2.3	313 (22.4)	1256 (24.6)	5.1
Diabetes	246 (17.6)	780 (15.2)	6.4	241 (17.3)	810 (15.8)	3.8
Cardiac arrhythmias	157 (11.2)	649 (12.7)	4.4	184 (13.2)	635 (12.4)	2.3
Rheumatoid arthritis/collagen vascular disease	105 (7.5)	389 (7.6)	0.3	125 (8.9)	392 (7.7)	4.6
Liver disease	89 (6.4)	305 (6.0)	1.7	71 (5.1)	311 (6.1)	4.5
Valvular disease	81 (5.8)	248 (4.8)	4.2	82 (5.8)	261 (5.1)	3.2
Deficiency anemias	79 (5.7)	264 (5.2)	2.2	65 (4.6)	268 (5.2)	2.7
Solid tumor without metastasis	66 (4.7)	182 (3.6)	5.9	64 (4.6)	200 (3.9)	3.2
Congestive heart failure	52 (3.7)	176 (3.4)	1.5	96 (6.9)	188 (3.7)	14.5

ED, Emergency department; *FF*, fluticasone furoate; *HRU*, healthcare resource utilization; *MITT*, multiple-inhaler triple therapy; *OCS*, oral corticosteroid; *Quan-CCI*, Quan-Charlson Comorbidity Index; *SCS*, systemic corticosteroid; *SD*, standard deviation; std. diff., standardized difference; *UMEC*, umeclidinium; *VI*, vilanterol.

Demographics and physician specialty were evaluated at the index date, whereas all other clinical characteristics were evaluated during the 12-month baseline period.

*For continuous variables, the std. diff. was calculated by dividing the absolute difference in means of the control and the case by the pooled SD of both groups. The pooled SD is the square root of the average of the squared SDs. For dichotomous variables, the std. diff. was calculated using the following equation where P is the respective proportion of participants in each group: $|(P_{case} - P_{control})|/\sqrt{[(P_{case}(1 - P_{case}) + P_{control}(1 - P_{control}))/2]}$. A std. diff. of <10% was considered a negligible imbalance between cohorts.

†Based on medical claims within 30 days prior to the index date, including the index date; the claim closest to the index date was selected. Respiratory specialist was prioritized among patients with both primary care and respiratory specialist on the closest claim to the index date (ie, primary care and respiratory specialist are mutually exclusive). Primary care includes family/general medicine practitioners, nurse practitioners, internal medicine, and pediatricians. Respiratory specialists include pulmonologists and allergists.

‡Exacerbations were SCS-defined or hospitalization-defined. SCS-defined: an asthma-related ED visit or outpatient visit with an OCS or SCS dispensing and/or administration with ±5 days; hospitalization-defined: an inpatient visit with a primary or secondary diagnosis of asthma, or an ED visit with a primary diagnosis of asthma and resulting in an inpatient visit within +1 day.

§Asthma-related HRU episodes and costs were identified as any claim with a primary diagnosis of asthma, and costs were inflation-adjusted to $US 2019 using the US Medical Care consumer price index from the Bureau of Labor Statistics from the US Department of Labor.

‖Occurring in >4% of patients in ≥1 cohort.

characteristics between the FF/UMEC/VI and MITT cohorts. Propensity scores were calculated separately for the main analysis and for the subgroup analyses. Variables used in the propensity score for the main analysis among patients with ≥3 months of follow-up and the subgroup analysis among patients with ≥6 months of follow-up included age, sex, year and quarter of index date, region, insurance plan type, physician specialty, Quan-Charlson Comorbidity Index (Quan-CCI), asthma medication ratio, asthma exacerbations during

the baseline period and on the index date, asthma controller and rescue medication use, all-cause and asthma-related HRU and costs, and Elixhauser comorbidities[31] (with ≥1% prevalence in either cohort). Among the subgroup of patients with ≥12 months of follow-up, the same variables were included in the propensity score model with the exception of year and quarter of index date and included Elixhauser comorbidities with a ≥10% prevalence in either cohort.

Baseline characteristics were summarized using mean and standard deviation (SD) for continuous variables and frequencies and proportions for categorical variables. Differences in characteristics between cohorts were assessed using standardized differences (std. diff.), with a threshold of <10% considered a negligible imbalance between cohorts.[32]

Multivariable models were used to adjust for remaining imbalances after weighting (ie, doubly robust approach). The doubly robust models adjusted for index year, physician specialty, and congestive heart failure for the 3-month analysis; for age, Quan-CCI, index year, hypertension, and antibiotic use for the 6-month analysis; and for insurance plan type, physician specialty, diabetes, antibiotic use, and systemic corticosteroid use for the 12-month analysis.

Adherence to triple therapy was compared between weighted cohorts using adjusted mean differences (aMDs) in PDC from multivariable generalized linear models; proportions of adherent patients were compared between weighted cohorts using adjusted risk ratios (aRRs) from multivariable log-binomial regression models. Non-parametric bootstrap procedures with 499 replications were used to calculate 95% confidence intervals (CIs) and *P*-values; this methodology was used to avoid making assumptions about the distribution of the data. Persistence on triple therapy was assessed with Kaplan-Meier analysis and compared between weighted cohorts at 3, 6, and 12 months of follow-up using adjusted hazard ratios (aHRs), 95% CIs, and *P*-values from multivariable Cox proportional hazards regression models.

All analyses were conducted using SAS Enterprise Guide, Version 7.15, or its latest version (SAS Institute Inc., Cary, NC).

RESULTS

Study population and baseline characteristics

A total of 1396 and 5115 patients in the FF/UMEC/VI and MITT cohorts, respectively, were included in the main analysis (patients with ≥3 months of follow-up). The mean follow-up periods were similar between the weighted FF/UMEC/VI and MITT cohorts (296 and 292 days, respectively) (Table I[33]). Baseline demographics and clinical characteristics were generally well balanced between the weighted FF/UMEC/VI and MITT cohorts (std. diff. <10%). Mean age was similar for FF/UMEC/VI versus MITT users (50.6 vs 50.2 years), as was the proportion of females (63.8% vs 64.5%), the mean Quan-CCI score (1.5 vs 1.4), the proportion of patients with ≥1 asthma-related exacerbation (48.0% vs 51.1%), ≥1 asthma-related emergency department visit (9.2% vs 9.5%), ≥1 asthma-related hospitalization (2.5% vs 2.7%), and the mean total all-cause healthcare costs ($19,696 vs $19,034). However, more patients in the weighted FF/UMEC/VI cohort were treated by a respiratory specialist compared with the weighted MITT cohort (std. diff. 12.2%). The most common comorbidities for the FF/UMEC/VI and MITT cohorts were hypertension, obesity, diabetes, and cardiac arrhythmias (Table I[33]).

Baseline asthma medication use was well balanced between patients initiating FF/UMEC/VI and MITT after weighting (Table II). The most common controller medication used in the baseline period was ICS/LABA (79.7% vs 77.7%), which was similar between the 2 groups as was use of short-acting β_2-agonist (SABA); (81.9% vs 80.0%), antibiotics (81.4% vs 78.6%), and systemic corticosteroids (76.6% vs 75.4%).

In the subgroup analysis of patients with ≥6 months of follow-up, 1119 and 4239 patients were included in the FF/UMEC/VI and MITT cohorts, respectively, whereas in the 12 months of follow-up subgroup analysis, a total of 524 and 2666 patients were included. The mean follow-up time after weighting and baseline demographics, clinical characteristics, and asthma medication use were generally well balanced across patients initiating FF/UMEC/VI and MITT with ≥6 months (see Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org) and 12 months (see Tables E3 and E4 in this article's Online Repository at www.jaci-inpractice.org) of follow-up.

Adherence

At 3 months of follow-up, patients initiating FF/UMEC/VI had significantly higher mean SD (median) PDC compared with MITT users (0.68, 0.27 [0.67] vs 0.59, 0.30 [0.60]; aMD [95% CI]: 0.09 [0.06-0.13]; $P < .001$). This improvement was maintained at 6 months (0.56, 0.31 [0.58] vs 0.46, 0.31 [0.37]; aMD [95% CI]: 0.10 [0.05-0.14]; $P < .001$) and 12 months (0.46, 0.33 [0.41] vs 0.35, 0.30 [0.25]; aMD [95% CI]: 0.12 [0.07-0.17]; $P < .001$) of follow-up (Figure 2).

Moreover, patients initiated on FF/UMEC/VI were 31% more likely to be adherent (PDC ≥0.8) than those initiated on MITT (40.6% vs 31.3%; aRR [95% CI]: 1.31 [1.13-1.54]; $P < .001$). The difference between cohorts increased in the subgroup analyses among patients with ≥6 and ≥12 months of follow-up. At 6 months of follow-up, patients who initiated FF/UMEC/VI were 51% more likely to be adherent versus patients initiating MITT (30.9% vs 20.4%; aRR [95% CI]: 1.51 [1.23-1.81]; $P < .001$), and at 12 months, FF/UMEC/VI users were twice as likely to be adherent (24.7% vs 12.9%; aRR [95% CI]: 2.01 [1.61-2.60]; $P < .001$) (Figure 3). Similar trends were observed when using PDC ≥0.5 as the threshold to define adherent patients (Figure 4).

Persistence

Based on a treatment discontinuation gap of >45 days to define non-persistence, the FF/UMEC/VI cohort had a longer median persistence duration compared with the MITT cohort (131 days vs 66 days) (Figure 5). Patients initiating FF/UMEC/VI were 49% more likely to persist at 12 months versus the MITT cohort (25.9% vs 15.1%, aHR [95% CI]: 1.49 [1.39-1.60]; $P < .001$) (Figure 5).

Results of the sensitivity analyses using a >60-day and >90-day gap to define non-persistence were supportive of these findings, where FF/UMEC/VI users were 48% and 60% more likely to persist on triple therapy at 12 months (see Figure E1, *A* and *B*, in this article's Online Repository at www.jaci-inpractice.org). Subgroup analyses of treatment persistence based on a gap of >45 days to define nonpersistence among patients with ≥6 and ≥12 months of follow-up were consistent with the main analysis results (see Figure E2, *A* and *B*, in this article's Online Repository at www.jaci-inpractice.org).

TABLE II. Baseline respiratory medication use among patients initiating FF/UMEC/VI and MITT with ≥3 months of follow-up

	Unweighted cohorts			Weighted cohorts		
	FF/UMEC/VI (N = 1396)	MITT (N = 5115)	std. diff. (%)*	FF/UMEC/VI (N = 1396)	MITT (N = 5115)	std. diff. (%)*
Baseline controller medication, n (%)						
ICS/LABA	842 (60.3)	4187 (81.9)	47.5	1113 (79.7)	3975 (77.7)	4.9
Leukotriene modifiers	709 (50.8)	3272 (64.0)	26.7	899 (64.4)	3139 (61.4)	6.2
ICS	185 (13.3)	1059 (20.7)	19.8	300 (21.5)	986 (19.3)	5.5
Biologics	64 (4.6)	309 (6.0)	6.5	80 (5.8)	295 (5.8)	0.1
LAMA/LABA	48 (3.4)	112 (2.2)	7.6	39 (2.8)	136 (2.7)	0.9
LAMA	26 (1.9)	1225 (23.9)	65.9	274 (19.6)	988 (19.3)	0.8
Methylxanthines	15 (1.1)	47 (0.9)	1.6	14 (1.0)	51 (1.0)	0.0
LABA	7 (0.5)	39 (0.8)	3.3	5 (0.3)	35 (0.7)	5.1
Mast cell stabilizers	1 (0.1)	9 (0.2)	3.0	1 (0.1)	8 (0.2)	3.1
Other respiratory medications, n (%)						
Antibiotics	1097 (78.6)	4032 (78.8)	0.6	1136 (81.4)	4023 (78.6)	6.8
SABA	991 (71.0)	4203 (82.2)	26.4	1143 (81.9)	4090 (80.0)	4.8
SCS	987 (70.7)	3922 (76.7)	13.6	1069 (76.6)	3859 (75.4)	2.7
SABA/SAMA	165 (11.8)	667 (13.0)	3.7	222 (15.9)	657 (12.8)	8.8
SAMA	35 (2.5)	186 (3.6)	6.5	50 (3.6)	174 (3.4)	1.2

FF, Fluticasone furoate; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist; *LAMA*, long-acting muscarinic antagonist; *MITT*, multiple-inhaler triple therapy; *SABA*, short-acting β_2-agonist; *SAMA*, short-acting muscarinic antagonist; *SCS*, systemic corticosteroid; *std. diff.*, standardized difference; *UMEC*, umeclidinium; *VI*, vilanterol. Medication use was evaluated during the 12-month baseline period, excluding the index data.

*The std. diff. was calculated using the following equation where P is the respective proportion of participants in each group: $|(P_{case} - P_{control})|/\sqrt{[(P_{case}(1 - P_{case}) + P_{control}(1 - P_{control}))/2]}$.

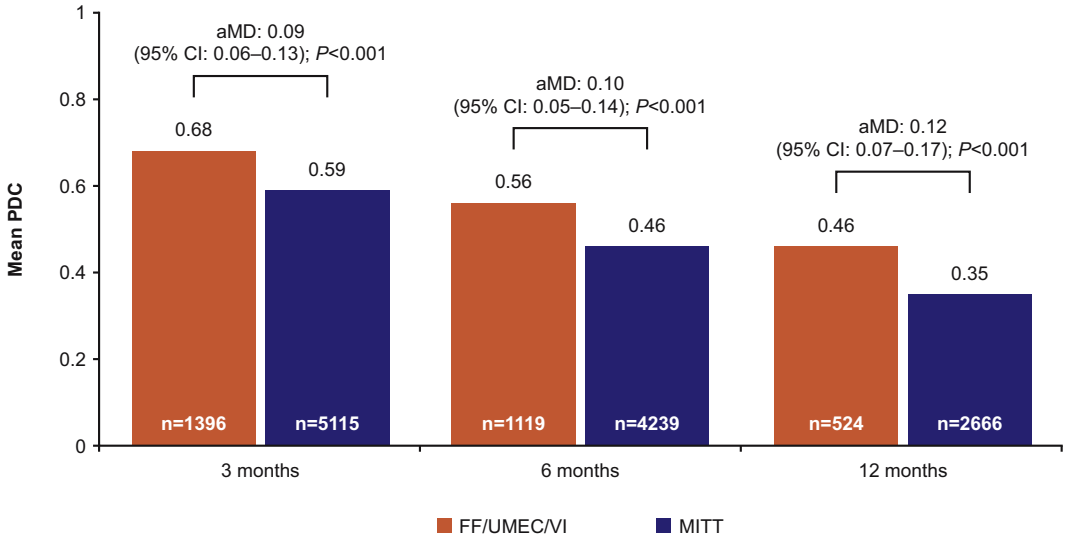

FIGURE 2. Mean PDC among the weighted FF/UMEC/VI and MITT cohorts at 3, 6, and 12 months after initiation. *aMD*, Adjusted mean difference; *CI*, confidence interval; *FF*, fluticasone furoate; *MITT*, multiple-inhaler triple therapy; *PDC*, proportion of days covered; *UMEC*, umeclidinium; *VI*, vilanterol.

DISCUSSION

In this real-world observational study, initiation of FF/UMEC/VI in a single inhaler was associated with significantly higher adherence and persistence compared with initiation of MITT. Patients initiated on FF/UMEC/VI had significantly higher adherence to triple therapy than those initiated on MITT (higher mean PDC and higher likelihood to adhere) at 3, 6, and 12 months after triple therapy initiation, and these differences increased among patients with longer follow-up periods. Treatment persistence was significantly higher among patients who initiated FF/UMEC/VI compared with those who initiated MITT, with an approximately 50% higher likelihood of persistence among the FF/UMEC/VI cohort at all time points analyzed up to 12 months. Persistence results were consistent in sensitivity analyses that used varying definitions of non-persistence, illustrating their robustness.

Our results are consistent with existing observational studies among patients with asthma, which show that adherence and

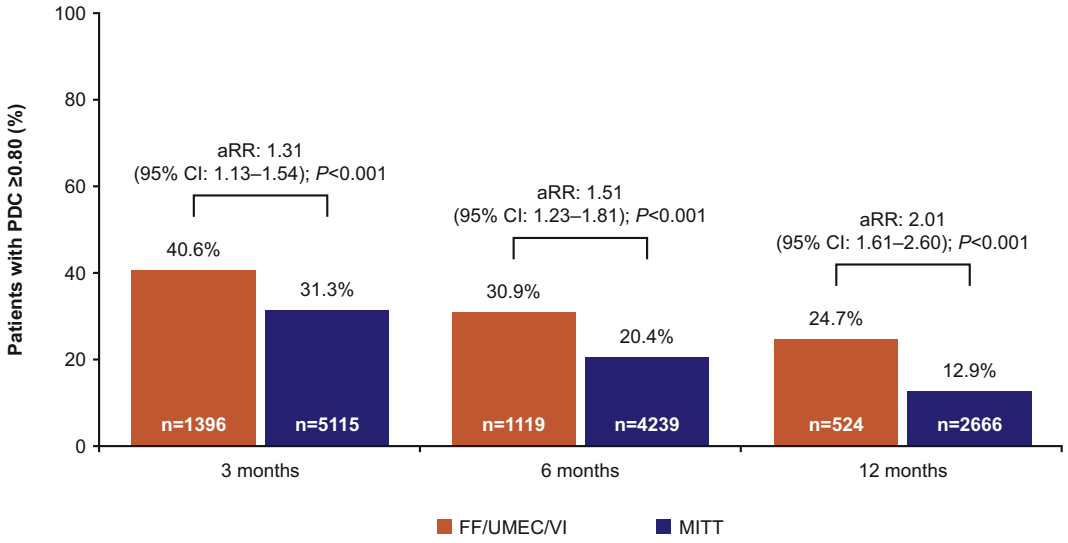

FIGURE 3. Patients with PDC ≥0.8 among the weighted FF/UMEC/VI and MITT cohorts at 3, 6, and 12 months after initiation. *aRR*, Adjusted risk ratio; *CI*, confidence interval; *FF*, fluticasone furoate; *MITT*, multiple-inhaler triple therapy; *PDC*, proportion of days covered; *UMEC*, umeclidinium; *VI*, vilanterol.

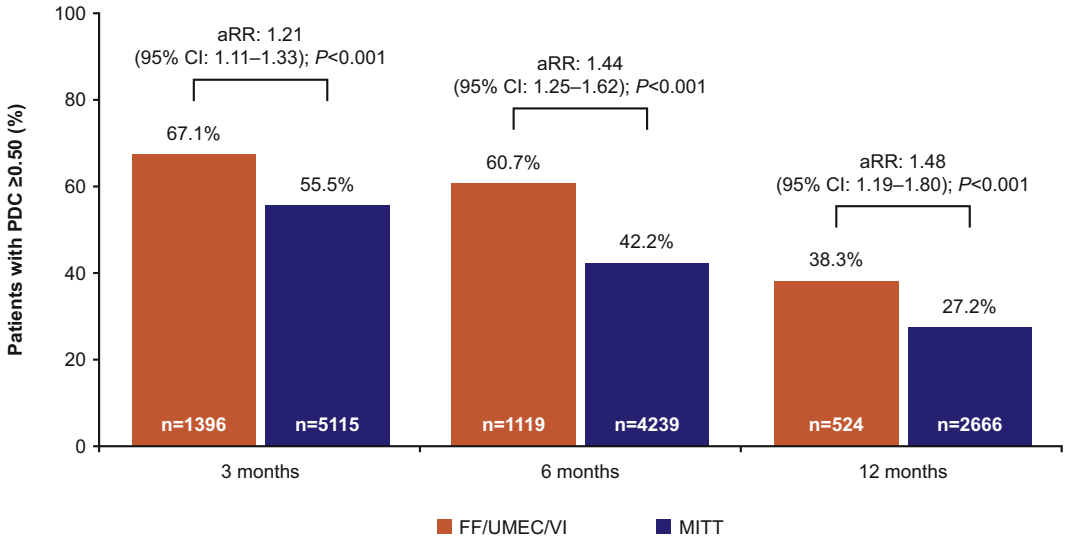

FIGURE 4. Patients with PDC ≥0.5 among the weighted FF/UMEC/VI and MITT cohorts at 3, 6, and 12 months after initiation. *aRR*, Adjusted risk ratio; *FF*, fluticasone furoate; *CI*, confidence interval; *MITT*, multiple-inhaler triple therapy; *PDC*, proportion of days covered; *UMEC*, umeclidinium; *VI*, vilanterol.

persistence are higher when using a single inhaler versus multiple inhalers in dual therapy.[34,35] In 2 retrospective cohort studies in the United States examining adherence to dual therapy via a single inhaler versus 2 inhalers, the mean number of prescription refills and treatment days were higher for single inhaler versus multiple inhalers.[34,35] Additionally, previous studies in asthma have shown that regimens with lower dosing frequencies are associated with improved adherence.[29,36,37] This suggests that once-daily FF/UMEC/VI overcomes the complexities of using multiple inhalers with different dosing regimens in triple therapy.[2,11,22] A predictive modeling study in Spain reported that a 20% increase in the use of SITT in patients with COPD on MITT could potentially increase the proportion of adherent patients up to 52%.[38] In this study, approximately 41% of patients were adherent to single-inhaler FF/UMEC/VI at 3 months of follow-up, though this rate dropped to 25% after 12 months of follow-up.

MITT is associated with low adherence and persistence. A real-world study in the United States among patients with asthma found rates of adherence and persistence to MITT similar to those observed in this study, with a mean (SD) PDC of 0.31 (0.27) at 12 months after initiation and 12% of patients remaining on MITT at 12 months.[22] Suzuki et al[21] published a cohort study in patients with asthma and asthma/COPD overlap

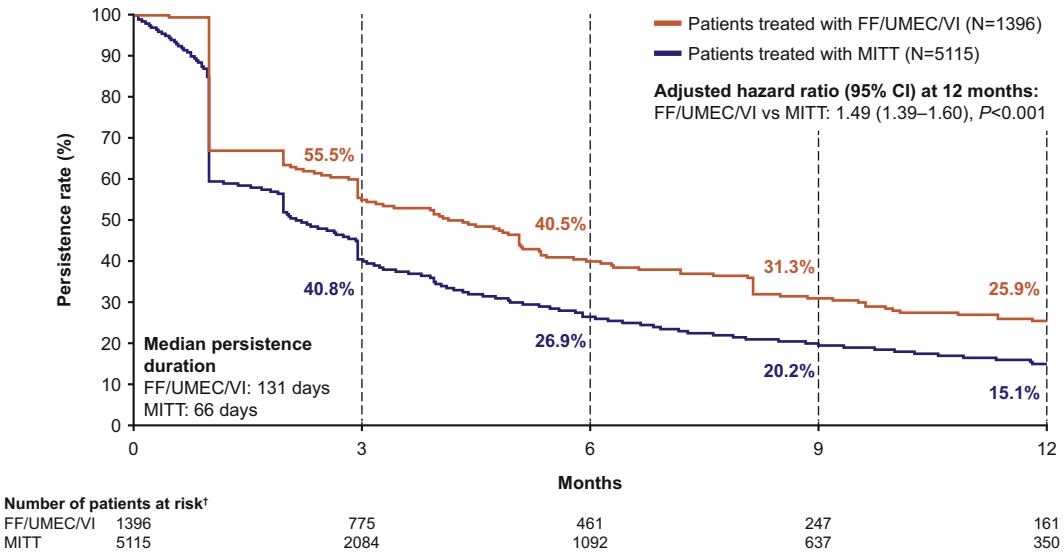

FIGURE 5. Kaplan-Meier persistence rates among the weighted FF/UMEC/VI and MITT cohorts using a gap of 45 days* with ≥3 months of follow-up. *For FF/UMEC/VI, nonpersistence was defined as a gap of 45 days between the end of the days' supply of a dispensing and the start date of the next fill, or between the end of the days' supply of the last dispensing and the end of the observation period. For MITT, nonpersistence was defined as noted above, but for any of the 3 components of the triple therapy (ie, ICS, LABA, or LAMA); the earliest date of non-persistence for any of the 3 components was selected. †Number of patients still observed at the specific point in time. *CI*, Confidence interval; *FF*, fluticasone furoate; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist; *LAMA*, long-acting muscarinic antagonist; *MITT*, multiple-inhaler triple therapy; *UMEC*, umeclidinium; *VI*, vilanterol.

who initiated MITT in Japan. Adherence and persistence rates were slightly higher in the asthma-only cohort than those reported here, but still generally low (mean [SD] PDC of 0.51 [0.36] over 12 months, and 38.5% of patients persistent to MITT at 12 months);[21] however, the sample size was considerably smaller than the present study.

The benefits of FF/UMEC/VI with regard to adherence and persistence among patients with asthma may translate into improved clinical outcomes. The association between better adherence and symptom control is well established, and treatment guidelines echo the importance of adherence in asthma management and control.[1,2,11,39] Moreover, better adherence may also translate into economic benefits, as highlighted by the observational study in the United States showing that adherent patients (PDC ≥80%) had lower medical healthcare costs and asthma-related exacerbation costs, although total costs were numerically higher in the adherent group, reflecting, as expected, higher pharmacy costs among adherent patients (PDC ≥80%).[22]

Although significant improvements relative to MITT were observed, the rates of adherence and persistence to FF/UMEC/VI in this study are still relatively low and decreased over follow-up. This heavily burdened, moderate/severe population of triple-therapy–eligible patients with asthma would clearly benefit from the improved lung function, symptom control, and lower asthma exacerbations rates known to be associated with high adherence.[16,18,19] The reasons for poor adherence and persistence to asthma maintenance therapy are unknown, but possible explanations include required lifestyle changes after therapy initiation, lack of understanding and awareness of the benefits of therapy, emotional response to the disease, side effects, mistrust in health care professionals (HCPs) and in the healthcare system, treatment beliefs, and little to no follow-up or monitoring after treatment initiation.[2,11,40] Educational programs, such as active participation of patients in treatment planning and phone calls from HCPs addressing medication concerns, have been shown to improve adherence in adults with asthma,[41] as have the use of electronic monitoring devices.[42,43] Additionally, frequent monitoring of adherence and inhaler technique by HCPs is currently recommended by GINA before stepping up controller medication, which has been shown to increase adherence rates to asthma treatment.[2,41,44-46] Improved patient education and active monitoring of patient adherence by HCPs may therefore contribute to improved adherence, and thus better outcomes, for patients with asthma.

Our findings have several limitations inherent to observational retrospective studies. First, our analyses indirectly measured adherence using pharmacy claims, which were not prospectively measured, and it is unknown whether patients used the medication as prescribed. Additionally, some physicians may intentionally choose MITT in preference to SITT as it provides an option to up-/down-titrate the individual components of triple therapy. Thus, some of the observed non-adherence to medication in the MITT group may not actually represent non-adherence *per se* but may have occurred based on physician recommendation to alter the therapy. Secondly, the definition of non-adherence to MITT in this study included patients who discontinued their LAMA but continued with their ICS/LABA therapy, whereas nonadherence to SITT would mean the patient received no controller therapies at all. Thus, nonadherence to MITT could be less consequential than nonadherence to SITT in some cases where patients continue on their ICS/LABA and as such might potentially skew the proportion of patients with nonadherence toward the MITT cohort. Future studies may be needed to examine long-term

adherence to the ICS component of MITT versus SITT. Thirdly, although propensity score weighting and doubly robust adjustment were used to account for observed differences between the FF/UMEC/VI and MITT cohorts, the possibility of unmeasured confounding cannot be excluded. Fourth, over-the-counter drugs and most medications received during an inpatient stay were not captured in the database. Fifth, these results may have limited generalizability to the US population with no insurance or public insurance (eg, Medicaid, Medicare). Sixth, FF/UMEC/VI was the only SITT formulation examined in this study. No other SITT was approved in the United States for the treatment of asthma covering the follow-up period in our study (to December 31, 2019). However, FF/UMEC/VI was available in the United States for the maintenance treatment of COPD, and thus, its use in this study reflects off-label use in asthma. As such, our results may not be generalizable to all other SITT formulations. Finally, the objective of the current study was solely to compare adherence and persistence to SITT versus MITT in adult patients treated in real-world clinical practice. We acknowledge that further research of the association between adherence to triple therapy and clinical and economic outcomes would be of value. Despite these limitations, this study used a large, geographically diverse database with detailed medical and pharmacy data and with good representation of the commercially insured US population. In addition, this study presents real-world data on the use of FF/UMEC/VI versus MITT in patients with asthma, which was previously scarce in the literature. Finally, the FF/UMEC/VI and MITT cohorts were weighted without excluding any patients, thereby enabling a representative assessment of each treatment and minimizing potential confounding.

CONCLUSIONS

Results from this real-world, retrospective cohort study showed that once-daily single-inhaler FF/UMEC/VI was associated with better adherence and persistence compared with once- or twice-daily MITT among patients with asthma. Findings were consistent over time and across sensitivity definitions. However, adherence and persistence were still relatively low, highlighting unmet health care need for strategies to improve adherence in this population with moderate/severe asthma. Further research is warranted to assess how the adherence and persistence benefits of single-inhaler FF/UMEC/VI may translate into improved clinical and economic outcomes.

Data availability

The data that support the findings of this study are available from IQVIA and are not publicly available. Restrictions apply to the availability of these data, which were used under license for the current study.

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W. W. Busse and C. B. Abbott contributed to data analysis/interpretation. G. Germain, F. Laliberté, and S. D. MacKnight contributed to the conception/design of the study, acquisition of data, and data analysis/interpretation. Y. Jung contributed to acquisition of data and data analysis/interpretation. M. S. Duh and C. M. Averell contributed to conception/design of the study and data analysis/interpretation. All authors were involved in preparation and review of the manuscript and approved the final version to be submitted. All authors take complete responsibility for the integrity of the data and accuracy of the data analysis.

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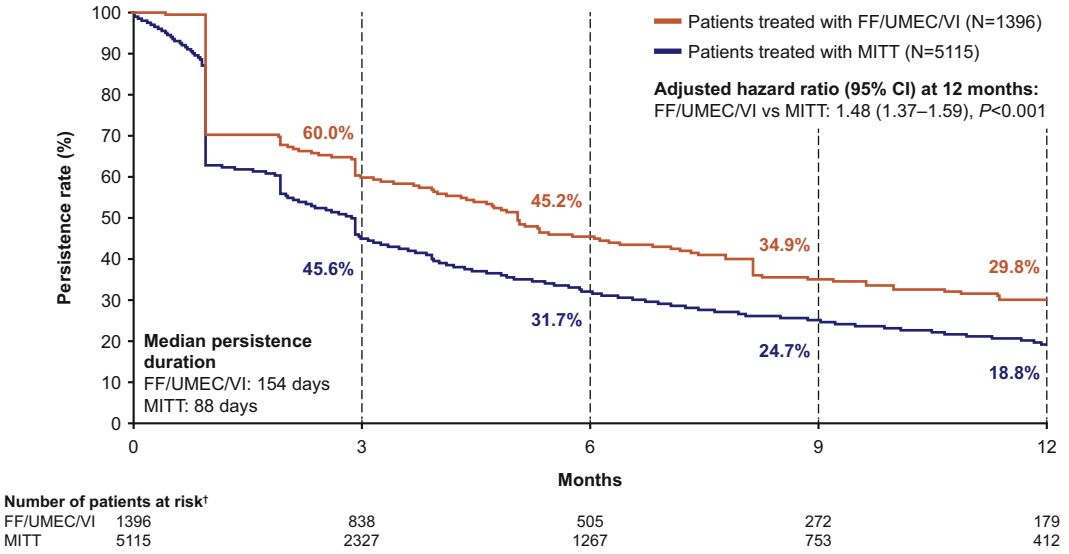

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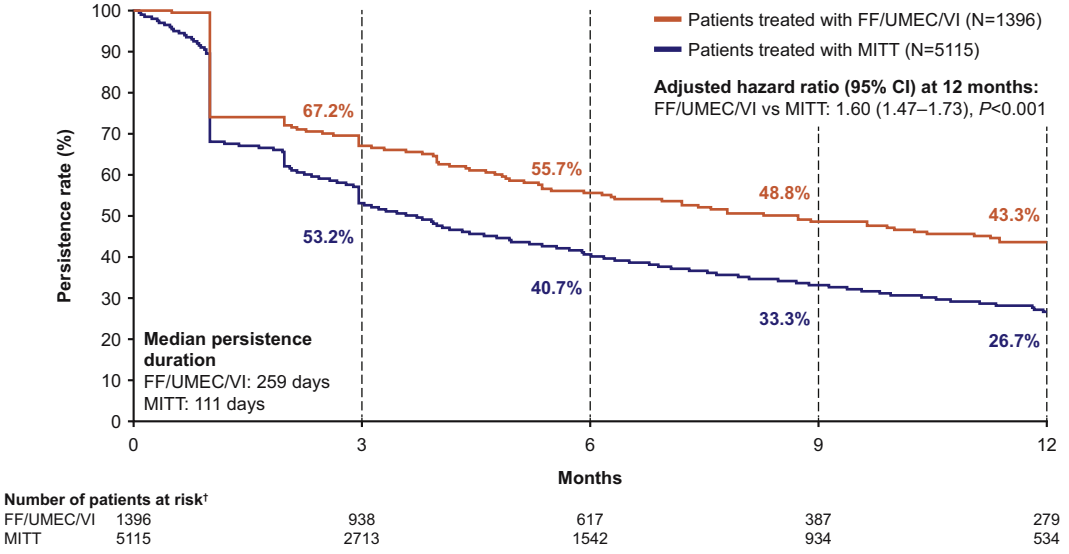

B

FIGURE E1. Kaplan-Meier persistence rates among the weighted FF/UMEC/VI and MITT cohorts with ≥3 months of follow-up (non-persistence defined as a gap of [**A**] 60 days and [**B**] 90 days*). *For FF/UMEC/VI, non-persistence was defined as a gap of 60 days (**A**) or 90 days (**B**) between the end of the days' supply of a dispensing and the start date of the next fill, or between the end of the days' supply of the last dispensing and the end of the observation period. For MITT, nonpersistence was defined as noted above, but for any of the 3 components of the triple therapy (ie, ICS, LABA, or LAMA), the earliest date of non-persistence for any of the 3 components was selected. †Number of patients still observed at the specific point in time. *CI*, Confidence interval; *FF*, fluticasone furoate; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist; *LAMA*, long-acting muscarinic antagonist; *MITT*, multiple-inhaler triple therapy; *UMEC*, umeclidinium; *VI*, vilanterol.

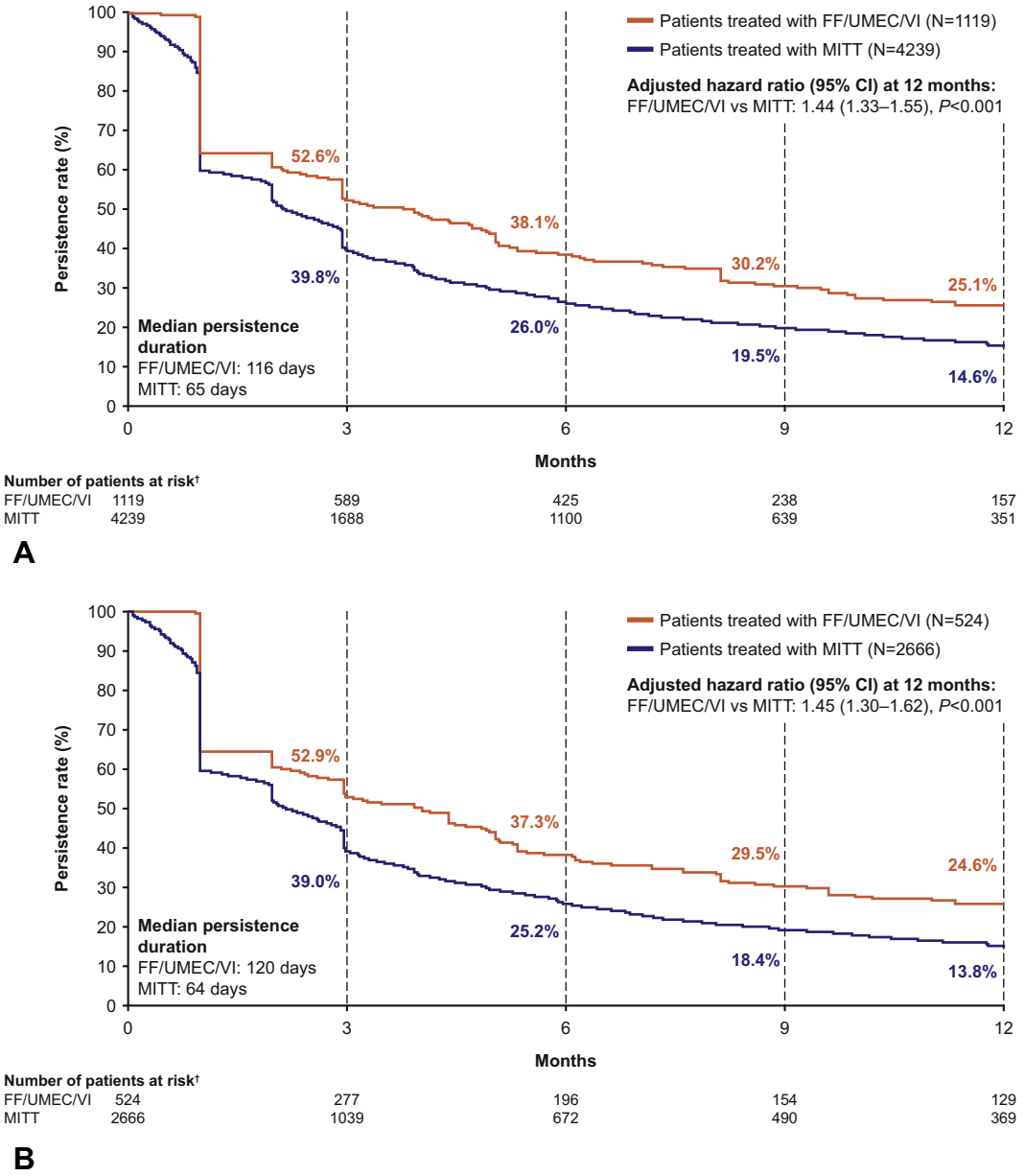

FIGURE E2. Kaplan-Meier persistence rates among the weighted FF/UMEC/VI and MITT cohorts using a gap of 45 days with (**A**) ≥6 months of follow-up* and (**B**) ≥12 months of follow-up.* *For FF/UMEC/VI, non-persistence was defined as a gap of 45 days between the end of the days' supply of a dispensing and the start date of the next fill, or between the end of the days' supply of the last dispensing and the end of the observation period. For MITT, non-persistence was defined as noted above, but for any of the 3 components of the triple therapy (ie, ICS, LABA, or LAMA), the earliest date of non-persistence for any of the 3 components was selected. †Number of patients still observed at the specific point in time. *CI*, Confidence interval; *FF*, fluticasone furoate; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist; *LAMA*, long-acting muscarinic antagonist; *MITT*, multiple-inhaler triple therapy; *UMEC*, umeclidinium; *VI*, vilanterol.

TABLE E1. Baseline demographics and clinical characteristics among patients initiating FF/UMEC/VI and MITT with ≥6 months of follow-up

	Unweighted cohorts			Weighted cohorts		
	FF/UMEC/VI (N = 1119)	MITT (N = 4239)	std. diff. (%)*	FF/UMEC/VI (N = 1119)	MITT (N = 4239)	std. diff. (%)*
Post-index follow-up time, mean (SD) (d)	310.2 (63.3)	328.6 (56.8)	30.7	327.9 (58.3)	325.6 (58.3)	3.9
Age, mean (SD) (y)	51.9 (11.3)	49.7 (12.9)	18.4	51.1 (11.9)	50.2 (12.6)	7.8
Female, n (%)	644 (57.6)	2762 (65.2)	15.6	707 (63.2)	2705 (63.8)	1.4
Quan-CCI,[E1] mean (SD)	1.4 (1.1)	1.4 (1.0)	1.4	1.5 (1.1)	1.4 (1.1)	9.8
Physician specialty, n (%)†						
Primary care	481 (43.0)	1346 (31.8)	23.2	353 (31.6)	1437 (33.9)	5.0
Respiratory specialist	436 (39.0)	2199 (51.9)	25.9	608 (54.4)	2121 (50.0)	8.7
Others	202 (18.1)	694 (16.4)	4.5	158 (14.1)	682 (16.1)	5.6
Overall asthma-related exacerbations‡						
Asthma exacerbation, mean (SD)	0.7 (1.2)	0.9 (1.3)	17.4	0.9 (1.2)	0.9 (1.3)	2.1
≥1 asthma exacerbation, n (%)	448 (40.0)	2238 (52.8)	25.6	578 (51.6)	2135 (50.4)	2.5
All-cause HCU, n (%)						
≥1 ED visit	405 (36.2)	1670 (39.4)	6.6	421 (37.6)	1645 (38.8)	2.5
≥1 hospitalization	67 (6.0)	389 (9.2)	12.0	128 (11.5)	363 (8.6)	9.7
Asthma-related HCU, n (%)§						
≥1 ED visit	89 (8.0)	419 (9.9)	6.8	92 (8.2)	400 (9.4)	4.4
≥1 hospitalization	21 (1.9)	127 (3.0)	7.3	31 (2.7)	119 (2.8)	0.5
All-cause health care costs $US 2019, mean (SD)						
Total costs (medical + pharmacy)	15,338 (23,674)	19,306 (54,419)	9.5	20,394 (28,007)	18,689 (49,982)	4.2
Asthma-related health care costs $US 2019, mean (SD)§						
Total costs (medical + pharmacy)	3517 (9386)	5032 (10,703)	15.1	4948 (9800)	4802 (10,571)	1.4
Patient-paid cost of index medication fill	97 (174)	69 (125)	18.5	91 (166)	76 (145)	9.4
Comorbidities, n (%)‖						
Hypertension	532 (47.5)	1752 (41.3)	12.5	533 (47.6)	1799 (42.4)	10.4
Obesity	262 (23.4)	1036 (24.4)	2.4	247 (22.0)	1034 (24.4)	5.6
Diabetes	189 (16.9)	636 (15.0)	5.2	216 (19.3)	655 (15.5)	10.1
Cardiac arrhythmias	123 (11.0)	527 (12.4)	4.5	145 (13.0)	512 (12.1)	2.7
Rheumatoid arthritis/collagen vascular disease	82 (7.3)	305 (7.2)	0.5	95 (8.5)	309 (7.3)	4.5
Liver disease	65 (5.8)	241 (5.7)	0.5	57 (5.1)	246 (5.8)	3.2
Valvular disease	61 (5.5)	200 (4.7)	3.3	70 (6.3)	210 (5.0)	5.7
Deficiency anemias	59 (5.3)	209 (4.9)	1.6	53 (4.7)	210 (5.0)	1.3
Solid tumor without metastasis	48 (4.3)	151 (3.6)	3.7	66 (5.9)	160 (3.8)	9.9
Congestive heart failure	41 (3.7)	142 (3.3)	1.7	81 (7.3)	152 (3.6)	16.2

ED, Emergency department; *FF*, fluticasone furoate; *HRU*, health care resource utilization; *MITT*, multiple-inhaler triple therapy; *OCS*, oral corticosteroid; *Quan-CCI*, Quan-Charlson Comorbidity Index; *SCS*, systemic corticosteroid; *SD*, standard deviation; *std. diff.*, standardized difference; UMEC, umeclidinium; VI, vilanterol.

Demographics and physician specialty were evaluated at the index date, whereas all other clinical characteristics were evaluated during the 12-month baseline period.

*For continuous variables, the std. diff. was calculated by dividing the absolute difference in means of the control and the case by the pooled SD of both groups. The pooled SD is the square root of the average of the squared SDs. For dichotomous variables, the std. diff. was calculated using the following equation where P is the respective proportion of participants in each group: $|(P_{case} - P_{control})|/\sqrt{[(P_{case}(1 - P_{case}) + P_{control}(1 - P_{control}))/2]}$. A std. diff. of <10% was considered not statistically significant.

†Based on medical claims within 30 days before the index date, including the index date; the claim closest to the index date was selected. Respiratory specialist was prioritized among patients with both primary care and respiratory specialist on the closest claim to the index date (ie, primary care and respiratory specialist are mutually exclusive). Primary care includes family/general medicine practitioners, nurse practitioners, internal medicine, and pediatricians. Respiratory specialists include pulmonologists and allergists.

‡Exacerbations were SCS-defined or hospitalization-defined. SCS-defined: an asthma-related ED visit or outpatient visit with an OCS or SCS dispensing and/or administration with ±5 days; hospitalization-defined: an inpatient visit with a primary or secondary diagnosis of asthma, or an ED visit with a primary diagnosis of asthma and resulting in an inpatient visit within +1 day.

§Asthma-related HRU episodes and costs were identified as any claim with a primary diagnosis of asthma, and costs were inflation-adjusted to $US 2019 using the US Medical Care consumer price index from the Bureau of Labor Statistics from the US Department of Labor.

‖Occurring in >4% of patients in ≥1 cohort.

TABLE E2. Baseline respiratory medication use among patients initiating FF/UMEC/VI and MITT with ≥6 months of follow-up

	Unweighted cohorts			Weighted cohorts		
	FF/UMEC/VI (N = 1119)	MITT (N = 4239)	std. diff. (%)*	FF/UMEC/VI (N = 1119)	MITT (N = 4239)	std. diff. (%)*
Baseline controller medication, n (%)						
ICS/LABA	671 (60.0)	3453 (81.5)	47.2	886 (79.2)	3286 (77.5)	4.1
Leukotriene modifiers	563 (50.3)	2695 (63.6)	26.8	709 (63.4)	2588 (61.1)	4.8
ICS	150 (13.4)	885 (20.9)	19.8	243 (21.7)	829 (19.6)	5.3
Biologics	50 (4.5)	254 (6.0)	6.8	58 (5.2)	241 (5.7)	2.3
LAMA/LABA	38 (3.4)	97 (2.3)	6.7	25 (2.2)	130 (3.1)	5.3
LAMA	25 (2.2)	1037 (24.5)	65.4	214 (19.1)	845 (19.9)	2.0
Methylxanthines	14 (1.3)	41 (1.0)	2.7	15 (1.4)	44 (1.0)	2.9
LABA	7 (0.6)	35 (0.8)	2.4	4 (0.3)	33 (0.8)	5.7
Mast cell stabilizers	1 (0.1)	7 (0.2)	2.1	0 (0.0)	6 (0.1)	3.3
Other respiratory medications, n (%)						
Antibiotics	893 (79.8)	3339 (78.8)	2.6	930 (83.1)	3347 (79.0)	10.6
SABA	794 (71.0)	3470 (81.9)	25.7	909 (81.3)	3382 (79.8)	3.8
SCS	792 (70.8)	3244 (76.5)	13.1	863 (77.1)	3202 (75.5)	3.7
SABA/SAMA	131 (11.7)	559 (13.2)	4.5	179 (16.0)	550 (13.0)	8.6
SAMA	27 (2.4)	160 (3.8)	7.9	28 (2.5)	148 (3.5)	5.8

FF, Fluticasone furoate; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist; *LAMA*, long-acting muscarinic antagonist; *MITT*, multiple-inhaler triple therapy; *SABA*, short-acting β_2-agonist; *SAMA*, short-acting muscarinic antagonist; *SCS*, systemic corticosteroid; *std. diff.*, standardized difference; *UMEC*, umeclidinium; *VI*, vilanterol.
Medication use was evaluated during the 12-month baseline period, excluding the index data.
*The std. diff. was calculated using the following equation where P is the respective proportion of participants in each group: $|(P_{case} - P_{control})|/\sqrt{[(P_{case}(1 - P_{case}) + P_{control}(1 - P_{control}))/2]}$.

TABLE E3. Baseline demographics and clinical characteristics among patients initiating FF/UMEC/VI and MITT with ≥12 months of follow-up

	Unweighted cohorts			Weighted cohorts		
	FF/UMEC/VI (N = 524)	MITT (N = 2666)	std. diff. (%)*	FF/UMEC/VI (N = 524)	MITT (N = 2666)	std. diff. (%)*
Postindex follow-up time, mean (SD) (d)	365.0 (0.0)	365.0 (0.0)	0.0	365.0 (0.0)	365.0 (0.0)	0.0
Age, mean (SD) (y)	52.2 (11.2)	49.6 (12.6)	21.3	50.0 (12.1)	50.0 (12.5)	0.3
Female, n (%)	296 (56.5)	1726 (64.7)	16.9	337 (64.3)	1695 (63.6)	1.6
Quan-CCI,[E1] mean (SD)	1.3 (0.9)	1.4 (1.0)	4.6	1.4 (1.0)	1.4 (1.0)	3.7
Physician specialty, n (%)†						
Primary care	189 (36.1)	874 (32.8)	6.9	168 (32.1)	883 (33.1)	2.2
Respiratory specialist	238 (45.4)	1349 (50.6)	10.4	293 (56.0)	1330 (49.9)	12.2
Others	97 (18.5)	443 (16.6)	5.0	63 (11.9)	453 (17.0)	14.4
Overall asthma-related exacerbations‡						
Asthma exacerbation, mean (SD)	0.73 (1.21)	0.95 (1.27)	17.3	0.99 (1.36)	0.92 (1.25)	5.8
≥1 asthma exacerbation, n (%)	223 (42.6)	1409 (52.9)	20.6	282 (53.8)	1373 (51.5)	4.7
All-cause HCU, n (%)						
≥1 ED visit	186 (35.5)	1036 (38.9)	7.0	187 (35.7)	1023 (38.4)	5.5
≥1 hospitalization	28 (5.3)	250 (9.4)	15.4	59 (11.3)	233 (8.8)	8.4
Asthma-related HCU, n (%)§						
≥1 ED visit	33 (6.3)	251 (9.4)	11.6	52 (9.8)	237 (8.9)	3.2
≥1 hospitalization	10 (1.9)	78 (2.9)	6.6	18 (3.5)	75 (2.8)	4.0
All-cause health care costs $US 2019, mean (SD)						
Total costs (medical + pharmacy)	14,780 (22,066)	18,452 (30,362)	13.8	17,900 (23,332)	17,986 (29,516)	0.3
Asthma-related health care costs $US 2019, mean (SD)§						
Total costs (medical + pharmacy)	3738 (9371)	5083 (11,110)	13.1	4981 (9913)	4918 (11,037)	0.6
Patient-paid cost of index medication fill	89 (167)	68 (123)	14.6	69 (124)	71 (130)	2.0
Comorbidities, n (%)‖						
Hypertension	246 (46.9)	1105 (41.4)	11.1	246 (47.0)	1128 (42.3)	9.4
Obesity	129 (24.6)	643 (24.1)	1.2	130 (24.9)	642 (24.1)	1.8
Diabetes	89 (17.0)	406 (15.2)	4.8	104 (19.9)	413 (15.5)	11.5
Cardiac arrhythmias	56 (10.7)	325 (12.2)	4.7	63 (12.0)	317 (11.9)	0.3
Rheumatoid arthritis/collagen vascular disease	36 (6.9)	191 (7.2)	1.2	46 (8.8)	189 (7.1)	6.2
Deficiency anemias	28 (5.3)	137 (5.1)	0.9	40 (7.6)	136 (5.1)	10.0
Liver disease	24 (4.6)	134 (5.0)	2.1	25 (4.8)	133 (5.0)	0.9
Valvular disease	23 (4.4)	116 (4.4)	0.2	21 (3.9)	118 (4.4)	2.5
Solid tumor without metastasis	20 (3.8)	87 (3.3)	3.0	22 (4.1)	87 (3.3)	4.4
Congestive heart failure	19 (3.6)	95 (3.6)	0.3	25 (4.7)	98 (3.7)	5.2

ED, Emergency department; *FF*, fluticasone furoate; *HCU*, health care resource utilization; *MITT*, multiple-inhaler triple therapy; *OCS*, oral corticosteroid; *Quan-CCI*, Quan-Charlson Comorbidity Index; *SCS*, systemic corticosteroid; *SD*, standard deviation; *std. diff.*, standardized difference; *UMEC*, umeclidinium; *VI*, vilanterol.

Demographics and physician specialty were evaluated at the index date, whereas all other clinical characteristics were evaluated during the 12-month baseline period.

*For continuous variables, the std. diff. was calculated by dividing the absolute difference in means of the control and the case by the pooled SD of both groups. The pooled SD is the square root of the average of the squared SDs. For dichotomous variables, the std. diff. was calculated using the following equation where P is the respective proportion of participants in each group: $|(P_{case} - P_{control})|/\sqrt{[(P_{case}(1 - P_{case}) + P_{control}(1 - P_{control}))/2]}$. A std. diff. of <10% was considered not statistically significant.

†Based on medical claims within 30 days before the index date, including the index date; the claim closest to the index date was selected. Respiratory specialist was prioritized among patients with both primary care and respiratory specialist on the closest claim to the index date (ie, primary care and respiratory specialist are mutually exclusive). Primary care includes family/general medicine practitioners, nurse practitioners, internal medicine, and pediatricians. Respiratory specialists include pulmonologists and allergists.

‡Exacerbations were SCS-defined or hospitalization-defined. SCS-defined: an asthma-related ED visit or outpatient visit with an OCS or SCS dispensing and/or administration with ±5 days; hospitalization-defined: an inpatient visit with a primary or secondary diagnosis of asthma, or an ED visit with a primary diagnosis of asthma and resulting in an inpatient visit within +1 day.

§Asthma-related HRU episodes and costs were identified as any claim with a primary diagnosis of asthma, and costs were inflation-adjusted to $US 2019 using the US Medical Care consumer price index from the Bureau of Labor Statistics from the US Department of Labor.

‖Occurring in >4% of patients in ≥1 cohort.

TABLE E4. Baseline respiratory medication use among patients initiating FF/UMEC/VI and MITT with ≥12 months of follow-up

	Unweighted cohorts			Weighted cohorts		
	FF/UMEC/VI (N = 524)	MITT (N = 2666)	std. diff. (%)*	FF/UMEC/VI (N = 524)	MITT (N = 2666)	std. diff. (%)*
Baseline controller medication, n (%)						
ICS/LABA	323 (61.6)	2155 (80.8)	42.4	423 (80.6)	2085 (78.2)	6.0
Leukotriene modifiers	267 (51.0)	1687 (63.3)	24.9	344 (65.7)	1638 (61.4)	8.8
ICS	72 (13.7)	567 (21.3)	19.8	110 (21.0)	541 (20.3)	1.9
Biologics	30 (5.7)	157 (5.9)	0.7	31 (6.0)	152 (5.7)	1.3
LAMA	19 (3.6)	662 (24.8)	60.7	117 (22.4)	572 (21.4)	2.3
LAMA/LABA	18 (3.4)	74 (2.8)	3.8	9 (1.7)	89 (3.3)	10.1
Methylxanthines	7 (1.3)	23 (0.9)	4.5	6 (1.1)	25 (0.9)	1.6
LABA	2 (0.4)	26 (1.0)	7.2	1 (0.3)	25 (0.9)	8.8
Mast cell stabilizers	0 (0.0)	3 (0.1)	4.7	0 (0.0)	3 (0.1)	4.5
Other respiratory medications, n (%)						
Antibiotics	424 (80.9)	2109 (79.1)	4.5	433 (82.5)	2116 (79.4)	8.1
SCS	375 (71.6)	2035 (76.3)	10.9	418 (79.7)	2017 (75.6)	9.7
SABA	371 (70.8)	2198 (82.4)	27.5	436 (83.2)	2152 (80.7)	6.6
SABA/SAMA	59 (11.3)	353 (13.2)	6.0	84 (16.0)	345 (12.9)	8.6
SAMA	12 (2.3)	96 (3.6)	7.8	11 (2.2)	89 (3.4)	7.3

FF, Fluticasone furoate; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist; *LAMA*, long-acting muscarinic antagonist; *MITT*, multiple-inhaler triple therapy; *SABA*, short-acting β_2-agonist; *SAMA*, short-acting muscarinic antagonists; *SCS*, systemic corticosteroid; *std. diff.*, standardized difference; *UMEC*, umeclidinium; *VI*, vilanterol. Medication use was evaluated during the 12-month baseline period, excluding the index data.

*The std. diff. was calculated using the following equation where P is the respective proportion of participants in each group: $|(P_{case} - P_{control})|/\sqrt{[(P_{case}(1 - P_{case}) + P_{control}(1 - P_{control}))/2]}$.

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